ISBN 0-315-89683-3

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

To my parents

Acknowledgements

I would like to express my deepest gratitude to my supervisor, Professor Howard Alper for his kind supervision, expert guidance and continual encouragement all through the course of this work. He is a wonderful supervisor, especially with computer like memory. Learning chemistry from him has been a fantastic experience. His understanding and kindness was invaluable to me during my physical or mental troublesome time. Thank you very much Dr. Alper.

I wish to express my gratitude to Professor Robert Fraser for his timely help to determine the structure of the novel rearrangement products. Many thanks are also to Professors Sandro Gambarotta, Margaret Back, Christian Detellier, René Roy, Tony Durst, Alex Fallis, John Milne, Darrin Richeson and Paul Wilde for teaching, helping and stimulating discussions during my stay at this department.

Thanks are owed to Dr. Corrine Bensimon for the X-ray analyses; Mr. Raj Capoor, Dr. Tony Williams and Dr. Glenn Facey for efficiently recording a large number of NMR spectra; Dr. Clem Kazakoff and Dr. John Krause for timely providing mass spectral data.

Thanks are also owed to many members of staff and faculty in this department: Fern Boucher, Dan Emard, Guia Garces, Dan Lafleur, Robert Nadon and Mario Savage; Annette Fournier, Cass Guthridge, Monique Levesque, Lise Maisonneuve, Wilma Nuyens and Mike Quimet; Francois Allard, Don Hopkins, John Hopkins, Egon Kristof, André Simard and Eva Szabo for their kind help and friendship, and to my friends and colleagues Rashmi Venkateswaran, J.C. Bradley, Richard C. Connors and Claudio Sturino for their help and encouragement.

It is my pleasure to thank my colleagues who have been members in Dr. Alper's group for their friendship, understanding, scientific help and good humour. Thank you everybody: Anna Masdeu, Amihai Eisenstadt, Anoma Somasunderam, Armando Cabrera, Attila Benyei, Bassam El-Ali, Cathy Crudden, Cathy Nagle, Daniel Perez, Daniele Delledone, Davit Zargarian, Dee Brandes, Dominique Roberto, Gustav Bitsi, Hagai Huminer, Ibrahim Amer, Ilan Pri-Bar, Ilhyong Ryu, Jack Azran, Jian-Quang Zhou, Jin-Ook Baeg, Jong-Tae Lee, Kanjai Khumtaveeporn (Dang), Karen Totland, Kelly Walsh,

Kun-Tae Huh, Lucille Vaysse, Manuel Saldana-Maldonado, Masayuki Kameyama, Milan Harustiak, Milan Struharik, Milena Sommovigo, Mirco Costa, Nagavelli Prabhakar Reddy, Nathalie Hamel, Nistala Satyanarayana, Pei Li, Pavel Krasik, G.(Pino) Vasapollo, Serge Calet, Shoichi Shimizu, Shiyamalie Amaratunga, Slaweck Falicki, Subramanian Iyer, Velaga Valli, Vladimir Grushin, Yu Jin Huang, Yuri Goldberg.

Many thanks to Yuri Goldberg, Rashmi Venkateswaran, Anoma Somasunderam and Vladimir Grushin for kindly proof reading this thesis; Pavel Krasik for continual help with "CHEMTEXT"; Kanjai Khumtaveeporn and Cathy Crudden for their enthusiastic help and encouragement.

I would like to take this opportunity to acknowledge the Ottawa-Carleton Chemistry Institute, University of Ottawa, NSERC and British Petroleum for scholarship and financial support for this research.

A heartfelt thank you to my family, in Canada and abroad, for their patience and support.

ABSTRACT

An important class of carbonylation reactions to construct lactams are those that involve the direct "stitching" of carbon monoxide into a nitrogen heterocycle resulting in ring expansion. Cobalt carbonyl catalyzed the carbonylation of a series of 2-substituted pyrrolidines to form piperidinones. The reaction is regiospecific in most cases and the yield of product is increased when ruthenium carbonyl is present as a second catalyst. Chapter 2 of this thesis describes this piece of work.

During the investigation of the ring expansion carbonylation reactions of pyrrolidines, a new rearrangement process was discovered which occurred with nitrogen heterocyclic ketones [$(CH_2)_nNCH_2COR$, n=4-7] to give lactams in 72-93% yields, catalyzed by the dual metallic [$Co_2(CO)_8/Ru_3(CO)_{12}$] system. Studies, including several labelling experiments, indicated a hydrogen-oxygen positional exchanging path. After rearrangement, $Ru_3(CO)_{12}$ could be recovered, and no Ru-Co clusters was detected. The most probable explanation for this finding may be that some of the steps in the reaction pathway are catalyzed by ruthenium while others are more effectively catalyzed by cobalt complexes. This work is discussed in detail in Chapter 3.

A novel cyclization reaction was also observed during mechanistic studies giving information on the rearrangement reaction. That is, when ketones in which only one of the hydrogen atoms at an α-carbon atom of a nitrogen-containing heterocycle is replaced by an alkyl group (e.g. 2-methyl (or 2,6-dimethyl)piperidinyl ketones), the reaction afforded the bicyclic 5,6,7,8-tetrahydroindolizines in 72-94% yields. In contrast to the rearrangement process which requires both $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ as catalysts,

$Co_2(CO)_8$ or $Ru_3(CO)_{12}$ only could catalyze the cyclization reactions in high yields. These bicyclic products are well known precursors of many alkaloids. Reaction of 2-aryl-5,6,7,8-tetrahydroindolizines with singlet oxygen, whether generated under sensitized photoreaction conditions or by cobalt catalyzed oxidation under mild conditions, gave 2-aryl-8a-hydroxy-6,7,8,8a-tetrahydro-3(5H)indolizinones in 63-71% yield. Chapter 4 dealts with these transformations.

Under phase transfer catalysis conditions some five and six-membered nitrogen-containing heteroaromatics reacted with acetylcobalt tetracarbonyl, generated in *situ* from CO, CH_3I and dicobalt octacarbonyl. Isoxazoles or isothiazoles gave N-acylated 1-amino-2-alken-3-ones or thiones, i.e. ring-cleavage reductive acylation products. The highest stereoselectivity (Z/E: 10/1) of the acylation reaction was found in the case of 5-methylisoxazole. Under the same conditions phthalazine, quinoline and isoquinoline gave N-acylated dimers in low to moderate yields. The reactivity of several other nitrogen-containing heterocycles such as pyrazoles was also investigated and the results are summarized in Chapter 5.

Abbreviations

AES	Auger electron spectroscopy
anal	analytical
atm	atmosphere (1atm=101325Pa)
bar	1bar=10^5Pa, 1pa=1Nm^{-2}
br	broad
bp	boiling point
n-Bu	n-butyl group
t-Bu	t-butyl group
^{0}C	degree celsius
calcd	calculated
CI	chemical ionization
1,5-COD	1,5-cyclooctadiene
COSY	shift correlation spectroscopy
d	doublet
dba	dibenzylidene acetone, $(PhCH=CH)_2CO$
dd	doublet of doublets
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminum hydride (=DIBAH)
DMF	N,N-dimethylformamide
dt	doublet of triplets
E	entgegen
e.e	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
Et	ethyl group
FT-IR	Fourier-transform infrared
GC	gas chromatography
h	hour
HETCOR	heteronuclear correlation
HMQC	heteronuclear multiple quantum coherence
HOMO	highest occupied molecular orbital
Hz	Hertz, cycles/second

hv	photolysis
IR	infrared spectroscopy
J	coupling constant, in Hz
L	ligand
LEED	low energy electron diffraction
LUMO	lowest unoccupied molecular orbital
M	metal
M	molar concentration, moles/litre
$[M]^+$	parent molecular ion
Me	methyl group
MHz	megaHertz, 10^6Hz
min	minute
ml	milliliter ($10^{-6}m^3$)
mmHg	1mmHg=1Torr, unit of pressure
mmol	millimole
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
Nu^-	nucleophile
ORTEP	Oak Ridge thermal ellipsoid plot
pH	measure of solution acidity
Ph	phenyl group
ppm	parts per million, 10^{-6}
PPh_3	triphenylphosphine
psi	pounds per square inch
P.T.agent	phase transfer agent
PTC	phase transfer catalysis
q	quartet
RT(rt)	room temperature
s	singlet
sub	substrate
t	triplet
TLC	thin layer chromatography
Z	zusammen

Table of Contents

List of Tables

Chapter 1

Introduction

In this introduction some important aspects of organometallic chemistry will be briefly reviewed including homogeneous and heterogeneous catalysis, phase transfer catalysis, transition metal carbonyl complexes, carbonylation reactions, and mixed-metal homogeneous catalysis. A more detailed survey will then be made of the ring expansion carbonylation reaction.

1.1 Homogeneous and Heterogeneous Catalysis

Catalysis using metal-complexes is now an integral part of organic synthesis in the laboratory and in industry. Complexes containing transition metals with partly filled d or f shells (mainly d-block) are extremely versatile in bonding ability, ligand effects, variability of oxidation state and coordination number. A transition metal catalyst can thus provide a site where the rate-determining step of a reaction can take place faster. Organotransition metal complexes are useful in organic synthesis, as they can offer different pathways to a given organic reactant depending on the nature of metal and ligands.

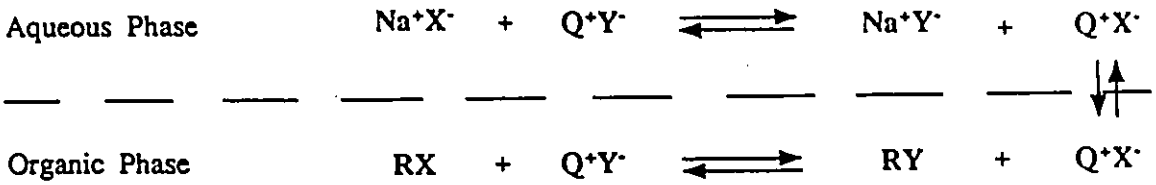
Metal catalyzed reactions are classified as homogeneous or heterogeneous processes. By definition, in homogeneous catalysis the catalyst and the reactants are molecularly dispersed in the same phase, either liquid or gaseous. It implies that the catalyst is a discrete entity, i.e. a single transition-metal complex or a combination of discrete complexes. A heterogeneous reaction is one in which one or more of the constituents are in different phases. The catalyst is usually present as a solid and the reactants as liquids or gases. Thus a vacant coordination site of the metal complex is located at a phase boundary, i.e., only the surface atoms are catalytically active.

Being bulky solids and generally thermal stable, heterogeneous catalysts are easily separated from their reaction products, i.e. they can be simply recycled. This particular advantage has, up to recently, been of an over-riding importance in the large scale industrial applications of catalyst systems, e.g. methanol synthesis, Fischer-Tropsch synthesis etc.. The past two decades has witnessed the development of new surface techniques e.g. LEED, ESCA and AES providing new information regarding surface atomic and electronic structure, but yet few surface reactions are well understood at the molecular level.[1] At the same time, homogeneous catalysts are becoming increasingly important.[2] Such catalysts are highly active and selective, and often work under mild conditions. Studies on the mechanism of homogeneous catalytic reactions have advanced rapidly owing to the possibility of using spectroscopic methods and kinetic meassurements, as well. Homogeneously catalyzed carbonylation, hydroformylation, hydrogenation, isomerization, oligomerization, polymerization, oxidation and metathesis are well known processes. That is why, all of them are industrially important. There are numerous reviews on homogeneous transition metal catalysis in the literature.[2-5]

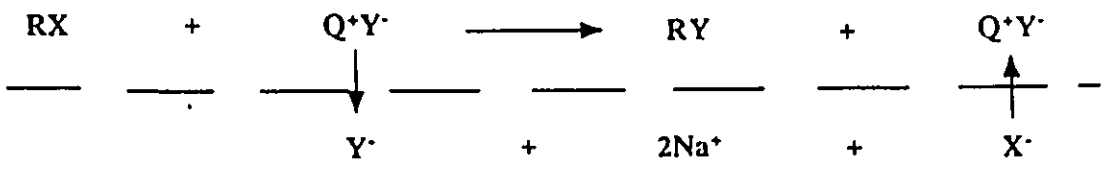
1.2 Phase Transfer Catalysis

Phase transfer catalysis (PTC) is the most widely used method for solving the problem of mutual insolubility of nonpolar and ionic compounds. Two compounds in immiscible phases are able to interact because of the phase transfer agent. The latter provides lipophilic cations, which transfer the anion of the reagent from the aqueous or solid phase to the organic phase. PTC can be grouped into three categories based on the physical states of the two phases : liquid/liquid, liquid/solid and liquid/gas.

Quaternary ammonium salts and compounds possessing cation-solvating or bonding properties such as crown ethers, cryptands or podands are commonly used catalysts. The mechanism of PTC with a quaternary ammonium salt (Q^+Y^-) catalyst was first proposed by Starks:[6]

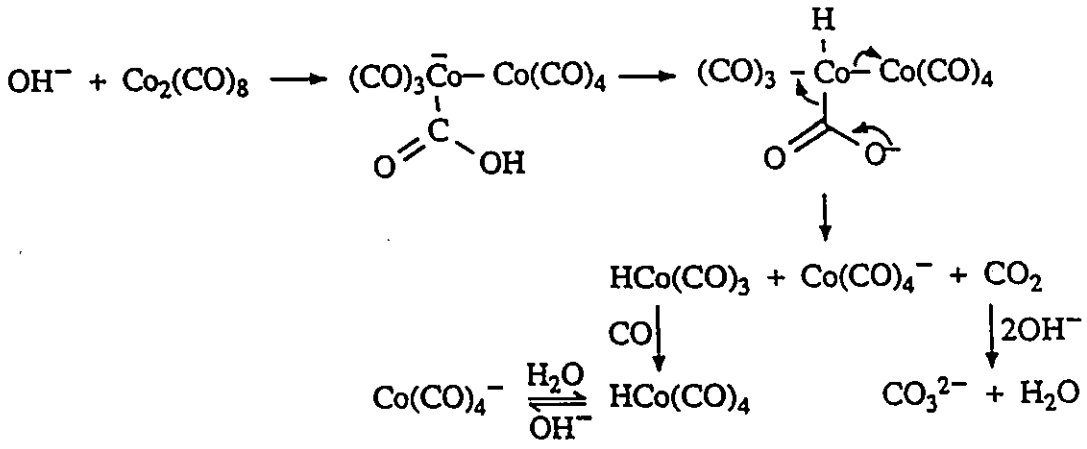


Further studies have demonstrated that migration of the lipophilic quaternary onium salts to the aqueous phase is not necessary for the anion exchange that occurs at the interface:[7]



The use of phase transfer catalysis in reactions involving metal complexes began in the mid seventies.[8,9] This is one of the most intensively developing variants of two or three-phase catalytic techniques.[10] "Some of the most innovative work in this area has been done by Alper and his co-workers. He illustrated that gas-liquid-liquid transfers with complex catalyst systems provided methods for catalytic hydrogenations with gaseous hydrogen, catalytic carbonylation of halides, olefins and acetylenes with carbon monoxide gas".[11]

A particularly important phase transfer process is the conversion of dicobalt octacarbonyl to the mononuclear cobalt tetracarbonyl anion using aqueous alkali hydroxide, organic solvent (e.g. $CHCl_3$, CH_2Cl_2, C_6H_6, $CH_3C_6H_5$, hexane) and quaternary ammonium halide under CO atmosphere. A possible mechanism follows:[12]



In the presence of alkyl halide, such as methyl iodide, acetylcobalt tetracarbonyl is generated in situ, subsequently reacting with unsaturated substrates or strained ring compounds to give mono[13]-, double[14]- or even triple[15]-carbonylated products.

Reactions carried out in two-phase systems, in the presence of a phase transfer

agent and transition metal complex are considered in detail in a recent monograph (see Ref. 5, Chapter 4).

1.3 Transition Metal Carbonyl Complexes

Studies on metal carbonyls have not only produced a rich chemistry with enormous scientific value but have also proved to be very useful in synthetic chemistry.[16] Numerous books and reviews discuss the preparation and structure of metal carbonyls.[17-22] It has been over 100 years, since Mond first discovered the formation of $Ni(CO)_4$ from metallic nickel and carbon monoxide. A variety of transition metal carbonyls have been prepared and served as starting materials for the preparation of many other organometallic compounds. Virtually all transition metals coordinate with carbon monoxide, as CO is an excellent π-acceptor ligand, stabilizing the low oxidation state of the metal center.

Anionic transition metal carbonyls are usually prepared by reacting bi/polynuclear carbonyls with alkali/alkali hydroxide, for example:

$$Fe_3(CO)_{12} + Na \longrightarrow Na_2[Fe(CO)_4]^{2-}$$

$$Co_2(CO)_8 + Na/Hg \longrightarrow Na^+[Co(CO)_4]^-$$

$$Ru_3(CO)_{12} + OH^- \longrightarrow Ru_6(CO)_{18}^{2-}$$

The anionic metal carbonyls are useful starting materials for synthesizing other

organotransition metal complexes. Nucleophilic attack of an anion on a positive center leads to important intermediate complexes.

$$Co(CO)_4^- + RCOX \longrightarrow RCOCo(CO)_4 + X^-$$

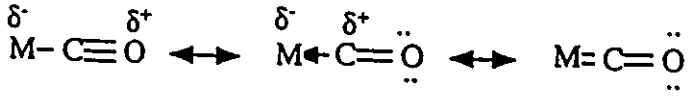
$$Co(CO)_4^- + MeI \longrightarrow MeCo(CO)_4 \longrightarrow MeCOCo(CO)_4$$

The latter is widely involved in important acylation reactions of olefins and amines, even under mild phase transfer catalysis conditions. The formation of substituted metal carbonyl complexes by a ligand exchange process is a common feature of transition metals. Substitution of carbon monoxide by another ligand may take place through a dissociative path or an associative path:[23]

$$M(CO)_x \xrightarrow{-CO} M(CO)_{x-1} \xrightarrow{+L} M(CO)_{x-1}L$$

$$M(CO)_x \xrightarrow{+L} M(CO)_xL \xrightarrow{-CO} M(CO)_{x-1}L$$

Association reactions of binary carbonyl complexes are not commonly observed. The ease of carbonyl dissociation as well as the strength of the metal carbonyl bond decrease with the electron density at the metal center which is equivalent with the metal basicity. They are both unfavoured by electron rich metals, and basic ligands. This is due to the weak σ-donor and the strong π-acceptor properties of CO which removes charges from the metals (illustrated by the resonance structures).



A B C

The MO terms may be more appropriately describe the feature of M-CO bonding.[16]

Most of the early work on transition metal carbonyl complexes focused on the physical properties of this class of compounds.[24] Mechanistic studies started with Basolo and coworkers in the early 1960's.[25] In the past three decades advances have been made in understanding transition metal carbonyl reactivity.[26] Recently, based on kinetic data, Atwood and co-workers concluded that: (1) the effect of charge and oxidation state on the metal in CO substitution are not as straightforward as expected; (2) the ground state weakening of the M-CO bond, as charge and oxidation state are increased, is offset by a similar increase in the energy of the transition state, resulting in very small rate changes; (3) odd electron complexes with either 17 or 19 electrons react at least 10 orders of magnitude more rapidly than similar 18 electron complexes; (4) electronic configuration has a large effect on CO substitution with the order of reactivity: $d^{10}>d^{4}>d^{6}>d^{8}$ for 18 electron complexes; (5) changing a metal atom in a cluster complex affects the reactivity of the other metal centers; (6) dissociative reactions are accelerated by the presence of a stronger σ-donor/weaker π-acceptor that stabilizes the 16 electron transition states. Since many transition metal carbonyls are quite electron-rich, they react as nucleophiles and as electron-transfer reducing agents. Additionally, the ease of migration of CO, insertion, as well as that of metal carbonyl anion formation are reactions being used extensively in industrial and laboratory processes both in stoichiometric and catalytic reactions. Carbonyls of nickel, iron and cobalt are inexpensive and often applied to organic synthesis.[27] Anionic transition metal carbonyls such as $[Rh_5(CO)_{15}]^-$ have been found to be most active in CO hydrogenation and anionic complexes such as $[Co(CO)_4]^-$, $[Rh(CO)_2I_2]^-$, $[Ni(CO)_3I]^-$ or $[HRu(CO)_{11}]^-$

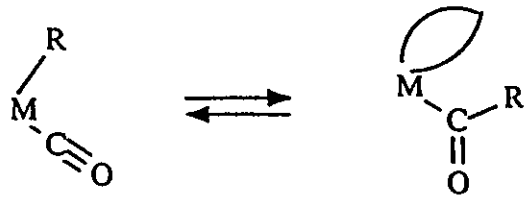
have been postulated as active species for carbonylation reactions.[28] There are numerous literature reports describing the application of the transition metal carbonyls in organic synthesis.[29-35] In the past three decades the parent ligand of the transition metal carbonyl family, CO, has been joined by a series of relatives such as CS, CNH and $C{=}CH_2$, which, though short-lived in the free state, form stable complexes with transition metals.

1.4 Carbonylation Reactions

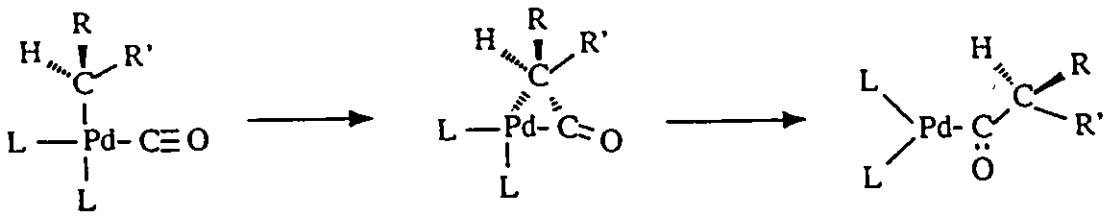
One of the most fascinating reactions in catalysis is the direct insertion of a functional group into substrate molecules giving rise to useful products. Since the carbon monoxide moiety is the simplest synthon for introducing a carbonyl group into an organic compound, carbonylation reactions have become one of the most attractive of homogenous catalytic reactions. Carbonylation of various compounds has been extensively studied and some of these reactions are used in industry.[36-40] These processes can often be carried out under mild conditions, with good yields and high selectivities.

Free carbon monoxide is a rather unreactive compound. There are 14 electrons in CO molecule. Four of them are nonbonding and the remaining ten valence electrons are distributed in the following five molecular orbitals: 3σ, 4σ, $1\pi_Y$, $1\pi_Z$ and 5σ which consists of two antibonding orbitals with a larger coefficient at the carbon atom.[41] The bonding between C and O involves 3σ, $1\pi_Y$ and $1\pi_Z$ molecular orbitals and consists of

one σ and two π-bonds, slightly asymmetric toward the oxygen atom. The synergistic type of bonding with a transition metal , in which carbon monoxide donates electron density from the HOMO weakly antibonding 5σ orbital and accepts electron density from filled or partly filled d-orbitals of a transition metal into the LUMO strongly antibonding orbital $2\pi^*$. It leads to the weakening of the carbon oxygen triple bond, the first presumed step of CO activation. Thus, the carbon and oxygen of the coordinated CO ligand become susceptible to nucleophilic and electrophilic attack respectively. The transition metal carbonyl complexes may undergo some key reactions, among these reactions, the insertion process being one of the most important.[42]



The carbon of the carbonyl ligand is attacked by another ligand and the reaction occurs within the coordination sphere of the metal. The reaction is readily reversible if some additional ligand is not present to occupy the coordination site vacated by the migration of the alkyl, aryl or other 1-electron ligand group. The reverse reaction, decarbonylation, also has synthetic utility.[43,44] The insertion of carbon monoxide is normally stereospecific. It has been shown to proceed with complete retention of configuration at the migrating carbon atom, which is consistent with "front-side" attack implied by concerted migration. For example:[45]



The extensive thermodynamics and kinetics[46-48] as well as molecular orbital studies[49] of CO insertion and decarbonylation of different complexes,[50] substrates, and solvents[51,52] have received widespread attention. Generally, the reactivity of the carbon monoxide ligand is modified by the interaction between CO and the metal. Destabilization of the ground state with respect to the M-CO and M-R bonds and stabilization of the transition state for the formation of acyl intermediates increase the rate of reaction. The reactivity depends in part on the strength of the metal-carbon bond. The first and second-row transition metals undergo this reaction more easily than the third row transition metals of the same subgroup.[53] All transition metals of group VIII, especially those in a low valent state, have proved to be active homogeneous catalysts for CO activation.[36,54]

The second key reaction is nucleophilic attack of a carbonyl ligand by an anionic reagent to form a series of adducts:

Nu : OH, OR, NRR', H, R, X, etc.

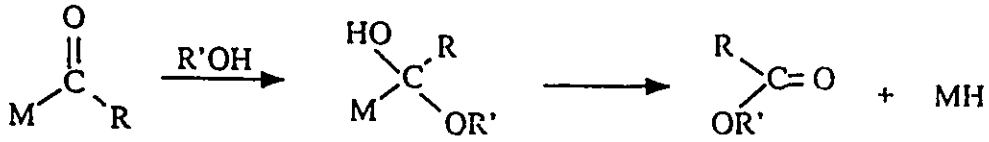
Carbon monoxide is a weak σ-donor ligand. The bonding with the transition metal is

reinforced by back-donation from filled d-orbitals to the CO antibonding orbitals of appropriate symmetry. If a partial positive charge exists on the carbon atom, then attack by a nucleophilic reagent can occur. It can be qualitatively correlated with the electrophilicity of the carbon of the coordinated carbonyl group. Thus, a more electron-withdrawing LnM fragment would be expected to make the carbonyl more positive and more susceptible to reaction with nucleophiles. For example, the cationic Re(I) complex, $Re(CO)_6^+$ undergoes facile ^{18}O enrichment of the carbonyls by exchange with oxygen of ^{18}O-labelled water presumably via intermediacy of a hydroxycarbonyl species formed by the attack of water on the coordinated CO[54,55].

$$Re(CO)_6^+ + H_2O^* \longrightarrow Re(CO^*)_6^+ + H_2O$$

Both stoichiometric and catalytic reactions involving nucleophilic activation of metal carbonyls are well-known.[56] Such reactions include substitution, insertion of alkene, hydrogenation, decarbonylation, etc. The Water Gas Shift Reaction (WGSR) has received renewed attention because of the need to produce hydrogen from non-petroleum sources. Using alkaline solutions of various metal carbonyls, the reaction can proceed homogeneously, via attack of hydroxide on LnMCO presumably forming an anionic carboxylic acid intermediate.

Another useful reaction is an attack of coordinated CO at the oxygen atom by electrophiles:[57]



Depending on the reaction conditions, the M-acyl group may be liberated as RCHO, RCOOH, RCOX, RCONRR', RCOR' or RCOOCOR'.[42]

The importance of carbon monoxide "insertion" into a metal-carbon bond should be emphasized, but in carbonylation chemistry there are several other reactions in which a one-electron ligand migrates from the metal to an unsaturated ligand. For example, in hydroformylation or hydroesterification, the migration of hydride to a coordinated alkene generates an alkyl ligand that subsequently migrates to coordinated carbon monoxide. Similarly, alkyne ligands can insert into both M-H and M-C bonds, and the resulting vinyl ligands migrate to coordinated carbon monoxide. Even acyl groups can migrate from the metal to coordinated alkenes forming keto-alkyl ligands. Thus, by the mechanistic patterns carbonylation reactions may be grouped into six classes:[58] direct carbonylation, substitutive carbonylation, additive carbonylation, multicomponent carbonylations, oxidative carbonylation and decarbonylation. Carbonylation chemistry is being developed increasingly in research and on a larger scale for fine chemicals production.

1.5 Mixed-Metal Homogeneous Catalysis

Mixed-metal homogeneous catalysis can be carried out using two different metal complexes or with mixed-metal clusters as a catalyst precursor.[59] The goal of this discussion of mixed-metal homogeneous catalysis is to evaluate its achievements and potentials. The use of mixed-metal clusters in homogeneous catalysis is in its beginning,

and almost nothing is known about the actual role of such species in catalytic transformations. One of the characteristic features of mixed-metal catalysts is synergism. "Synergism" may be defined as a disproportionate increase in reaction rate observed upon mixing two catalytic systems, both of which will individually catalyze the reaction in question".[60]

In mixed-metal homogeneous catalysis the adjacent metal centers offer the possibility for cooperative reactivity and the intrinsic polarity of heterometallic bonds. The stereochemical properties of each metal center can direct the selectivity of substrate-cluster interaction. Some metal-specific reactions may occur simultaneously or consecutively on the multi-sites during the activation and transformation of substrate molecules. Because of the high mobility of ligands in clusters, it may promote reactions between different partners, and the reactions of ligands themselves in mixed metal clusters may be proceeding differently (reduction, oxidation, oxidative addition, reductive elimination, etc.).

Generally, reactions of clusters may lead to changes in their structure or may only change the clusters' coordination sphere. These reactions may also cause changes within the ligands themselves.[61] It should also be recognized that mixed-metal complexes often fragment into homonuclear species under catalytic conditions while they can be produced in situ upon mixing of the individual metal complexes. Due to their unusual properties, mixed metal clusters find application as catalysts in organic synthesis, synthesis of inorganic complexes and organometallic compounds, etc.

It is known that ruthenium carbonyls are active catalysts for the water gas shift reaction (WGSR) under basic conditions:

$$H_2O(g) + CO(g) \longrightarrow H_2(g) + CO_2(g)$$

Interestingly, it has been found that $Fe(CO)_5$ increases the activity of the ruthenium complexes and the mixed-metal complex $H_2FeRu_3(CO)_{13}$ proved to be more active than either ruthenium carbonyl or iron carbonyl individually.[62,63] Spectral characterization as well as isolation of various reaction components indicates the presence of several mixed-metal clusters, including $H_2FeRu_3(CO)_{13}$ in these alkali solutions of mixture of $Fe(CO)_5$ and $Ru_3(CO)_{12}$. This synergetic catalysis is consistent with catalytic cycles in which the rate-limiting path is reductive elimination of H_2 from a cluster hydride species, with mixed-metal clusters being more reactive toward H_2 elimination. Further, more research work has been done on the catalytic activity of mixed-metal carbonyl precursors of group 8 and 9 in the WGSR.[64]

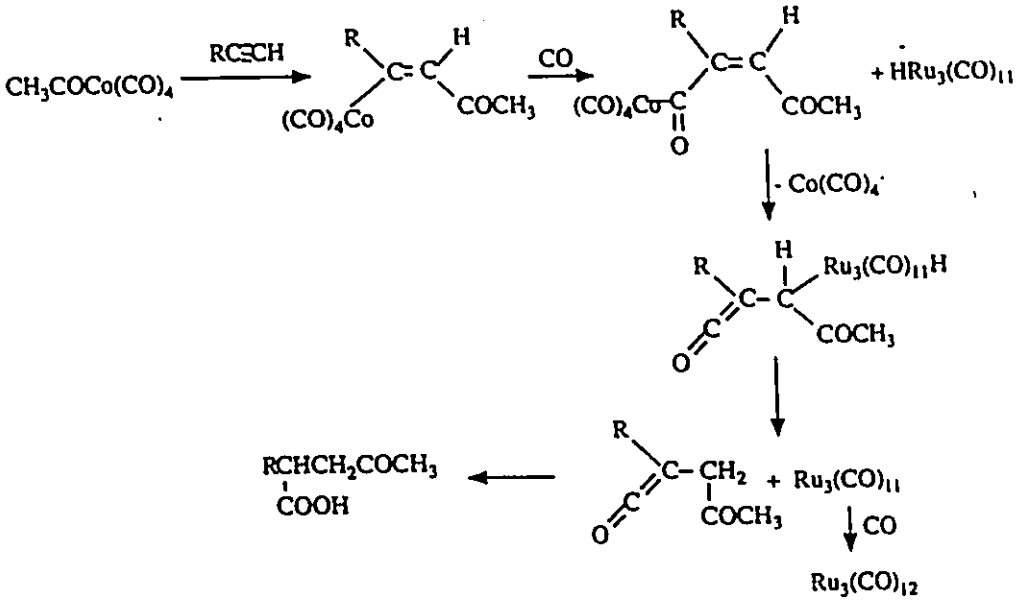
The rhodium-catalyzed synthesis of ethylene glycol from CO hydrogenation is promoted by ruthenium carbonyl complexes.[65,66] Optimum results were achieved with Rh:Ru ratios of 1:1 when quaternary phosphonium salts were used, and in this case a mixed Rh-Ru carbonyl cluster $Ru_2Rh(CO)_{12}$ has been isolated from the reaction product. With tetraglyme as a solvent, the highest selectivities and reaction rates were observed at surprisingly low Rh concentrations (Rh:Ru=1:10). No mixed-metal clusters have been found in the reaction mixtures. The most probable explanation for these findings may be that some of the individual steps are catalyzed by rhodium and others more effectively by ruthenium complexes.

The hydrogenation of alkenes, dienes and alkynes as well as the isomerization of alkenes and dienes were also investigated with a variety of mixed metal clusters.[67]

Interestingly, ruthenium complexes have been employed as cocatalysts with

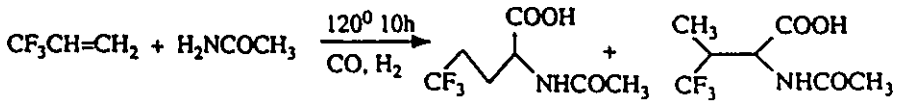
$Co_2(CO)_8$ to improve the selectivity of methanol homologation, and the influence of the Ru:Co ratios on the yields of ethanol and acetaldehyde has been studied.[68]

Under basic phase transfer catalysis conditions, in the presence of $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ (1:1) alkynes react with CO and methyl iodide to give β-keto acids.[69] With $Co_2(CO)_8$ alone, but-2-enolides are formed;[70] $Ru_3(CO)_{12}$ alone is inactive. The surprising effect of $Ru_3(CO)_{12}$ is ascribed not to the formation of a mixed-metal cluster catalyst, but rather to the nucleophilic addition to the intermediate:



One of the most fascinating goals in mixed-metal catalysis is to create effective multicatalyst systems which can promote sequential multistep reactions cooperatively giving useful chemical substances from simple starting materials, that is, mimicking enzymes. One of the successful examples is reported by Ojima.[31] He has found that the hydroformylation-amidocarbonylation process is effectively promoted by the homogeneous binary catalyst system $Co_2(CO)_8/Rh_6(CO)_{16}$ to give a variety of N-acyl-α-

amino acids (1) directly from allylic alcohols, oxiranes, and fluoroolefins. The use of $Co_2(CO)_8$ alone gave N-Ac-trifluoronovaline (2). Thus, the regioselective hydroformylation was successfully combined with amidocarbonylation.

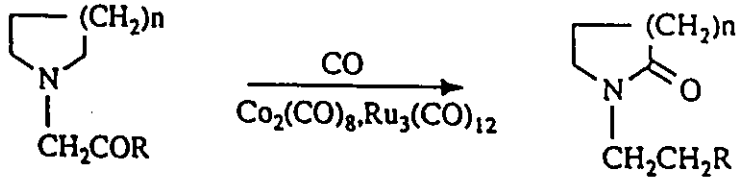


1 2

catalyst	yield (%)		
$Co_2(CO)_8$	83	96	4
$Co_2(CO)_8$-$Rh_6(CO)_{16}$	87	6	94

A unique Co-Rh mixed cluster, $CoRh(CO)_7$ was shown to be the active catalytic species.

More recently, the mixed-metal system $Co_2(CO)_8/Ru_3(CO)_{12}$ was shown to have synergistic effect in the ring expansion carbonylation reaction.[35] When $Co_2(CO)_8$ was used alone for the carbonylation of N-substituted pyrrolidines, the product piperidinones were generated in low yields. Addition of a second catalyst, $Ru_3(CO)_{12}$ changed the reaction pathway, resulting in a remarkable mixed-metal catalyzed rearrangement leading to a variety of lactams:



R = t-Bu, Ph, 2-$C_{10}H_7$, n-C_6H_{13}; n = 1, 2, 3

No Co-Ru mixed cluster was observed, only $Ru_3(CO)_{12}$ recovered.

The potential advantage of homogeneous mixed metal catalysis is the possibility of multisite activation of a substrate leading to an unusual product. Such a system occupies an intermediate position between molecular (homogeneous) and solid-state (heterogeneous) catalysis, so they may fill the gap that still exists between homogeneous and heterogeneous catalysis by transition metals. This project remains an active area of research, and has been subjected to several reviews.[67,71] The prospects in this area are bright owing to new technology for the preparation mixed-metal-derived catalysis and spectroscopic methods developed for their study such as IR spectroscopy, FT solid-state NMR, EXAFS (Extended X-ray Absorption Fine Structure), XPS (X-ray Photoelectron Spectroscopy), Mössbauer spectroscopy, STM (Scanning Tunnel and high-resolution electron microscopy).[72]

1.6 Ring Expansion Carbonylation Reaction

About half of the known organic compounds have structures that incorporate at least one heterocyclic compound.[73] Heterocyclic compounds are predominant among the types of compounds used as pharmaceuticals, agrochemicals and veterinary products. For example, research on design and synthesis of new antibacterial agents based on the β-lactam structure of penicillin are of continuing interested by chemists. Amongst the numerous synthetic ways to construct biologically important lactones and lactams, the process of ring expansion carbonylation via transition metal complex catalysis from heterocycles is one of the most simple, convenient and fascinating methods.

As distinguished from a large variety of carbonylation processes of functionalized organic substrates which lead to heterocyclic products, Alper has developed a number of heterocarbonylation reactions of three-five membered ring oxygen-, sulphur- and nitrogen-containing heterocycles that proceed under mild conditions and produce useful compounds.[2]

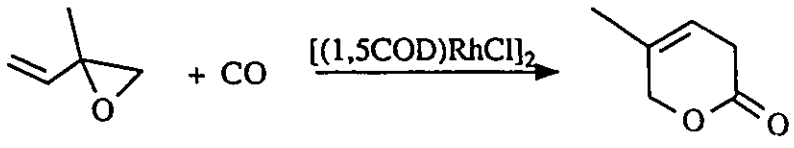
Ring Expansion Carbonylation Reactions of Three Membered Ring Heterocycles

The chemistry of three membered heterocycles is dominated by ring strain. This leads to enhanced reactivity in processes in which the strain is relieved. The

organotransition metal chemistry of oxiranes, thiiranes, azirines and aziridines shows that strained rings undergo appropriate ring opening and subsequent cyclization reactions to form other cyclic systems.[74,75]

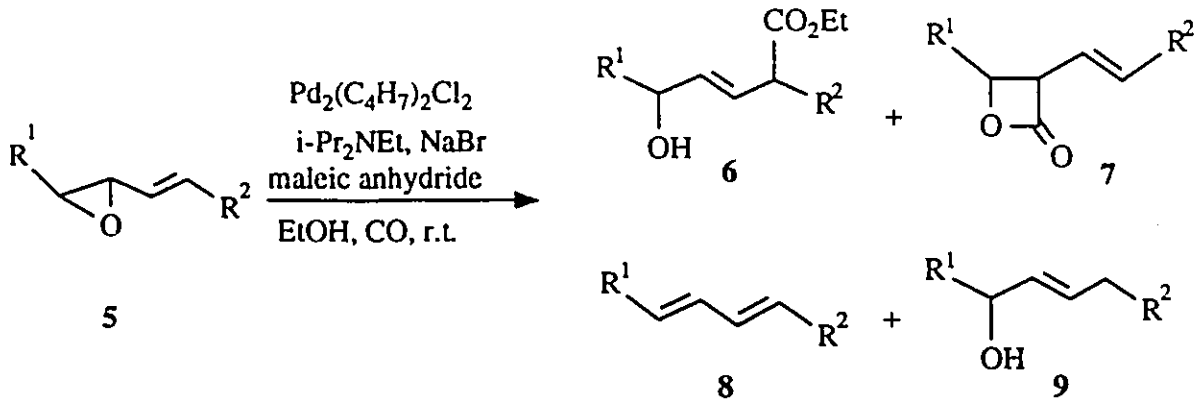
Oxiranes and Thiiranes

Oxiranes are commonly used reagents in synthetic chemistry because the ring system can be both created and destroyed easily in a highly selective manner. Transition metal complexes can be involved in such cases, for example, vinyl oxiranes react with carbon monoxide in the presence of a catalytic quantity of chloro(1,5-cyclooctadiene)rhodium dimer, to give unsaturated δ-lactones:[76]



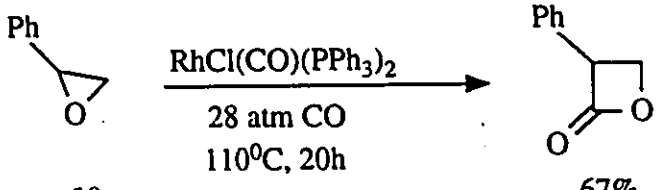
3 4 (75%)

Recently Yamamoto's group reported the results on palladium-catalyzed reaction of alkenyloxiranes with carbon monoxide. Four types of products are produced depending on the nature of the substituent R^2 of the alkenyloxirane **5**. Carbonylation products such as unsaturated esters **6** and β-lactones **7** were obtained in the reaction of terminal alkenyloxiranes and alkenyloxiranes having electron-donating substituents, whereas the reaction of alkenyloxiranes having electron-withdrawing groups gave dienes **8** and allylic alcohols **9** instead of carbonylation products.[77]



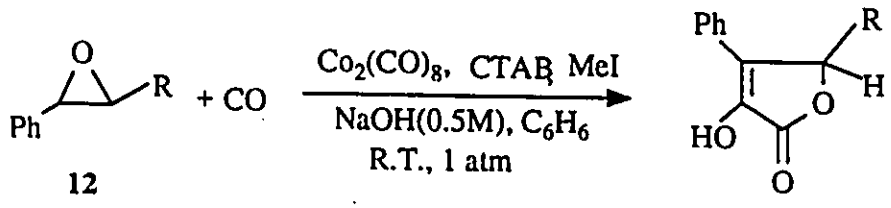
5 6 7 8 9

β-Lactone was produced using phenyl substituted epoxides (styrene oxides) and $RuCl(CO)(PPh_3)_2$:[78]



10 67% 11

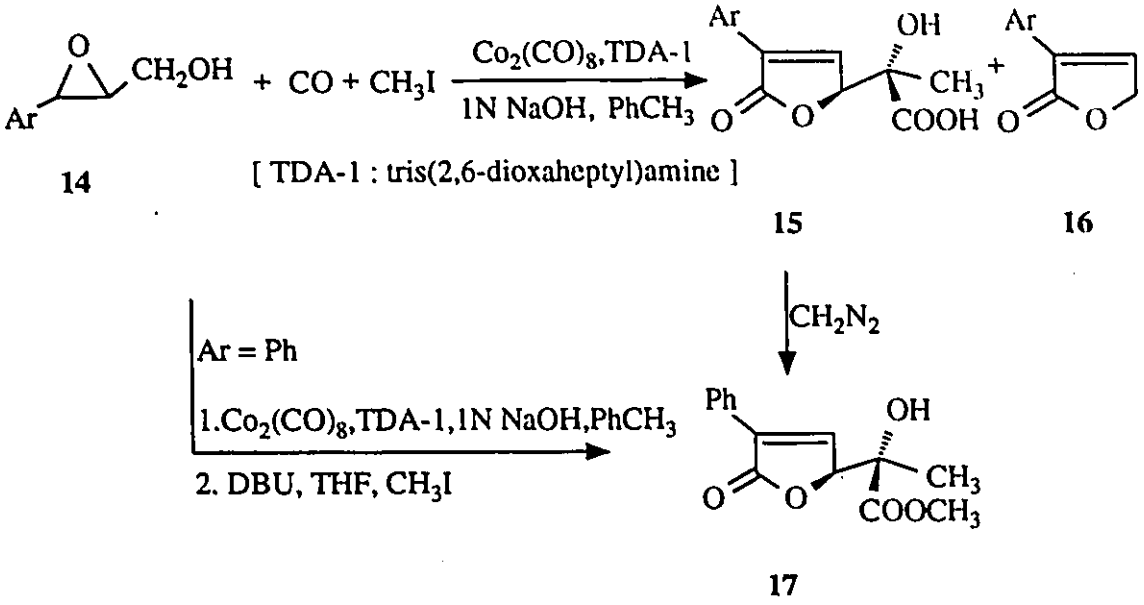
The application of transition metal complexes in phase transfer catalysis (PTC) was pioneered by Alper and coworkers, in the mid 1970's. Particularly useful is cobalt carbonyl as the metal catalyst under PTC conditions. Single and double carbonylation reactions occur by reactions of acylcobalt tetracarbonyl generated in situ (from $Co_2(CO)_8$, CH_3I, CO) with unsaturated and strained ring compounds. E.g., vinyl oxiranes undergo monocarbonylation to form unsaturated hydroxy acids[79] while styrene oxides experience double carbonylation, affording the enol tautomer of an α-keto lactone:[80]



12

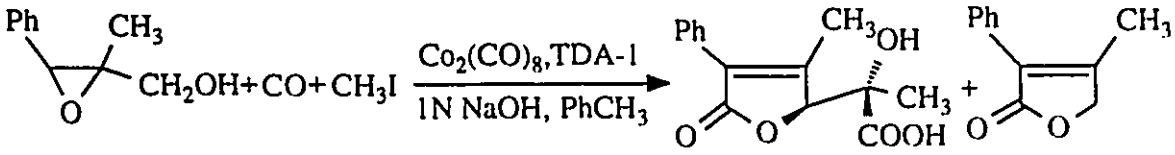
[CTAB = $C_{16}H_{33}N(CH_3)_3^+Br^-$] 13

β-Epoxy alcohols **14** undergo a unique phase transfer catalyzed triple carbonylation reaction to form lactonic hydroxy acids **15**:[81]



14 **15** **16** **17**

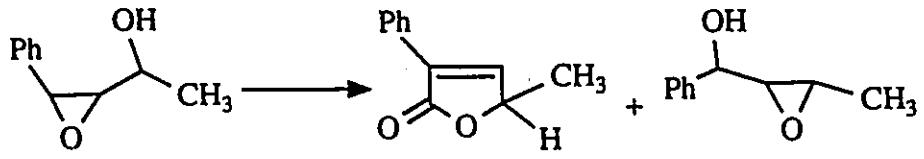
When the trisubstituted oxirane **18** was used as the reactant, approximately equal amounts of the triple carbonylation product **19** (33%) and monocarbonylation product **20** (36%) were formed.



18 **19** **20**

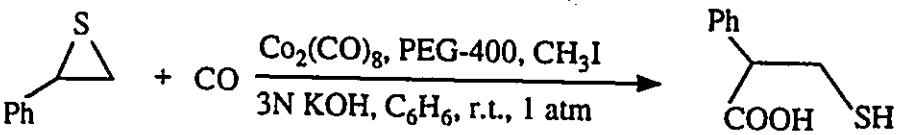
The process was diastereospecific where only the anti diastereomer was present in the

solid state and in solution, as shown by X-ray and NMR analyses of **17**, formed either by reaction of **15** with diazomethane or from **15** by a two step process in 44% yield. A labelling experiment using ^{13}CO resulted in labeling at the lactone carbonyl, carboxylic acid carbon, and the carbon bearing the hydroxyl group. This triple carbonylation reaction also requires primary alcohols, since the secondary alcohol **21** gave only the monocarbonylation product **22** and the rearrangement product **23**.



21 **22** **23**

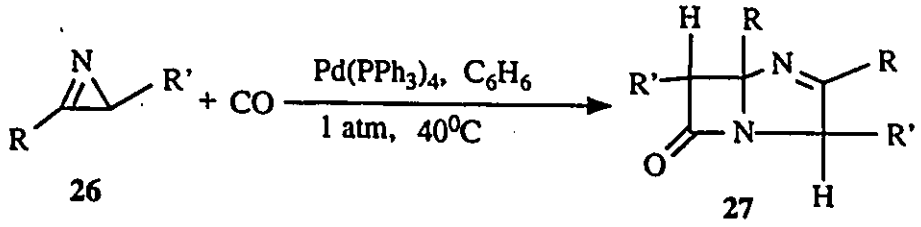
Thiiranes have much in common with the other three membered ring heterocycles, but some of their chemistry is associated specifically with the presence of the sulphur atom. For example, thiiranes undergo phase transfer catalyzed reaction with in situ generated acylcobalt carbonyls to give β-thiolactones which are hydrolyzed to β-mercapto acids under the basic conditions.[82]



24 **25**

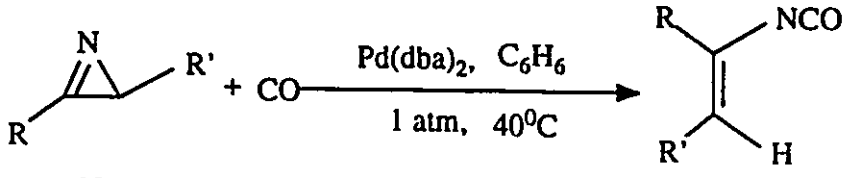
2H-Azirines

Generally, the chemistry of 2H-azirines is characterized by three main type of reactions : (1) reaction at the C=N bond, (2) cleavage of the N-C2 bond, and (3) cleavage of the C2-C3 bond with ultraviolet light. When azirines were treated with carbon monoxide and a transition metal complex, e.g. tetrakis(triphenylphosphine) palladium(0) under very mild conditions, aza analogues of penicillin were formed in 37-63% yield:[83,84]



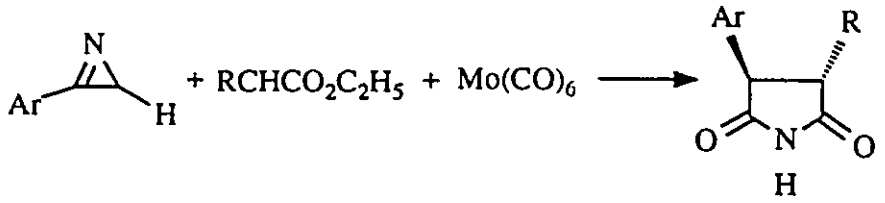
26 **27**

When bis(dibenzylideneacetone)palladium(0) was used as catalyst, vinyl isocyanates were obtained in high yields (77-99%):[84]



28 **29**

It was found that the presence of molybdenum carbonyl in the reaction of stabilized enolates with azirines results in a stereospecific production of cyclic imides:[85]

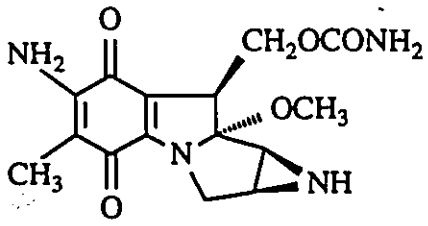


30 31 32 33

This novel reaction is applicable to a variety of azirines giving disubstituted imides in 27-68% yield. The carbanions can be derived from ethyl benzoylacetate **31** (R=PhCO and ethyl cyanoacetate R=CN).

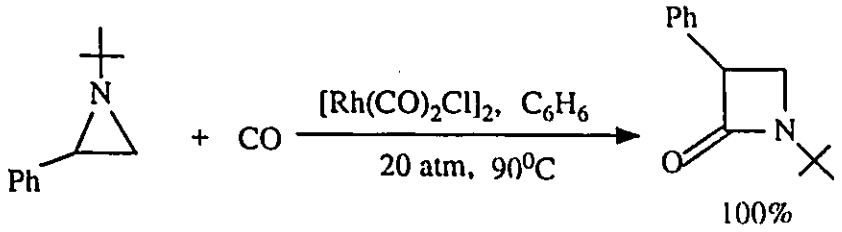
Aziridines

Aziridines have found wide use both as intermediates in laboratory synthesis and in industry. For example, aziridines are good alkylating agents because of their tendency to undergo ring-opening reactions with nucleophiles. Many aziridines are thus actively mutagenic and toxic. The naturally occurring mitomycin C **34**, shows antibiotic and antitumour activity which are associated with the presence of an aziridine ring. The alkylating properties of aziridines have been investigated for potential industrial applications, e.g., as monomers for polymerization and as components of reactive dyes for cellulose fibres.[86]



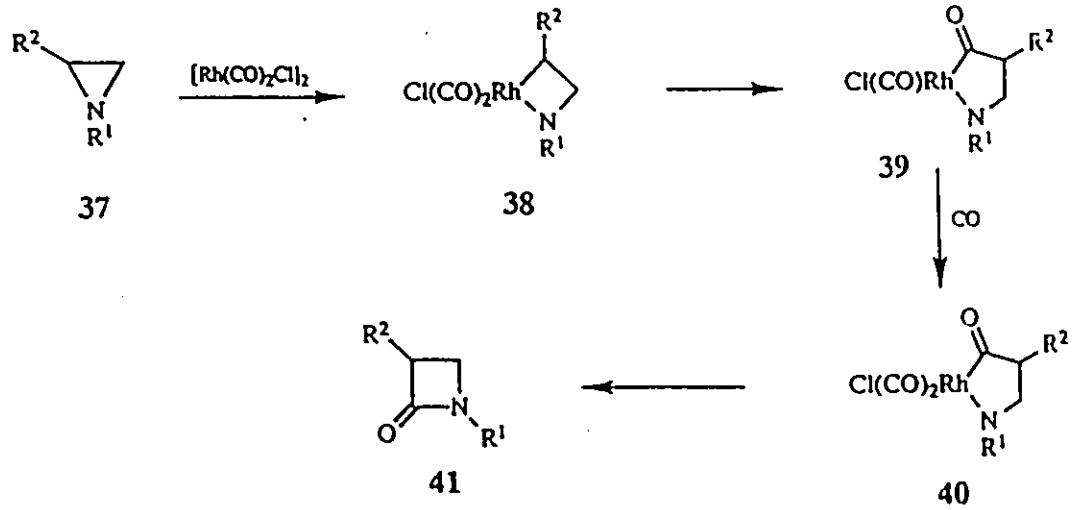
34

Catalytic chemistry involving aziridines has attracted wide interest in recent years. When azirines were treated with a stoichiometric quantity of chlorodicarbonyl rhodium(I) dimer, only vinyl isocyanates were obtained, but not any heterocyclic compounds.[87] Use of catalytic quantities of the same Rh(I) dimer resulted in ring expansion of aziridines to β-lactams. The reaction is regiospecific, i.e. CO insertion occurs only in the more substituted C-N bond:[88]



35 36

Excellent yields were obtained when the reaction was effected at 90°C, under 20atm. of carbon monoxide in benzene. A metallacyclic complex may participate in the process.

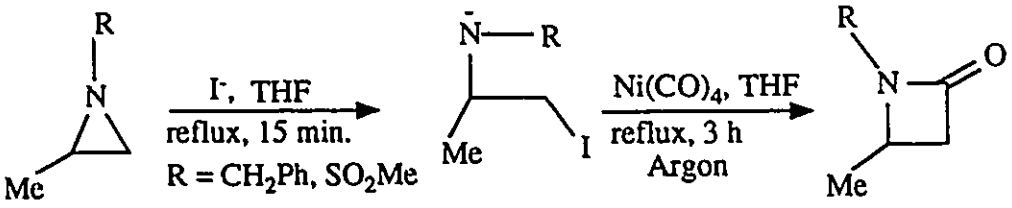


37 38 39 40 41

Oxidative addition of rhodium(I) to the more substituted carbon-nitrogen bond of the aziridine 37 can give an azametallacyclobutane 38. Subsequent CO insertion followed

by reductive elimination affords the β-lactam **41**. Recently a similar azairidocyclobutane has been isolated and characterized.[89]

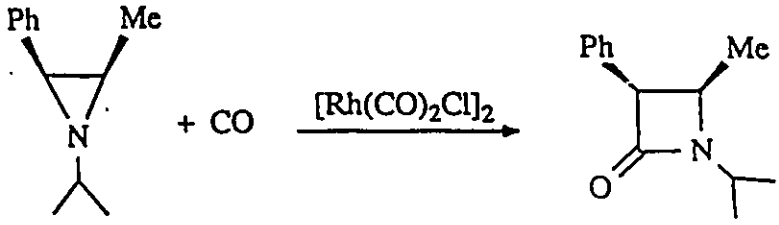
In 1988 a reaction with opposite regioselectivity was reported[90] by use a stoichiometric amount of nickel carbonyl under an inert atmosphere with carbonylation occurring onto the less substituted C-N bond of the aziridine:



42 **43** **44**

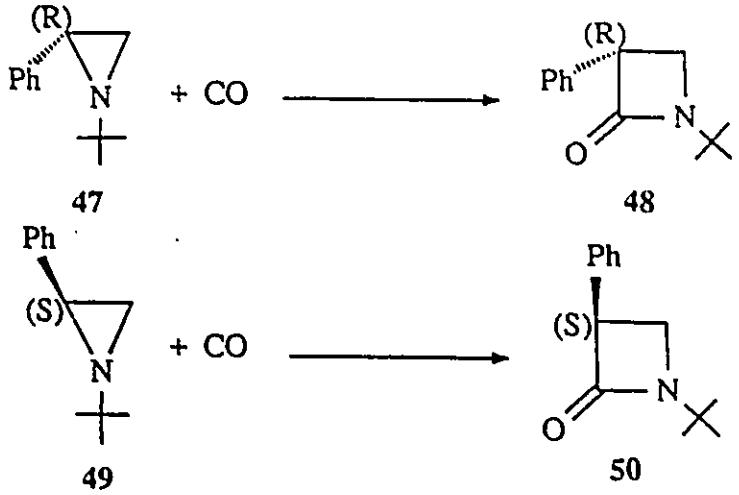
For R=CH_2Ph, the yield of β-lactam was 51%. When nitrogen was substituted by an electron withdrawing group (e.g. methyl sulphone SO_2Me), the lactam was formed only in 18% yield.

Further research[91] on the stereochemistry and enantioselectivity of ring expansion and carbonylation of aziridines shows that the process is both stereo- and enantiospecific, occurring with retention of configuration e.g., S-1-tert-butyl-2-phenylaziridine is converted to S-1-tert-butyl-3-phenylazetidin-2-one: stereospecific:

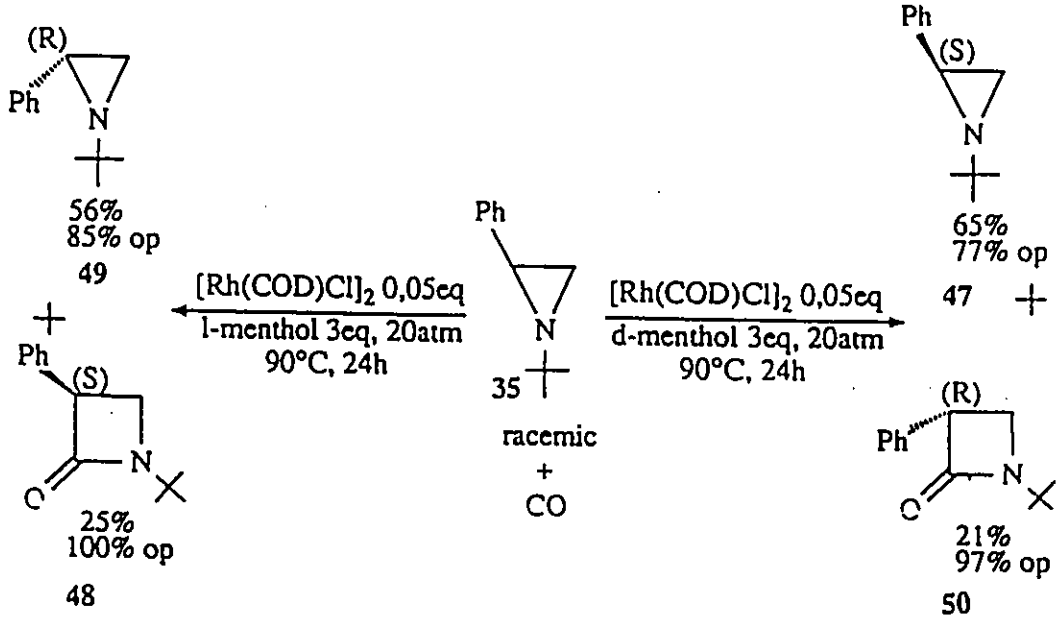


45 **46**

enantiospecific:

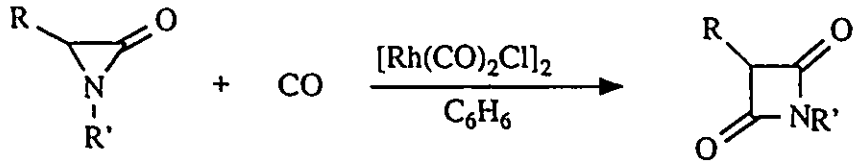


In addition, use of d- or l-menthol as a chiral ligand in the carbonylation of racemic aziridines leads to the asymmetric synthesis of β-lactams with high optical purity (87-99% e.e). It was also found that the R enantiomer reacts more rapidly in the presence of d-menthol than in the presence of l-menthol and the recovered aziridine is also obtained in fine optical yield (77-85% e.e).



It is conceivable that binuclear rhodium complexes, containing bridging menthoxy ligands, are primarily responsible for the observed chiral discrimination.

Aziridinones experience regiospecific ring expansion and carbonylation to azetidin-2,4-diones in fine yields using rhodium or cobalt complexes.[92]



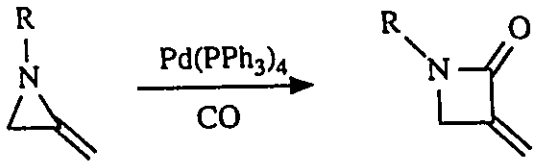
51 52

Rh(I): $[Rh(CO)_2Cl]_2$, $[RhCl(1,5\text{-}COD)]_2$, $[RhCl(1,5\text{-}HD)]_2$

Co(0): $Co_2(CO)_8$, $Co_4(CO)_{12}$.

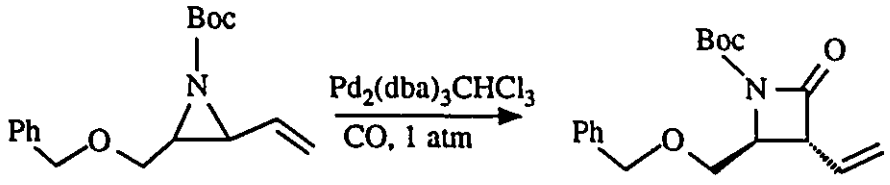
The two processes are significantly different: the rhodium reaction occurs under carbon monoxide and is catalytic; the cobalt reaction is inhibited by carbon monoxide and is not catalytic.

The palladium complex, $Pd(PPh_3)_4$, catalyzes the conversion of methyleneaziridines to α-methylene-β-lactams with coordination of the nitrogen lone pair and the π-electrons of the double bond to palladium, fixing the site of incorporation of carbon monoxide:[93]



53 54

Highly stereoselective conversion of 2-benzyloxymethyl-1-(tert-butoxycarbonyl)-3-vinylaziridine **55** into trans-4-benzyloxymethyl-1-(tert-butoxycarbonyl)-3-vinyl-2-azetidine **56** via ring opening, carbonylation and ring closure, was accomplished by use of palladium (0) [$Pd_2(dba)_3CHCl_3$] and CO (1 atm).[94]

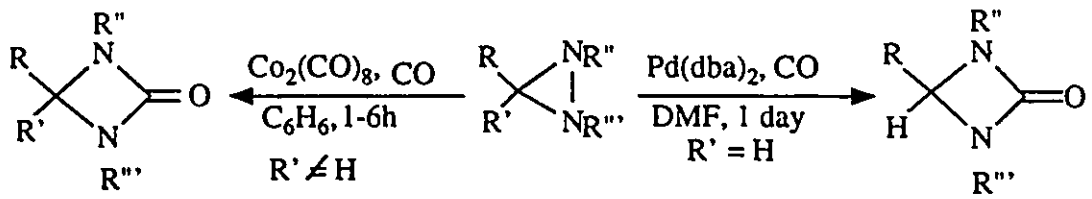


55 (cis/trans=1/3) **56**

Diaziridines

Carbonyl insertion into the weak nitrogen-nitrogen bond, rather than the carbon-nitrogen bond occurs when diaziridines are employed as substrates in the presence of palladium or cobalt complexes.[95] It was found that while $[Rh(CO)_2Cl]_2$, $[(1,5\text{-}COD)RhCl]_2$, $Rh_4(CO)_{12}$ and palladium acetate or trifluoroacetate were inert, the electrophilic palladium(II) complex, $[Pd(CH_3CN)_4][BF_4]_2$, tetrakis(acetonitrile)palladium bis(tetrafluoroborate) did catalyze the carbonylation of 3-substituted-1,2-diaziridines to give the 1,3-diazetidinone in 37% yield. The use of the palladium(0) complex, $[Pd(dba)_2]$, in DMF at 120°C and 1 atm. of CO afforded the ring expansion carbonylation product in quantitative yield, except for 3,3-disubstituted diaziridines. In contrast, cobalt carbonyl, which was incapable of forming 1,3-diazetidinones from diaziridines monosubstituted at C-3, cleanly carbonylated 3,3-disubstituted diaziridines

to give aza-β-lactams in 11-65% yield, depending on the nature of the substituents.



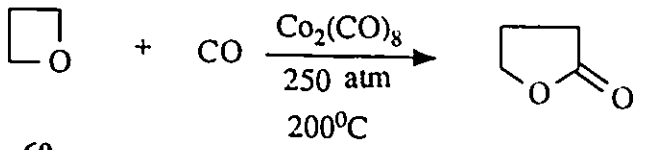
58 57 59

Ring Expansion Carbonylation Reactions of Four Membered Ring Heterocycles

Four membered ring heterocycles show much less evidence of ring strain, and they have found correspondingly less use as synthetic intermediates (β-lactams are exceptional).[73] The tendency to undergo ring expansion to five or six (seven in some cases) membered ring system via transition metal catalysis has greatly improved this feature.

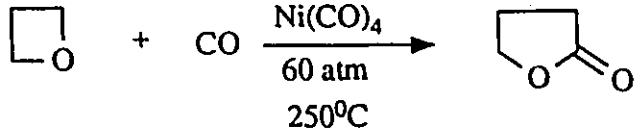
Oxetanes and Thietanes

Oxetanes undergo ring cleavage by nucleophiles, although the conditions required are generally more vigorous than those for the ring opening of oxiranes. Early work in the patent literature indicated that metal catalyzed ring expansion carbonylation reactions could be achieved for oxetane itself using a cobalt catalyst under forcing conditions:[96]

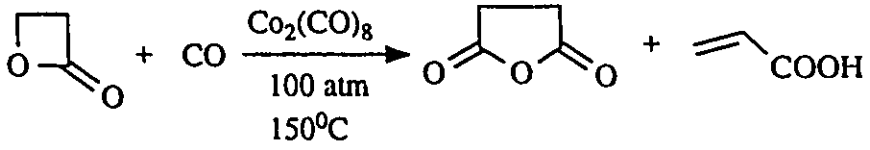


60 **61**

But when $Ni(CO)_4$ was used instead of $Co_2(CO)_8$ the reaction occurred at lower pressure (250°C, 60 atm.).

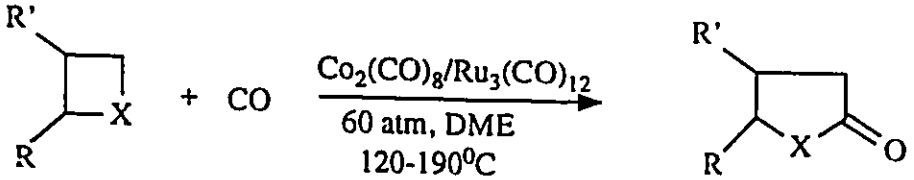


The four membered ring β-lactones **62** could also be carbonylated to five membered ring cyclic anhydrides **63**.[97]



62 **63** **64**

Recently investigations in our laboratory have shown that a wide range of oxetanes and thietanes may similarly be carbonylated under less vigorous conditions, affording thiobutyrolactones or butyrolactones:[34]



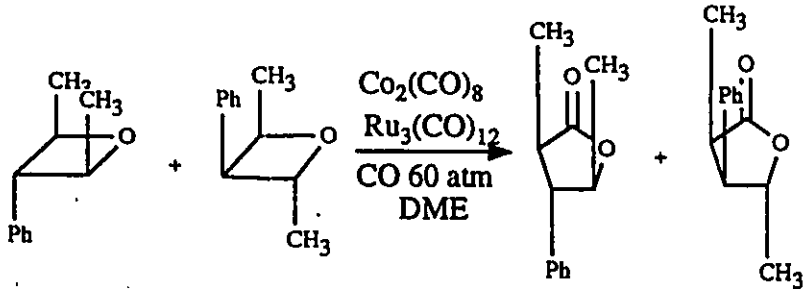
65 (X=O)
66 (X=S)

67 (X=O)
68 (X=S)

$R = CH_3$, n-C_6H_{13} ; $R' = CH_3$, CH_3O, CH_2OCOCH_3

Yield : 45 - 100%

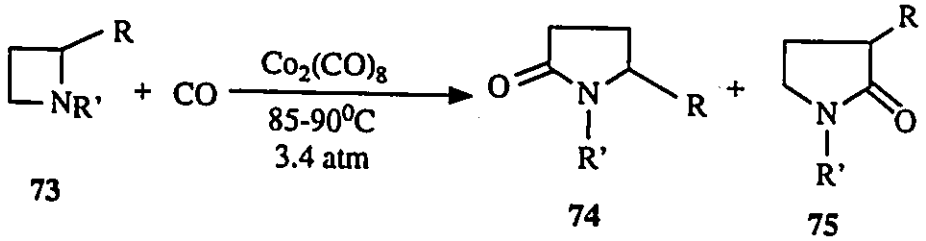
The reactions are regiospecific. Carbonylation occurs only at the least substituted carbon-heteroatom bond and the preferred catalyst appears to be a mixture of cobalt and ruthenium carbonyls. Because of the nature of the carbon-sulphur bond, the thietanes ring system is more easily carbonylated, as the reaction conditions are much milder than those required for the corresponding oxetanes and the product yields are also higher. This process occurs with retention of substituent group stereochemistry.



69 **70** **71** **72**

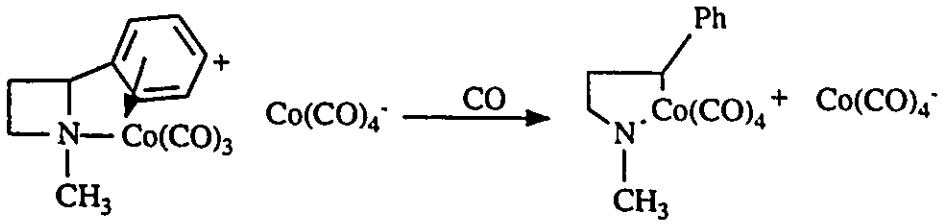
Azetidines

The azetidine ring is much less strained than that of aziridine, so its properties are much more like that of a normal secondary amine.[98,99] Direct carbonylation of azetidines, in the presence of cobalt carbonyl as catalyst has recently been shown to give high yields of pyrrolidinones (**74,75**) under mild conditions (85-90°C, 3.4 atm. CO):[100]



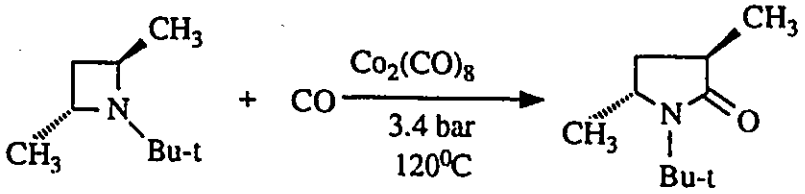
73 **74** **75**

The reaction proceeds with high regiospecificity depending on the type of substituent. In the case of 1-methyl-2-phenylazetidine, coordination of the arene ring to cobalt may generate **76**, which could undergo insertion of cobalt in the ring C2-N bond to give **77**.



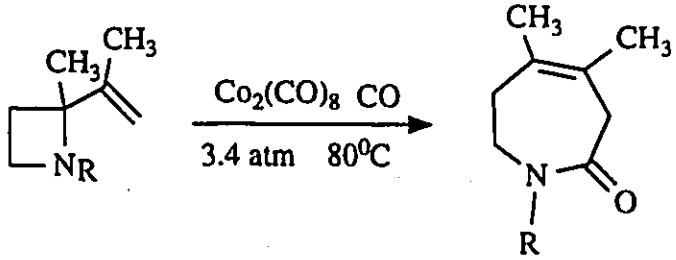
76 **77**

A stereospecific reaction was also observed when trans-2,4-dimethylazetidine was used as the substrate:



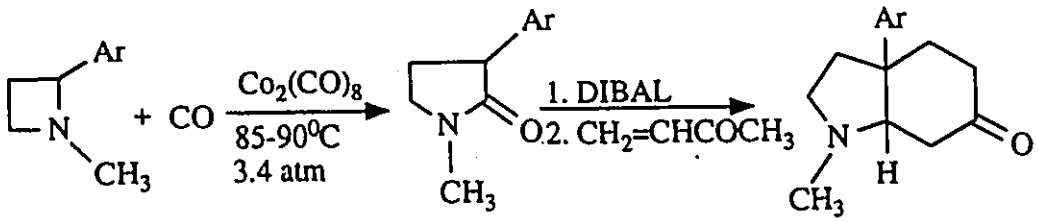
78 **79**

Carbonylation of 2-vinyl azetidines under these conditions, leaded to further ring expansion, with formation of seven membered lactones in good yield:[100]



80 **81**

An attractive feature of the reaction of all three classes of four membered ring heterocycles is the observed stereospecificity, and consequently this methodology is of value for the construction of five membered ring lactams, lactones or thiolactones, with stereochemically defined substituents. For example, this reaction provides a facile entry to the mesembrine alkaloids (e.g. **84**), several of which exhibit CNS activity.[101,102]



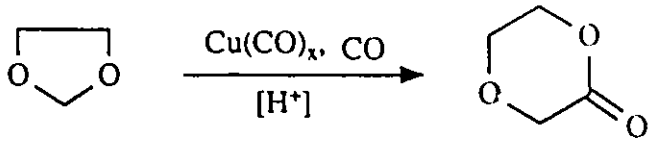
82 **83** **84**

A question arises whether the noted ring expansion-carbonylation process is limited to strained ring systems. If not, are the regio- and stereochemical features in accord with those found in the case of azetidines?

Ring Expansion Carbonylation Reactions of Five Membered Ring Heterocycles

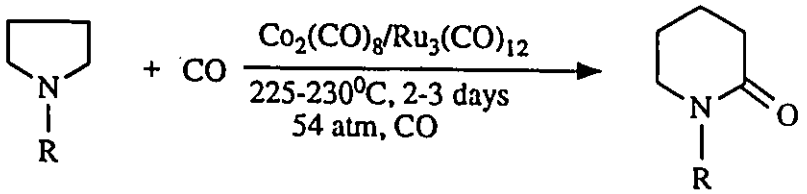
Five membered rings containing one or more heteroatoms are the most important group of heterocycles. Most of these ring systems are formally derived from furan, pyridine or thiophene or by replacement of one or more of the CH groups by sp^2-hybridized nitrogen. There have been few studies on the metal catalyzed expansion of

saturated or partially saturated five membered ring heterocycles. Recently, it was found that the carbonylation of 1,3-dioxolane with $Cu(CO)_x$ in acid solution afforded lactones:[103]



85 86

Some N-substituted pyrrolidines were investigated more recently.[104] The study of the effect of temperature and concentration on the reactions showed that pyrrolidines do experience ring expansion and carbonylation but needed comparatively more drastic conditions than those for azetidines.



87 88

R=H, CH_3, n-Pr, $CH_2COOC_2H_5$, $CH_2COC(CH_3)_3$ Yield: trace-59%

Only one vicinal substituted pyrrolidines has been tested: 1-methyl-2-(3'-pyridyl)pyrrolidine, the regioselective product 1-methyl-3-(3'-pyridyl)piperidin-2-one was obtained but in low yield (22%).

In conclusion, the direct metal catalyzed ring expansion carbonylation reactions can be used to construct larger cyclic carbonyl systems (from three to four or more membered ring, from four to five or more, from five to six). However, it is clear now that ring size does play an important role in this type of reactions (severity of conditions depends on ring size). The possible extension of these processes to larger ring systems may lead to new and interesting chemistry.

1.7 Aims of Research

The widespread occurrence and pharmacological activity of lactam rings make them attractive target systems to chemists who employ transition metal based methodologies to construct lactams. An important class of metal catalyzed carbonylation reactions to construct these interesting molecules are ring expansion carbonylation via transition metal activated carbon monoxide. Having the knowledge of the organotransition-metal chemistry of three and four membered ring heterocycles as well as 1,3-dioxolane and 1-substituted pyrrolidines in the presence of carbon monoxide, we were interested in learning what would happen to 2-substituted pyrrolidines and larger nitrogen-containing heterocycles such as piperidines, if they were treated with carbon monoxide and an organotransition-metal complex. Would they react and if so, would they undergo carbonylation with ring expansion to afford lactams? In that event, is the CO insertion regioselective mimicking that of the four-membered ring heterocycles?

Should azametallacycles be involved in the metal catalyzed reactions, then pyrrolidines would experience expansion to piperidinones via azametallacycloheptanes, assuming an analogous mechanistic pathway. What about the stability of azametallacyclooctanes? If the ring size is a determining factor to a metal catalyzed ring expansion carbonylation reaction, what is new about larger nitrogen-containing rings?

Mixed-metal homogeneous catalysis, for example $Co_2(CO)_8/Ru_3(CO)_{12}$ system in our previous works, usually has a synergistic effect, and it may lead to new transformations of starting molecules to useful molecules.

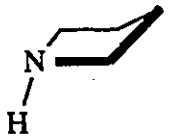
Chapter 2

Regioselective Synthesis of Piperidines by Metal Catalyzed Ring Expansion Carbonylation Reactions

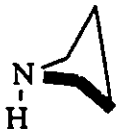
2.1 INTRODUCTION

Carbonylation based methodologies for the construction of lactams have attracted considerable interest in recent years.[105, 106] Both stoichiometric and catalytic processes have been developed including, among others, the photochemical reaction of carbene chromium complexes with imines to give β-lactams in good yield:[107] and the cyclization of N-alkyl-2-bromophenethylamines with carbon monoxide to form tetrahydroisoquinol-1-ones, a reaction catalyzed by palladium acetate in the presence of triphenylphosphine.[108]

A different strategy for the synthesis of lactams involves the metal catalyzed "stitching" of carbon monoxide into a nitrogen heterocycle. The size of the ring system and the overall shape of the molecule are important factors which determine the reactivity of heterocyclic compounds. Oxiranes, thiiranes, azirines, aziridines, diaziridines, due to ring strain, undergo facile ring cleavage reactions. Oxetanes, thietanes and azetidines can also experience ring expansion carbonylation in moderate to good yield. Pyrrolidines are not strained ring heterocycles. Their conformations are a series of freely interconverting nonplanar structures, such as the envelope form **89** and the half-chair form **90**, in which the eclipsing interactions of adjacent C-C bonds are relieved.[73]



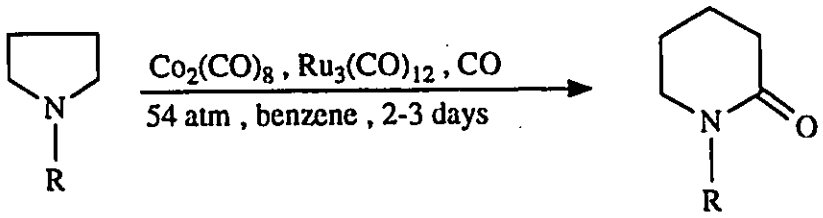
89



90

Pyrrolidines, unlike aziridines and azetidines, do not easily undergo ring cleavage reactions. Chemical properties of pyrrolidines are similar to those of secondary amines, However, some rather specific reactions of pyrrolidines are due to their cyclic structure. For example, pyrrolidine readily forms an N-nitroso derivative which can be lithiated in the 2-position, and subsequent reaction with electrophiles and deprotection yields 2-substituted pyrrolidines.[109] Pyrrolidines are dehydrogenated, for instance, when heated with palladium on carbon, to give the corresponding pyrroles.[110] Pyrrolidine telomerizes butadiene in the presence of palladium complexes.[111]

In principle, pyrrolidines **87** can experience carbonylation and ring expansion to give piperidinones **88** possibly via azametallacycloheptanes.[100] Limited experiments by Roberto showed that the carbonylation of 1-substituted pyrrolidines can undergo ring expansion:[104]



87 **88**

R=H, CH_3, n-Pr, $CH_2COOC_2H_5$, $CH_2COC(CH_3)_3$ yield: trace-59%

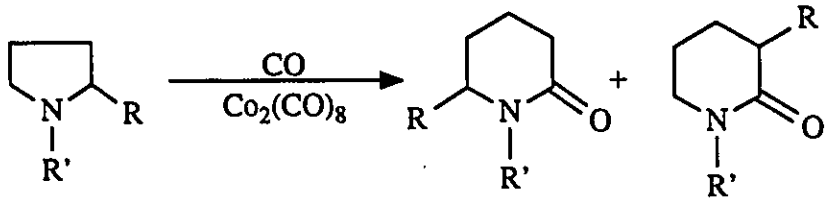
The optimized ratio of pyrrolidine : $Co_2(CO)_8$: $Ru_3(CO)_{12}$ was found to be 4 : 1 : 0.5 at a temperature of 225-230^{0}C and a concentration of 0.11M in benzene.

What about the regiochemical feature of the reaction? The results described below demonstrate the excellent regiochemical control being realized in nearly all cases, and the yield of piperidinones is increased when ruthenium carbonyl is a co-catalyst with cobalt carbonyl.

During this investigation, a remarkable rearrangement process was discovered which occurs with appropriately substituted pyrrolidines and some other nitrogen heterocycles to give a series of lactams. The mixed-metal catalytic system [$Co_2(CO)_8$/$Ru_3(CO)_{12}$] is also useful for this novel reaction.

2.2 RESULTS AND DISCUSSION

The carbonylation of 1,2-disubstituted pyrrolidines **91** was investigated in the presence of cobalt carbonyl or cobalt/ruthenium carbonyls as catalysts.



91a-f **92a-f** **93a-f**

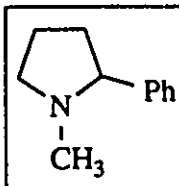
a, R = Ph, R' = CH_3;
b, R = CH_2Ph, R' = CH_3;
c, R = CH_2OCH_3, R' = $CH_2COOC_2H_5$;
d, R = CH_2OCH_3, R' = $CH_2COC(CH_3)_3$;
e, R = 1-$C_{10}H_7$, R' = CH_3;
f, R = H, R' = $CH_2COOC_2H_5$

Initially, 1-methyl-2-phenylpyrrolidine (**91a**, R=Ph, R'=CH_3) was used as a model substrate. Reaction conditions were found to affect regiospecific ring expansion and carbonylation of 1,2-disubstituted pyrrolidines. Indeed, 56% of 1-methyl-3-phenylpiperidin-2-one (**93a**) was isolated with no other regioisomer (**92a**) detected, when the pyrrolidine was treated with dicobalt octacarbonyl in dry benzene . The reaction was carried out at 200-205^{0}C for 72 hrs under 54 atm of carbon monoxide. If one repeats the reaction with added triruthenium dodecacarbonyl, the isolated yield of **93a** increases to 63%.

It is important to keep constant temperature and vigorous stirring during the reaction. At higher temperature (e.g. 240-245^{0}C), a greater conversion of 1-methyl-2-phenylpyrrolidine was achieved (95%), but the yield of the regiospecific product **93a** was not higher. Some polymerization may occur at higher temperatures. At lower temperature (160-164^{0}C for 5 days), the reaction was also regiospecific, but the conversion of pyrrolidine was very poor (less than 10%). See Table 1 for experimental results.

The structure of **93a** was assigned on the basis of spectral data. Nuclear magnetic resonance (NMR spectroscopy) results were especially helpful for establishing the structure, e.g., the proton NMR spectrum gave a triplet at δ 3.63 due to the methine proton at C3. If isomer **92a** was formed the signal for the methine proton at the 6-position would occur at lower field. The DEPT of the ^{13}C NMR spectrum gave a signal at δ 48.36 due to the methine carbon at the 3-position. In the isomer **92a** the CH at the 6-position would occur at δ > 55 ppm (reference data in section 2.3). The resonance at δ3.62 for the proton at C3 and at δ 47.72 for the carbon at the 3-position is also consistent with the structure of 1-methyl-3-phenylpyrrolidin-2-one.[100]

Table1 Ring Expansion Carbonylation of 1-Methyl-2-Phenylpyrrolidine (91a)

 :$Co_2(CO)_8$:$Ru_3(CO)_{12}$	T,^{0}C	time, day	conversion of substrate, %	Yield,[a] %
4 : 1 : 0	200-205	3	71	56
4 : 1 : 0.5	200-205	3	82	63
4 : 1 : 0.5	160-164	5	9	
4 : 1 : 0.5	240-245	3	95	56
4 : 1 : 0.5	245	5	97	trace [b]

[a] isolated yield of product **93a**

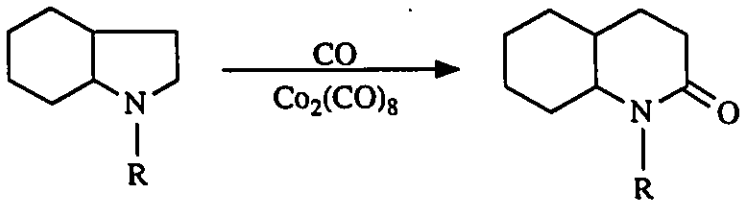
[b] 4-methyl-2-pentanone as solvent

It seemed conceivable that one could induce chirality in the cobalt and ruthenium carbonyl catalyzed carbonylation of 1-methyl-2-phenylpyrrolidine in the presence of an added chiral ligand. For this reason, (R)-(+)-1,1'-bi-2-naphthol and (1S, 2R, 5S)-(+)-menthol were used as chiral ligands for the reaction. When using a 1:1.5 ratio of cobalt/ruthenium carbonyls to (R)-(+)-1,1'-bi-2-naphthol, only traces of racemic product were formed. With (1S, 2R, 5S)-(+)-menthol as the chiral ligand, and a reaction time of five days, good conversion of 1-methyl-2-phenylpyrrolidine (96%) occurred affording 1-methyl-3-phenylpiperidin-2-one (66%), but no asymmetric induction took place ($[\alpha]^{25}_D$= +0.07).

1-Methyl-2-(1'-naphthyl)pyrrolidine (**91e**) was treated with dicobalt octacarbonyl and ruthenium dodecacarbonyl (ratio of 4:1:0.33), at 220-235^{0}C for 3

days, and gave only 6% yield of the ring expansion carbonylated product, 1-methyl-3-(1'-naphthyl)piperidin-2-one (**93e**).

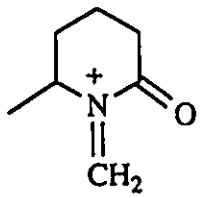
The process is regiospecific for two pyrrolidines having a methoxymethyl substituent at the 2-position (**91c** or **91d**), with insertion occurring solely into the least substituted ring C-N bond to give **92c** or **92d**. The observed regiochemistry is in accord with that found for the analogous azetidines.[100] The bicyclic perhydroindoles (**94a** and **94b**) underwent regiospecific carbonylation to **95a** and **95b** in 46% and 49% isolated yield, respectively. The remainder was unreacted starting material.



94a,b **95a,b**

a, $R = CH_2COOC_2H_5$; b, $R = CH_2COC(CH_3)_3$

The structures of **92c**, **92d**, **95a** and **95b** were determined by spectroscopic data, i.e., IR, ^1H NMR, ^{13}C NMR, MS data. Most of these products gave parent ions in the mass spectrum. The fragment ion of type **97** occured as the base peak in these MS spectra.



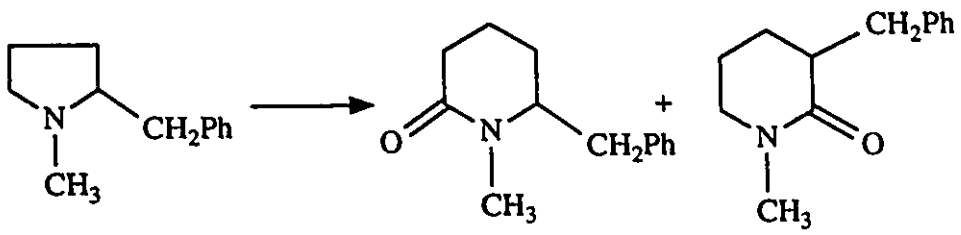
97

These ions are formed as a result of fragmentation of $COOC_2H_5$ or $COC(CH_3)_3$ from the molecular ion. The same trends are also observed in the mass spectra of the corresponding starting materials.

The proton and carbon-13 NMR spectroscopic data are especially helpful in detemining the structure of the product e.g., all the chemical shift values of the proton and carbon atoms of the CHN group in the ring expansion carbonylation product molecules are key to the determination of the structure of the regiospecific product. The chemical shift characteristic CHN value of δ 2.90-3.30 ppm in the proton NMR spectrum and δ 57.00-62.50 ppm in the carbon-13 NMR spectrum support **92c**, **92d**, **95a**, and **95b** as the structure. If **93c**,**93d** (or **96a**, **96b**) were formed, these signals should occur at higher field.

Another important characteristic feature of proton NMR data of these products is the regular pattern of protons of the CH_2 group at the 1-position [$CH_2COOC_2H_5$ or $CH_2COC(CH_3)_3$]. The chemical shift value of these protons is considerably different (the differences are between 0.15-0.52 ppm in the ^1H NMR spectra of the four products) and their coupling constant values are large (J= 18 Hz). The geminal coupling constant, $^2J_{HH}$, varies greatly, from approximately -17 to +42 Hz. Although the mathematical signs are important in the detailed theory of spin-spin coupling, differences in sign do not affect the appearance of NMR spectra. According to the rules of the effects of bonding features on the trends in $^2J_{HH}$ summarized by Pople and Bothner-By[112], the withdrawal of electron density from orbitals symmetric between hydrogen atoms (sigma orbital inductive effect) by C=O directly bonded to the C atom, leads to a negative shift in the coupling constant resulting in the 18 Hz negative value.

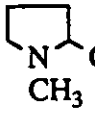
Using the benzyl analogue **91b** as the substrate in the presence of $Co_2(CO)_8$ at 215-220^{0}C for 3 days, **92b** and **93b** were isolated in a ratio of 1.5/1.0.



91b **92b** **93b**

Repetition of the reaction with $Ru_3(CO)_{12}$ as a second catalyst gave **92b/93b** in a ratio of 3.3/1.0. Note that use of higher temperatures and a 1/1 ratio of $Co_2(CO)_8/Ru_3(CO)_{12}$, gave no regioselectivity in the process.

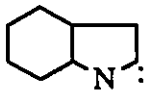
Table 2 Ring Expansion Carbonylation of 1-Methyl-2-benzylpyrrolidine (91b)

 CH_2Ph:$Co_2(CO)_8$:$Ru_3(CO)_{12}$	T,^{0}C	Time, day	Conversion of substrate, %	Yield [a] %	Ratio of Products,[b] **92b : 93b**
4 : 1 : 0	215-220	3	68	39	1.5 : 1.0
4 : 1 : 0.3	215-220	4	73	44	3.3 : 1.0
4 : 1 : 0.5	220	6	79	32	2 : 1
6 : 1 : 1	245-250	4	62	28	1 : 1

[a] isolated yield; [b] by GC

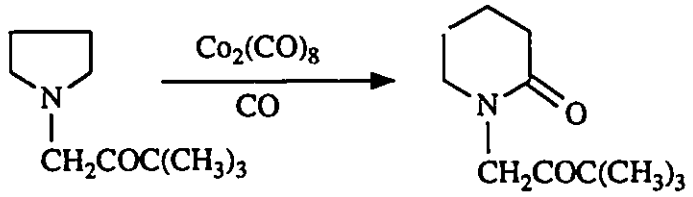
As mentioned in Chapter 1, Section 6, the mixed-metal catalyst system can provide high reactivity and selectivity in some reactions. Based on the results of Table 2, the role of the mixed-metal system is unclear. Nevertheless, some comparative experiments show the synergistic effect operating in this catalytic ring expansion carbonylation reaction [Table 3].

Table 3 Influence of the catalyst on the carbonylation of 91f and 94b at 205-210^{0}C

 $CH_2CO_2C_2H_5$: $Co_2(CO)_8$: $Ru_3(CO)_{12}$	Time, day	Conversion of substrate, %	Isolated yield of product, % **92f**
4 : 1 : 0	3	51	30
4 : 1 : 0.5	3	89	67
 $CH_2CO_2C_2H_5$: $Co_2(CO)_8$: $Ru_3(CO)_{12}$	Time, day	Conversion of substrate, %	Isolated yield of product, % **95b**
4 : 1 : 0	3	67	46
4 : 1 : 0.5	3	91	79

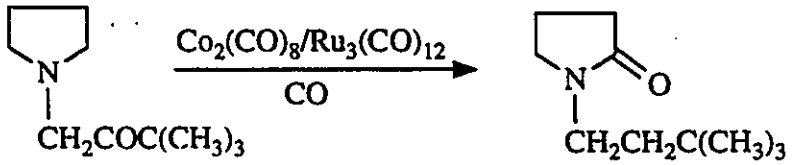
Such a mixed-metal catalytic system was shown to be effective for the conversion of oxetanes and the thietanes to lactones and thiolactones, respectively.[34]

The expected ring expansion occurred when 1-pyrrolidinyl-3,3-dimethyl-2-butanone (**91g**) was carbonylated in the presence of dicobalt octacarbonyl, affording **92g** in 42% yield:[34]



91g **92g**

However, when the reaction was repeated using both $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ as catalysts, a suprising product 1-(3,3-dimethyl-1-butyl)pyrrolidin-2-one (**119a**) was isolated in 72% yield, with none of the ring expansion product (**92g**) formed in the reaction:

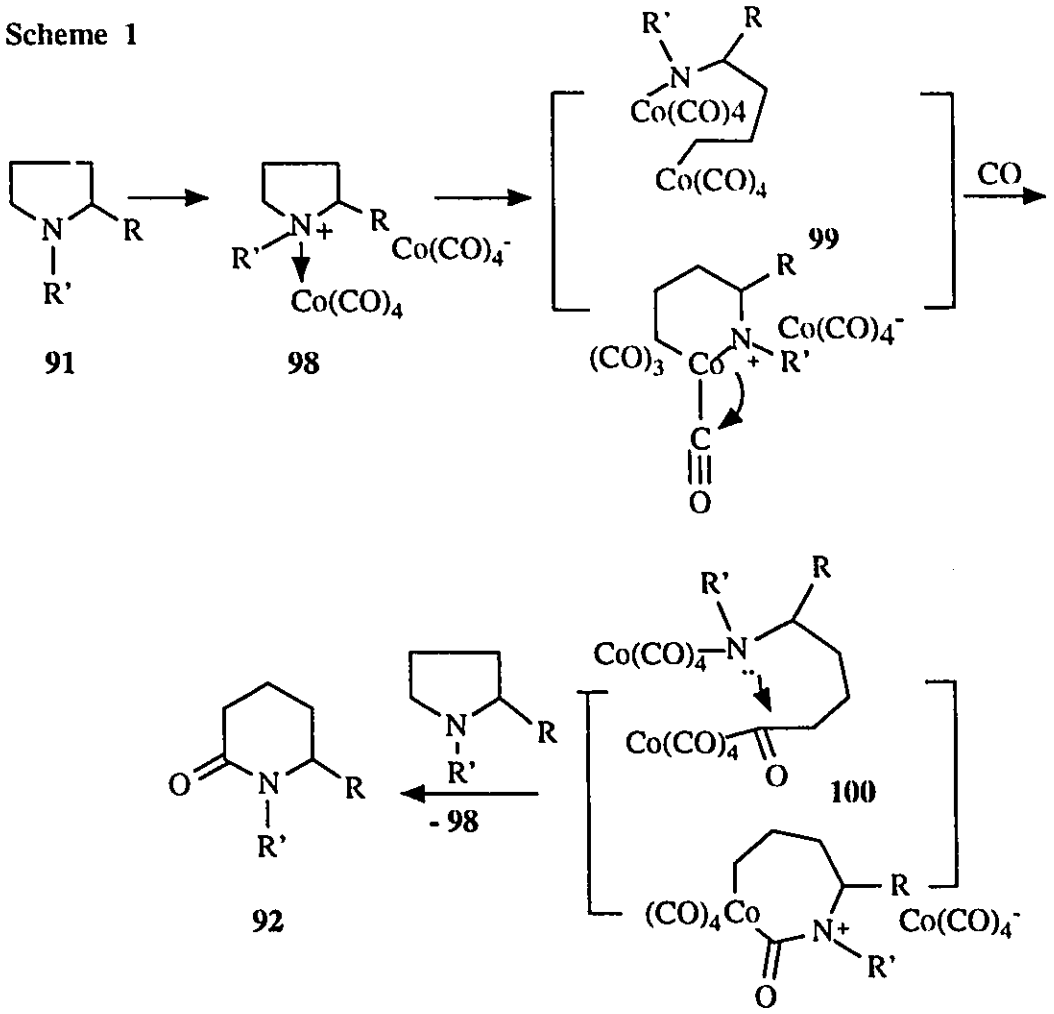


91g **119a**

This new rearrangement reaction will be discussed in Chapter 3.

The mechanism of dicobalt octacarbonyl induced ring expansion carbonylation of 1,2-disubstituted pyrrolidines may be similar to that proposed for the carbonylation of azetidines[100] (see Scheme 1).

Scheme 1

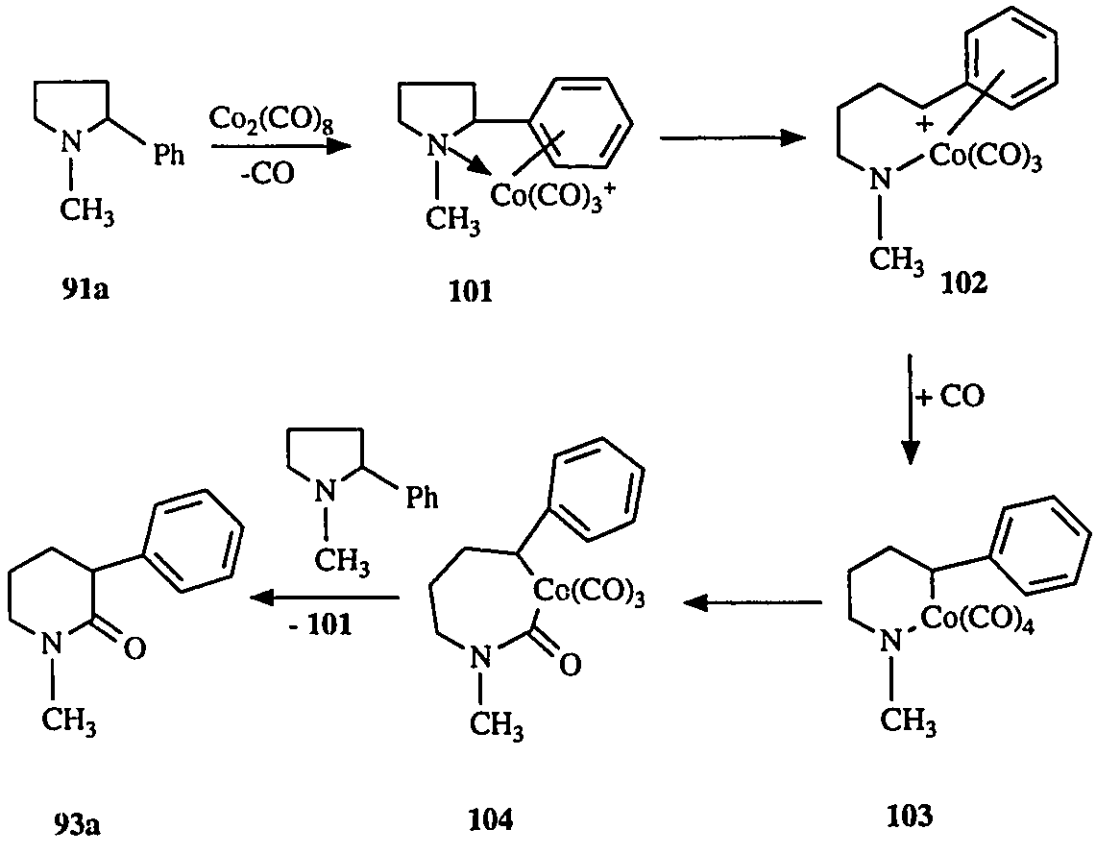


When the 2-substituent is an alkyl group, (e.g. methoxymethyl or fused carbon ring), the pyrrolidine coordinated with cobalt complex via nitrogen lone pair would form the cationic intermediate **98**. Cobalt insertion into the least substituted C-N bond of the pyrrolidine ring would be favoured on steric grounds, leading to the formation of the metallacycle **99**. The subsequent ligand migration involves the C-N bond rather than C-C bond[113], followed by reductive elimination of **98**, to give the regiospecific product **92**.

In the case of 1-methyl-2-phenylpyrrolidine **91a**, coordination of the π-system of the arene ring to cobalt may generate complex **101**, which could

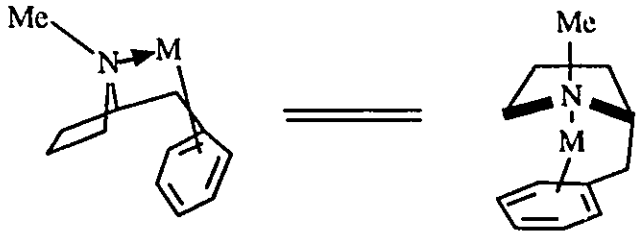
undergo cobalt insertion into the ring C2-N bond followed by the CO addition to give **103**. Ligand migration and subsequent reductive elimination can afford **93a** (Scheme 2).

Scheme 2



In the case of 1-Methyl-2-benzylpyrrolidine **91b**, the presence of an extra CH_2 group between the carbon of the 2-position and the phenyl group may make metal complex pieces more close to the ring and easy to attack both C-N bonds of the ring. (Scheme 3):

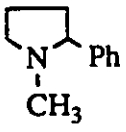
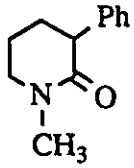
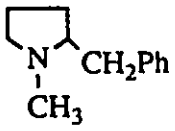
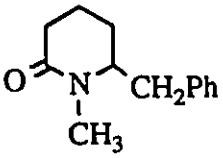
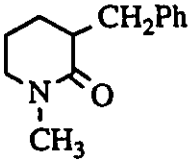
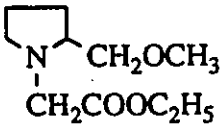
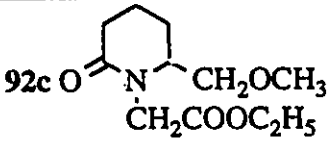
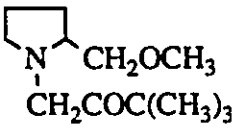
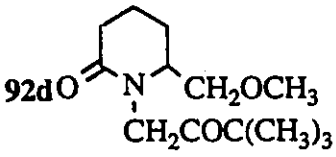
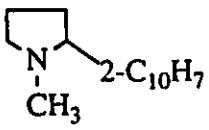
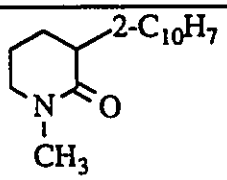
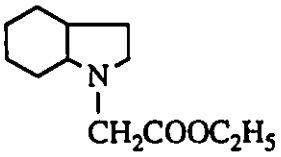
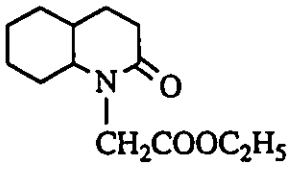
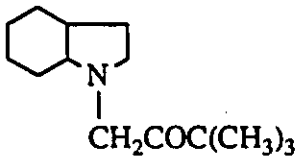
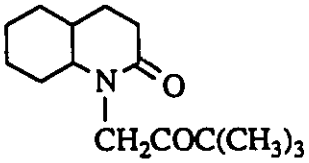
Scheme 3



105 **106**

This investigation of the metal catalysed chemistry of 1,2-disubstituted pyrrolidines has revealed that such compounds can experience cobalt carbonyl-catalyzed regiospecific ring expansion and carbonylation in most cases (summarized in Table 4). Use of the mixed-metal catalytic system $[Co_2(CO)_8/Ru_3(CO)_{12}]$ has a beneficial effect upon these carbonylation reactions. Triruthenium dodecacarbonyl alone is unable to catalyze the carbonylation of pyrrolidines.

Table 4 Regioselective Ring Expansion Carbonylation of 1,2-disubstituted Pyrrolidines

Pyrrolidine	Product	Isolated Yield %
91a 	**93a** 	56[a] 63[b]
91b 	**92b**  **93b** 	92b 24[a] 93b 15[a]
91c 	**92c** 	49[a]
91d 	**92d** 	61[a]
91e 	**93e** 	trace[a] 6[b]
94a 	**95a** 	46[a] 79[c]
94b 	**95b** 	49[a]

[a] pyrrolidine:$Co_2(CO)_8$=4:1, benzene, 200-220^{0}C, 54 atm CO, 3days, 0.1M

[b] using 1/3 $Ru_3(CO)_{12}/Co_2(CO)_8$, [c] using 1/2 $Ru_3(CO)_{12}/Co_2(CO)_8$

2.3 Experimental Section

2.3.1 GENERAL COMMENTS

Spectral data were obtained by use of the following instrumentation: Perkin-Elmer 783 spectrometer for infrared spectra, Gemini 200 or Varian XL 300 for proton and carbon-13 magnetic resonance spectra (decoupled from ^1H), and VG Micromass 7070E for mass spectra. GC-MS were obtained with a Varian 3300 chromatograph, fitted with a megabore DB5 capillary column in tandem with the VG Micromass 7070E spectrometer.

Gas chromatography was carried out with a Varian Vista 6000 or Varian 3400 gas chromatograph equipped with a flame ionization detector and a Varian 4270 integrator. Glass columns packed with 3% OV-101 or 3% OV-17 on chromosorb W, 80-100 mesh were utilized. FID weight percent response factors were relative to benzene. The absolute calibration or internal standardization were also used for GC yields or the convertion of starting materials.

Melting points were obtained with a Fisher-Johns apparatus.

Elemental analyses were carried out by MHW laboratories, Phoenix, Arizona.

Organic solvents were dried and distilled prior to use.

Cobalt and ruthenium carbonyls were purchased from commercial firms and used as received.

Gases were obtained from Air Products Company.

High pressure reactions were carried out in 45ml-series 4700 stainless steel, screw-cap autoclaves manufactured by Parr Instruments.

Thin layer chromatographic plates, and silica gel or neutral (type E) alumina

oxide for column chromatography were obtained from commercial sources.

A Perkin-Elmer 241 polarimeter (Na lamp) was used for the measurement of optical activity.

2.3.2 SYNTHESIS OF PYRROLIDINES

2.3.2.1 1-METHYL-2-PHENYLPYRROLIDINE (91a)

1-Methyl-2-phenylpyrrolidine **91a** was prepared in 65% yield from cyclopropyl phenyl ketone, N-methylformamide, and magnesium chloride, following the procedure of Blake and Gillies.[114]

The pure product is a colourless liquid. Yield 65%; b. p.: 56-58^{0}C/0.8 mmHg (Lit.: b. p.: 52-54^{0}C/0.7 mmHg);

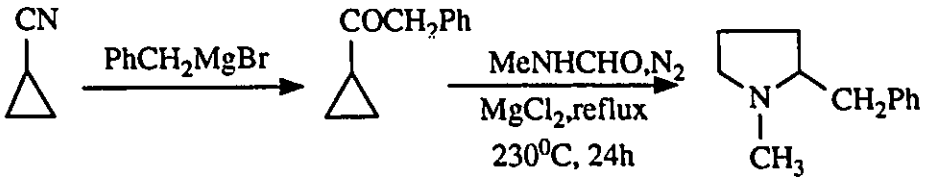
^{1}H NMR ($CDCl_3$): δ 1.68-2.32 (m, 5H, ring H); 2.15 (s, 3H, CH_3); 2.90 [m, 1H, (cis) 3-H]; 3.22 (m, 1H, CH); 7.18-7.38 (m, 5H, C_6H_5);

MS (EI): m/e 161 $[M]^+$; base peak m/e 84 $[M\text{-}Ph]^+$.

2.3.2.2 1-METHYL-2-BENZYLPYRROLIDINE (91b)

1-Methyl-2-benzylpyrrolidine **91b** was synthesized following the literature procedure[114], starting from cyclopropyl cyanide:

Scheme 4



107 **108** **91b**

Benzyl cyclopropyl ketone: colourless liquid, yield 75%, b.p.: 83°C/0.55 mmHg, yield 75% (Lit.[114]: b.p.: 80°C/0.5 mmHg).

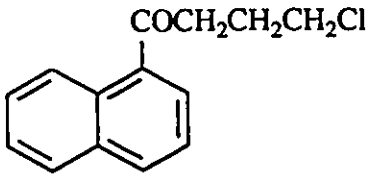
1-Methyl-2-benzylpyrrolidine: colourless liquid, yield 58% b.p.: 92-94°C/0.9 mmHg, yield 58% (Lit.[114]: b.p.: 70°C/0.2 mmHg)

^{1}H NMR ($CDCl_3$): δ 1.63-2.65 (m, 8H, 6 ring H and CH_2Ph); 2.52 (s, 3H, CH_3); 3.21-3.30 (m, 1H, CH); 7.28-7.46 (m, 5H, C_6H_5);

MS (EI): m/e 84 $[M\text{-}PhCH_2]^+$ base peak.

2.3.2.3 1-METHYL-2-(1'-NAPHTHYL)PYRROLIDINE (91e)

1-Methyl-2-(1'-naphthyl)pyrrolidine **91e** was prepared by the same procedure as that used to prepare 1-methyl-2-phenylpyrrolidine and 1-methyl-2-benzylpyrrolidine.[114] In the case of 1-naphthyl cyclopropyl ketone, the product from the Grignard reaction, after hydrolysis with aqueous hydrochloric acid, was found to be the chloroketone (**109**):



109

Crude yield 95% (Lit.[114]: 99%). Treatment of this compound with potassium t-butoxide in tetrahydrofuran resulted in ring closure to the cyclopropyl ketone in 61% yield, b.p.: 135^{0}C/0.1 mmHg, m.p.: 48-50^{0}C, (Lit.[114]: b.p.: 130^{0}C/0.04 mmHg, m.p.: 50-52^{0}C);

^{1}H NMR ($CDCl_3$) 60 MHz: δ 0.8-1.2 (m, 2H, trans ring-H); 1.2-1.5 (m, 2H, cis ring-H); 2.3-2.7 (m, 1H, CH); 7.3-8.0 (m, 6H, ArH); 8.3-8.6 (m, 1H, 8-H).

The crude yield of 1-methyl-2-(1'-naphthyl)pyrrolidine was 92%, and the pure product was isolated in 70% yield, b.p.: 118-120^{0}C/0.1 mmHg (Lit.[114]: b. p.: 99-100^{0}C/0.04 mmHg);

^{1}H NMR ($CDCl_3$) 200 MHz: δ 1.68-2.54 (m, 5H, ring-H); 2.27 (s, 3H, CH_3); 3.27-3.41 (m, 1H, cis 3-H); 3.78-3.87 (m, 1H, CH); 7.43-7.58 (m, 3H, ArH); 7.73-7.97 (m, 3H, ArH); 8.18-8.27 (m, 1H, 8'-H);

MS (EI): m/e 211 $[M]^+$, base peak m/e 84 $[M\text{-naphthyl}]^+$.

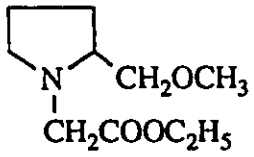
2.3.2.4 GENERAL PROCEDURE FOR THE PREPARATION OF 91c, 91d, AND 94a, 94b

(a) Deprotonation of pyrrolidine. A 10% molar excess of a solution of n-butyl or tert-butyl lithium in hexane, was added drop-by-drop to a stirred solution

of 10 mmol of 2-methoxymethyl pyrrolidine (or a perhydroindole) in 70-80 ml of dry ether at 0^0C under nitrogen. The reaction mixture was stirred for another hour at 0^0C, and then at room temperature for 2-4h.

(b) Alkylation. The solution obtained from the first step was added dropwise to a cold (0^0C), stirred ether (50 ml) solution of 10.5-11.0 mmol of α-bromo ketone or ester under a nitrogen atmosphere (the addition generally required 1.5-2.5 h). The reaction mixture was then stirred overnight at room temperature. Work-up was effected by washing the reaction mixture with water (3 × 20 ml), drying the organic phase using anhydrous K_2CO_3, and concentration by rotary evaporation. The crude product was purified by distillation under reduced pressure. Yields and characterization data for the products follow.

91c :

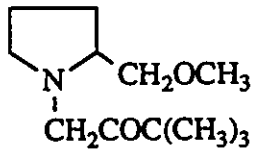


Light yellow liquid, yield: 57%, b. p.: 56-58^0C/0.45 mmHg;

IR ($CHCl_3$): ν (co) 1735 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, $C\underline{H}_3CH_2O$), 1.82 (m, 4H, CH_2CH_2), 2.38 (m, 2H, NCH_2ring), 2.79 (m, 1H, CH), 3.34 (s, 3H, OCH_3), 3.46 (m, 4H, $C\underline{H}_2OCH_3$ and $COOC\underline{H}_2CH_3$), 3.98 (m, 2H, NCH_2CO);

MS (EI): m/e 201 $[M]^+$, 156 $[M\text{-}OC_2H_5]^+$, 128 $[M\text{-}COOC_2H_5]^+$ base peak.

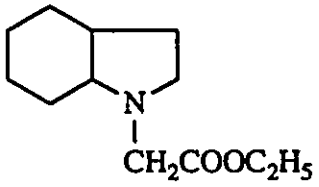
91d : 

Light yellow liquid, yield 85%, b. p.: 43-45^{0}C/0.35 mmHg;

IR ($CHCl_3$): ν (co) 1720 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H, $C(CH_3)_3$), 1.81 (m, 4H, CH_2CH_2), 2.32 (m, 2H, NCH_2ring), 2.82 (m, 1H, CH), 3.24 (s, 3H, OCH_3), 3.34 (m, 2H, CH_2O), 3.74 (m, 2H, NCH_2CO);

MS (EI): m/e 168 $[M\text{-}CH_2OCH_3]^+$, 138 $[M\text{-}COOC_2H_5]^+$ base peak.

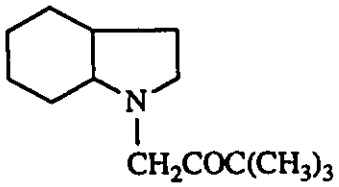
94a : 

Colourless liquid, yield 79%, b. p.: 94-96^{0}C/0.8 mmHg;

IR ($CHCl_3$): ν (co) 1733 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H, CH_2CH_3), 1.49-1.60 (m, 8H, protons at C4-C7), 1.82 (m, 2H, proton at C3), 2.05 (m, 1H, proton at C9), 2.63 (m, 2H, NCH_2ring), 3.13 (m, 1H, NCH), 3.18, 3.37 (d each, ^{2}J=16Hz, 2H, NCH_2COO), 4.19 (q, 2H, OCH_2);

MS (EI): m/e 211 $[M]^+$.

94b : 

Light yellow liquid, yield 65%, b. p.: 80^0C/0.55 mmHg;

IR ($CHCl_3$): ν (co) 1675 cm^{-1}, 1720 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H, $C(CH_3)_3$), 1.2-2.6 (m, 14H, ring H), 3.2, 3.4 (d each, J=16Hz, 2H, NCH_2CO);

MS (EI): m/e 223 $[M]^+$, m/e 138 $[M\text{-}COC(CH_3)_3]^+$ base peak.

2.3.3 GENERAL PROCEDURE FOR THE CARBONYLATION AND RING EXPANSION OF PYRROLIDINES

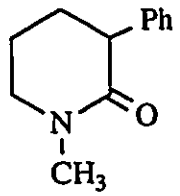
A mixture of the pyrrolidine (**91** or **94**, 1.32 mmol), dicobalt octacarbonyl (0.103g, 0.30 mmol), and dry benzene (10 ml) was placed in an autoclave containing a glass liner and a stirring bar. The autoclave was purged several times with carbon monoxide and pressurized to 54 atm. The reaction mixture was stirred at 200-205^{0}C for 3 days. The cooled autoclave was opened, and after standing in air, the mixture was filtered through Celite and the filtrate was concentrated by rotary evaporation. Purification of the resulting crude material was effected using preparative thin-layer chromatography on alumina with hexane-ethyl acetate or hexane-acetone as developer.

2.3.3.1 CARBONYLATION OF 1-METHYL-2-PHENYL PYRROLIDINE (91a)

2.3.3.1.1 GENERAL PROCEDURE

The reaction was carried out at 200-205^{0}C for 3 days. The crude product was purified by preparative TLC (alumina) using a mixture of 100 to 15 volume ratio of hexane-ethyl acetate as eluant to afford 1-methyl-3-phenylpiperidin-2-one (**93a**) in 56% yield.

93a :



IR (benzene) ν (co) 1640-1675 cm^{-1} br;

^{1}H NMR ($CDCl_3$) δ 1.60-2.10 (m, 4H, CH_2CH_2), 2.99 (s, 3H, NCH_3), 3.40 (m, 2H, CH_2N), 3.63 (m, 1H, CHPh), 7.11-7.33 (m, 5H, Ph);

^{13}C NMR ($CDCl_3$) δ 20.51, 30.33 (CH_2CH_2), 34.84 (NCH_3), 48.36 (CHPh), 50.13 (CH_2N), 126.41, 128.26, 128.42 CH at Ph), 141.72 (q-C at Ph), 170.83 (CO);

MS (EI): m/e 189 $[M]^+$;

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40

Found: C, 75.91; H, 8.30, N, 7.61.

2.3.3.1.2 VARIATION IN REACTION CONDITIONS

Optimization experiments were carried out and followed by GC using undecane as the internal standard.

The influence of catalyst upon the reaction was studied. The reaction was carried out at 200-205^{0}C using the general procedure, but with 0.064g (0.10mmol) of triruthenium dodecacarbonyl as the second catalyst and 72mg of undecane. Work up as described above gave 1-methyl-3-piperidin-2-one in 63% yield.

The effect of temperature was studied by using the same ratio of 1-methyl-2-phenylpyrrolidine to dicobalt octacarbonyl to triruthenium dodecacarbonyl = 4 : 1 : 0.33. At temperatures ranging from 160-245^{0}C, highly regioselective carbonylation with ring expansion occurred. At 160-164^{0}C, the reaction was very slow, since after 5 days, only 9% conversion of 1-methyl-2-phenylpyrrolidine was observed by GC, with **93a** being the only piperidinone formed. At 240-245^{0}C, the reaction was fast, but the regioselectivity was lower, because the ratio of **93a** to **92a** was found to be 8 : 1 by GC-MS. Unfortunately, attempts to isolate the by-product in pure form failed.

The influence of solvent upon the reaction was examined using 4-methyl-2-pentanone instead of the less polar solvent, benzene, at 245^{0}C for 5days. While the starting material reacted nearly completely, more than 20 compounds were formed according to GC and GC-MS analysis. Among these products, only a trace amount of 1-methyl-3-phenylpiperidin-2-one was produced.

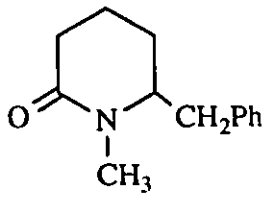
2.3.3.1.3 ATTEMPTED ENANTIOSELECTIVE CARBONYLATION OF 1-METHYL-2-PHENYLPYRROLIDINE (91a)

A mixture of 1-methyl-2-phenylpyrrolidine **91a** (0.115 g, 0.65 mmol), (R)-(+) 1,1'-bi-2-naphthol (0.086 g, 0.30 mmol), dicobalt octacarbonyl (0.051 g, 0.15 mmol), triruthenium dodecacarbonyl (0.051 g, 0.15 mmol), 40 mg undecane and benzene (6 ml) was stirred under 54 atm of carbon monoxide at 205^{0}C. After 1 day, the reaction was stopped, and GC indicated that only a trace amount of starting material was consumed. The reaction was continued for 2 more days. After work-up, 78 mg of starting material was recovered. If the same reaction was carried out for 3 days at 190-205^{0}C and at 220-230^{0}C for 2 more days using 0.062 g(0.4 mmol) of (1S, 2R, 5S)-(+)-menthol instead of (R)-(+)1,1'-bi-2-naphthol, the pure carbonylation product, 1-methyl-3-phenylpiperidin-2-one **93a** was isolated in 66% yield by using thick alumina TLC plate and a 100 : 13 hexane-ethyl acetate mixture as eluant. The product showed almost no optical activity ($[\alpha]_D^{25}$ = + 0.07, C=0.102, CH_2Cl_2).

2.3.3.2 CARBONYLATION OF 1-METHYL-2-BENZYL PYRROLIDINE (91b)

2.3.3.2.1 GENERAL PROCEDURE

The reaction was carried out at 215-220^{0}C for 3 days. The conversion of 1-methyl-2-benzylpyrrolidine **91b** was 68% (GC data). Using alumina TLC plate and a 100 : 15 mixture of hexane-ethylacetate as eluant, 1-methyl-6-benzylpiperidin-2-one (**92b**) was separated in 24% yield and its regioisomer, 1-methyl-3-benzylpiperidin-2-one (**93b**), in 15% yield.

92b : 

IR (C_6H_6) ν (co) 1645 cm^{-1};

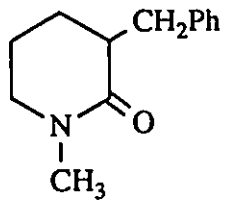
^1H NMR ($CDCl_3$) δ 1.28-1.84 (m, 4H, CH_2CH_2), 2.33 (m, 2H, CH_2CO), 2.60 (m, 2H, CH_2Ph), 2.93 (s, 3H, CH_3), 3.65 (m, 1H, CHN), 7.10-7.30 (m, 5H, Ph);

^{13}C NMR ($CDCl_3$) δ 17.31, 25.66 (CH_2CH_2), 31.97 (CH_2CO), 34.10 (NCH_3), 38.97 (CH_2Ph), 60.60 (CHN), 128.43, 128.56, 129.00, 137.91 (aromatic), 170.10 (CO);

MS (CI): m/e 204 $[M+1]^+$;

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89

Found: C, 77.02; H; 8.62; N, 6.66.

93b : 

IR (C_6H_6) ν (co) 1642 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.50-2.10 (m, 4H, CH_2CH_2), 2.32 (m, 2H, $PhCH_2$), 2.98 (s, 3H, CH_3), 3.11 (m, 1H, CH), 3.38 (m, 2H, CH_2N), 7.10-7.32 (m, 5H, Ph);

^{13}C NMR ($CDCl_3$) δ 21.90, 29.92 (CH_2CH_2), 32.92 (NCH_3), 38.24 (CH_2Ph), 42.09 (CHCO), 52.18 (NCH_2), 128.22, 128.32, 129.21, 137.40 (aromatic),

(CH_2Ph), 42.09 (CHCO), 52.18 (NCH_2), 128.22, 128.32, 129.21, 137.40 (aromatic), 169.70 (CO);

MS (EI): m/e 203 $[M]^+$.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89

Found: C, 76.21; H, 8.33; N, 6.97.

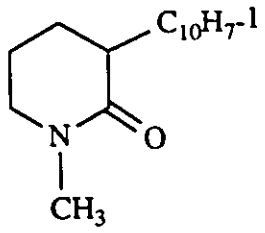
2.3.3.2.2 VARIATION IN REACTION CONDITIONS

When the carbonylation reaction described in section 2.3.3 was repeated in the presence of 0.064 g(0.10 mmol) of triruthenium dodecacarbonyl for 4 days, **92b** and **93b** were obtained in a ratio of 5 : 1.5. If 0.15 mmol of triruthenium dodecacarbonyl were added to the reaction mixture at 220^{0}C for 6 days, the ratio of **92b** to **93b** decreased to 2 : 1. At higher temperature, 245-250^{0}C, using the ratio of pyrrolidine : $Co_2(CO)_8$: $Ru_3(CO)_{12}$ = 6 : 1 : 1, the ratio of products **92b** to **93b** was nearly 1 : 1.

2.3.3.3 CARBONYLATION OF 1-METHYL-2-(1'-NAPHTHYL) PYRROLIDINE (91e)

Using the general procedure but adding 0.064 g(0.10 mmol) of triruthenium dodecacarbonyl at 220^{0}C for 3 days, **91e** reacted with CO to give only traces of product. Changing the ratio of pyrrolidine to dicobalt octacarbonyl to triruthenium dodecacarbonyl to 14 : 3 : 2, at 205-210^{0}C(4 days), gave 1-methyl-3-1'-naphthylpiperidin-2-one (**93e**) in 6% yield.

93e :



White solid, m. p.: 146-148^{0}C;

IR ($CHCl_3$) ν (co) 1683 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.45-1.98 (m, 4H, CH_2CH_2), 3.01 (s, 3H, NCH_3), 3.45 (m, 2H, CH_2N), 3.69 (t, 1H, CHAr), 7.24-8.08 (m, 7H, ArH);

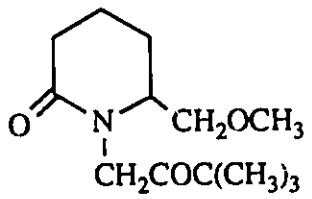
^{13}H NMR ($CDCl_3$) δ 17.97, 22.40 (CH_2CH_2), 34.20 (NCH_3), 44.02 (CH), 53.21 (CH_2N), 123.91, 125.64, 125.94, 126.42, 127.73,128.26,134.00, 145.20 (aromatic), 170.03 (CO);

MS (EI): m/e 239 $[M]^+$ base peak.

2.3.3.4 CARBONYLATION OF 91c, 91d USING THE GENERAL PROCEDURE

The reaction of **91d** with CO was carried out at 220^{0}C for 3 days to give **92d** in 61% isolated yield with the remainder being unreacted starting material.

92d :



IR (C_6H_6) ν (CO) 1647 cm^{-1}, 1720 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.10 [s, 9H, $C(CH_3)_3$], 1.60-1.82 (m, 4H, CH_2CH_2), 2.35 (m, 2H, CH_2CON), 3.20 (s, 3H, OCH_3), 3.25 (m, 1H, CHN), 3.35 (m, 2H, OCH_2), 4.19, 4.63 (d each, 2H, NCH_2CO (J=18Hz));

^{13}C NMR ($CDCl_3$) δ 18.18, 25.75 (CH_2CH_2), 26.45 ($C(CH_3)_3$), 31.76 (CH_2CO), 43.14 (q-C), 51.20 (NCH_2), 57.45 (CHN), 58.90 (OCH_3), 75.42 (CH_2O), 170.48 (NCO), 209.66 (CO);

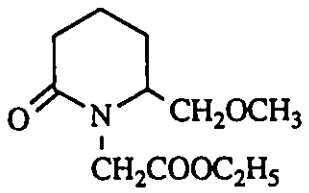
MS (EI): m/e 156 $[M-COC(CH_3)_3]^+$;

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80

Found: C, 64.72; H, 9.80; N, 6.04.

Reaction of 1-$CH_2COOC_2H_5$-2-methoxymethylpyrrolidine (**91c**) with CO at 220-225^{0}C for 3 days gave the ring expansion product **92c** in 49% yield.

92c :



Light yellow-green liquid;

IR (C_6H_6) ν (CO) 1645 cm^{-1}, 1735 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.18 (t, 3H, CH_3CH_2); 1.55-1.80 (m, 4H, CH_2CH_2); 2.28 (m, 2H, CH_2CO); 3.10 (m, 1H, CHN); 3.15 (s, 3H, OCH_3); 3.20-3.35 (complex, 4H, $2CH_2O$); 4.21, 4.35 (d, each, 2H, J=18Hz, NCH_2CO);

MS (EI): m/e 156 $[M-COOC_2H_5]^+$ base peak.

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62 H, 8.35 N, 6.11

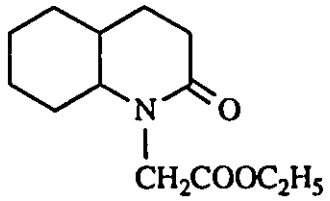
Found: C, 57.98 H, 8.90, N, 5.89

2.3.3.5 CARBONYLATION OF 94a and 94b

2.3.3.5.1 GENERAL PROCEDURE

Carbonylation of **94a** at 200-210^{0}C for 3days afforded **95a** in 46% yield after work-up by TLC (Al_2O_3) using 5/1 of hexane-acetone as developer.

95a :



IR (C_6H_6) ν (CO) 1650 cm^{-1}, 1740 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.20 (t J=7Hz, 3H, CH_3), 1.10 (m, 10H, protons at C4-C8), 2.40 (m, 2H, $NCOCH_2$), 2.47 (m, 1H, H4'), 2.96 (m, 1H, H8'), 4.12 (q J=7Hz, 2H, OCH_2), 4.00, 4.32 (d each, 2H, NCH_2COO (J=18Hz));

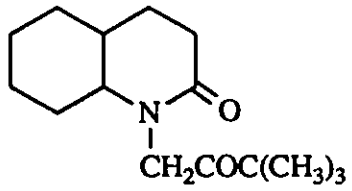
^{13}C NMR ($CDCl_3$) δ 14.20 (CH_3), 24.95, 25.30, 27.80, 31.23, 32.10, 32.50 (C3-C8), 40.91 (C4'), 53.70 (NCH_2CO), 61.00 (OCH_2), 62.30 (C8'), 169.60, 171.22 (CO);

MS (EI): m/e 239 $[M]^+$, 166 $[M\text{-}COOC_2H_5]^+$ base peak;

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85

Found: C, 64.97; H, 8.64; N, 5.89.

Application of the ring expansion carbonylation reaction for **94b** gave **95b** in 49% yield using the same isolation procedure as that described for 9a.

95b : 

IR (neat) ν (CO) 1645 cm^{-1}, 1720 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.08-1.83 (m, 10H, protons at C4-C8), 1.15 (s, 9H, $3CH_3$), 2.43 (m, 2H, $NCOCH_2$), 2.46 (m, 1H, H4'), 3.01 (m, 1H, H8'), 4.16, 4.67 (d each, 2H, NCH_2CO(J=18Hz));

^{13}C NMR ($CDCl_3$) δ 24.96, 25.29, 27.81, 31.23, 32.10 (C4-C8), 26.55 ($3CH_3$), 32.44 ($NCOCH_2$), 40.88 (C4'), 43.34 (q-C), 46.69 (NCH_2CO), 62.02 (C8'), 171.06, 209.85 (CO);

MS (EI): m/e 251 $[M]^+$, 166 $[M\text{-}COC(CH_3)_3]^+$ base peak.

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67 H, 10.03 N, 5.57

Found: C, 72.55 H, 10.31 N, 6.01

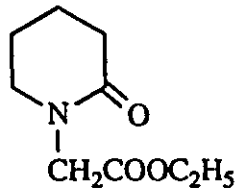
2.3.3.5.2 USING $Co_2(CO)_8/Ru_3(CO)_{12}$ (2/1) AS CATALYST

Using the same carbonylation conditions as described for reaction of **94a**, except for the use of the mixed $Co_2(CO)_8/Ru_3(CO)_{12}$ (0.30 mmol/0.15 mmol) catalyst system, ethyl 1-perhydroindolyl acetate was converted to **95a** in 96% crude yield and isolated as pure sample in 79% yield.

2.3.3.6 CARBONYLATION OF ETHYL 1-PYRROLIDINEACETATE (91f)

When a mixture of 0.207 g (1.32 mmol) of ethyl (1-pyrrolidyl)acetate (**91f**), 0.103 g(0.30 mmol) of dicobalt octacarbonyl, 0.071 g of undecane and 10 ml of dry benzene was heated at 215-220^{0}C for 3 days under 54 atm of carbon monoxide, the conversion of compound **91f** was 57% (by GC analysis). After work-up, the carbonylation product **92f** was isolated in 30% overall yield by alumina thin-layer chromatography.

92f :



IR (C_6H_6) ν (CO) 1648 cm^{-1}, 1740 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, CH_3CH_2), 1.71-1.86 (m, 4H, CH_2CH_2), 2.41 (m, 2H, CH_2CO), 3.34 (m, 2H, NCH_2ring), 4.10 (q, 2H, OCH_2), 4.08, 4.17 (d each, 2H, NCH_2CO(J=16Hz));

^{13}C NMR ($CDCl_3$) δ 14.23 (CH_3), 21.40, 23.21 (CH_2CH_2), 32.11 (CH_2CO), 48.67 (NCH_2ring), 54.23 (NCH_2CO), 61.13 (OCH_2), 169.00, 170.31 (CO);

MS (EI): m/e 185 $[M]^+$;

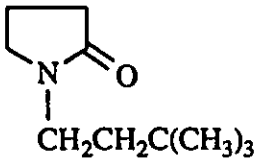
Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56

Found: C, 58.29; H, 8.41; N, 7.90.

Repetition of the reaction with added triruthenium dodecacarbonyl (0.095 g, 0.15 mmol) as the second catalyst gave **92f** in 67% yield.

2.3.3.7 ATTEMPTED CARBONYLATION OF 91g USING $Co_2(CO)_8/Ru_3(CO)_{12}$ AS CATALYST

A mixture of 0.223g (1.32mmol) of **91g**, 0.103g (0.30mmol) of dicobalt octacarbonyl, 0.089g (0.14mmol) of triruthenium dodecacarbonyl, and 10ml of dry benzene was heated at 210-220^{0}C for 3days under 54atm of carbon monoxide, and workup was carried out by alumina column chromatography with CH_2Cl_2/hexane and then ethyl acetate as the eluant. The unexpected product **119a** was isolated in 72% yield. The structure of **119a** was determined by spectral data (including COSY and HETCOR).

119g : 

IR (C_6H_6) ν (CO) 1656cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.92 (s, 9H, $C(CH_3)_3$), 1.39 (AA'XX', 2H, $CH_2C(CH_3)_3$), 2.00 (m, 2H, protons at C-4), 2.35 (t, 2H, CH_2CO), 3.26 (AA'XX', 2H, NCH_2), 3.35 (t, 2H, NCH_2 ring);

^{13}C NMR ($CDCl_3$) δ 17.93 (C4), 29.33 ($C(CH_3)_3$), 29.80 ($C(CH_3)_3$), 31.22 (C3), 39.17 ($CH_2C(CH_3)_3$), 40.45 (NCH_2), 47.06 (C5), 174.56 (CO);

MS (EI): m/e 169 $[M]^+$;

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.275

Found: C, 72.05; H, 11.60; N, 8.50

Chapter 3

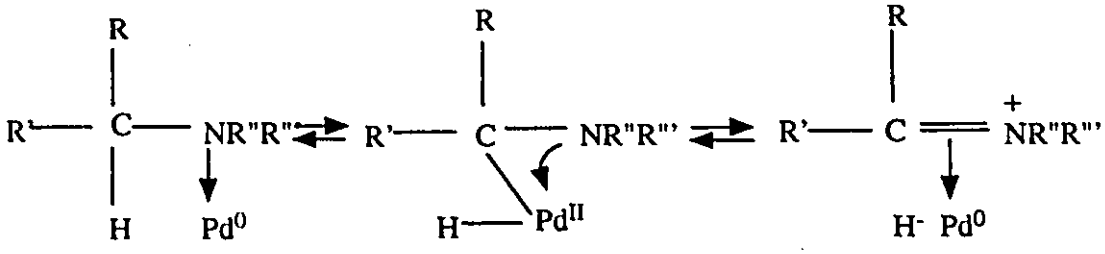
Metal Catalyzed Rearrangement of Alkyl(aryl) (N-Heteryl)Methyl Ketones to the Corresponding N-Alkyl(arylalkyl) Lactams

3.1 INTRODUCTION

The subject of metal-catalyzed rearrangements has attracted considerable attention in recent years.[115,116] Several topics related to rearrangements have been reviewed. These include silver(I)-promoted,[117] organoaluminum compounds and their Group III analogues,[118] and organomagnesium rearrangements,[119] aryl migration in organometallic compounds of the alkali metals,[120] fluxional and non-rigid behaviour of organo-transition metal π-complexes,[121] σ-π-rearrangements of organo-transition metal complexes including their role in catalysis,[115,116,122,123] molecular rearrangements in polynuclear transition metal complexes,[124] rearrangements involving ring-opening and ring-closure,[115,116] intramolecular exchange, isomerizations for a wide variety of monodinuclear and cluster organometallic compounds,[125,126] and mechanisms of skeletal rearrangements of hydrocarbons on metal.[127]

In the recent work on metal-catalyzed rearrangements, the palladium-catalyzed exchange reaction of tertiary amines has been reported.[128] The initial step in this reaction may be insertion of palladium into a carbon-hydrogen bond adjacent to nitrogen leading to a highly active iminium ion complex (Scheme 5).

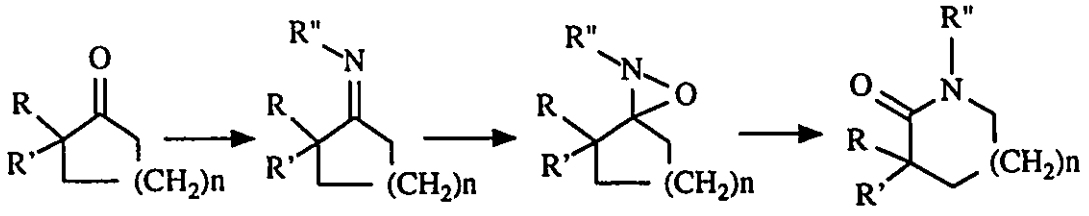
Scheme 5



110 **111** **112**

Herein we wish to demonstrate a novel rearrangement of alkyl(aryl) (N-heteryl)methyl ketones to the corresponding N-[β-aryl(alkyl)ethyl] lactams catalyzed by the dual catalytic system $[Co_2(CO)_8/Ru_3(CO)_{12}]$ in good yield. The rearrangement reaction is a process of considerable potential. The present method complements the nice work by Kuehne and Parsons[129] on the photochemical or thermal rearrangement of oxaziridines as a route to β-arylations (particularly with an indole) of the ethyl amine chain (Scheme 6, R" = β-arylethyl).

Scheme 6



113 **114** **115** **116**

This route is of synthetic potential for the synthesis of alkaloids and particularly for the synthesis of vincamine.

The rearrangement process involves a net oxidation at a ring carbon bonded to nitrogen. A number of such oxidations, including electrochemical processes, have been reported in the literature.[130]

3.2 RESULTS AND DISCUSSION

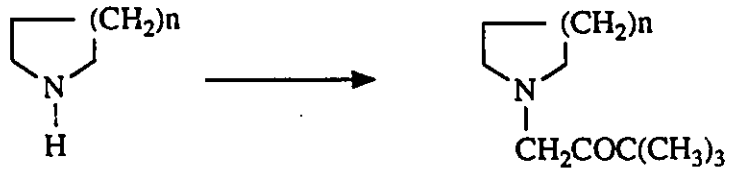
3.2.1 THE NEW CATALYTIC REARRANGEMENT

As mentioned in Chapter 2, the expected ring expansion occurred when 1-pyrrolidinyl-3,3-dimethyl -2-butanone (**91g**) was carbonylated in the presence of dicobalt octacarbonyl, affording **92g** in 42% yield.[104] However, when the reaction was repeated using both $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ as catalysts, 1-(3,3-dimethyl-1-butyl)pyrrolidin-2-one (**119a**) was isolated in 72% yield, with none of the ring expansion product (**92/93**) formed in the reaction. No reaction occurs with $Ru_3(CO)_{12}$ as the only catalyst. Fascinated by the mixed-metal $Co_2(CO)_8/Ru_3(CO)_{12}$ system catalysis of the remarkable carbonylation and ring expansion of oxetanes, thietanes[34] and pyrrolidines[104], we asked ourselves why in the case of 1-pyrrolidinyl-3,3-dimethyl-2-butanone (**91g**) did the surprising product 1-(3',3'-dimethylbutyl)pyrrolidin-2-one (**119a**) form. Further, the question arises as to what would happen with other (heteryl)methyl ketones which were treated with the same procedure as that used for ketone **91g**. Would they react and if so, could the rearrangement reaction be extended to other systems? In that event, the question of the origin of the carbonyl group (i.e. the carbon monoxide atmosphere or the carbonyl of the ketone in the molecule) arises. Is there carbon skeletal exchange or just oxygen-hydrogen positional exchange and if so, what mechanism could be considered for this novel metal-catalyzed rearrangement?

These intriguing questions prompted the following investigations.

3.2.2 THE REARRANGEMENT OF [(5-8 MEMBERED NITROGEN -CONTAINING HETEROCYCLE)-1-YL]METHYL KETONES

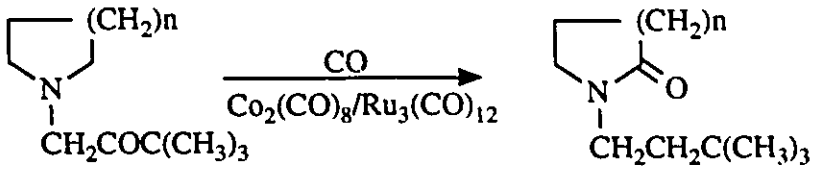
In order to study the transformations of different sized nitrogen heterocycle systems under the rearrangement conditions, we prepared the following representative (1-heteryl)methyl ketones (**118a-d**); (see Section 2.3.2.4):



117a-d **118a-d**

a, n=1; b, n=2; c, n=3; d, n=4

The (1-pyrrolidinyl)methyl tert-butyl ketone **118** (1.32 mmol) was treated with $Co_2(CO)_8$ (0.30 mmol) and $Ru_3(CO)_{12}$ (0.14 mmol) in dry benzene (10 ml) under 54 atm of carbon monoxide. After stirring and heating at 200-220^{0}C for 3 days, the reaction affords the corresponding rearrangement product **119** in 85-87% isolated yield without even trace amounts of normal ring expansion-carbonylation products:



118b-d **119b-d**

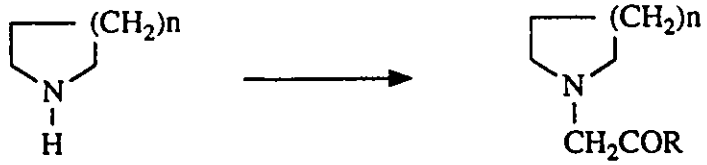
b, n=2; c, n=3; d, n=4

The structure of products (**119b-d**) was supported by spectral data (see Experimental data and discussion 3.2.5).

These results show the applicability of the rearrangement reaction to 5-8 membered-ring nitrogen heterocycles. There was no relation between ring size and the ease of the rearrangement e.g. yield of product. Further questions, such as the reaction of other substituted groups instead of the particular tert-butyl in starting molecules, naturally arose.

3.2.3 THE REARRANGEMENT OF (N-HETERYL)METHYL ARYL(OR ALKYL OTHER THAN t-BUTYL)KETONES

The new type of rearrangement reactions was extended to various sizes of heterocyclic nitrogen systems. If applicable to other ketones (e.g. aryl or other than t-butyl (N-heteryl)methyl ketones), this novel rearrangement reaction would be of general utility. For this reason, five representatives (**120a-e**) were synthesized. Compounds **120a** and **120c-e** were prepared by procedures similar to those in section 2.3.2.4 :



117b-d **120a-e**

b, n=2

c, n=3

d, n=4

a, n=2, R=Ph;

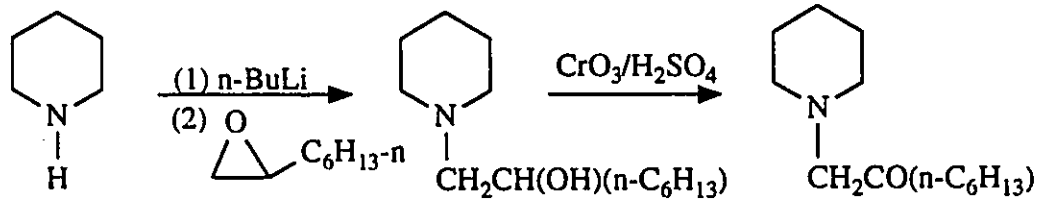
b, n=2. R=n-C_6H_{13};

c, n=2, R=2-naphthyl;

d, n=3, R=Ph;

e, n=4, R=Ph

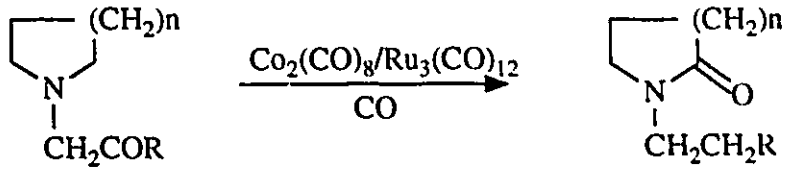
The procedure for synthesis of the 1-piperidinyl-2-octanone (**120b**) involved deprotonation of piperidine (**117b**) and subsequent reaction with 2-hexyloxirane followed by oxidation[131] of intermediate alcohol **121**. Compound **120b** was isolated in 64% total yield :



117b **121** **120b**

Interestingly, the reactions of compounds **120a-e** with CO in the presence of

$Co_2(CO)_8/Ru_3(CO)_{12}$ gave the expected rearrangement products (**122a-e**) in excellent yield (79-93%):



120a-e **122a-e**

a, n=2, R=Ph; Yield: a, 91%

b, n=2, R=n-C_6H_{13}; b, 79%

c, n=2, R=2-naphthyl; c, 88%

d, n=3, R=Ph; d, 93%

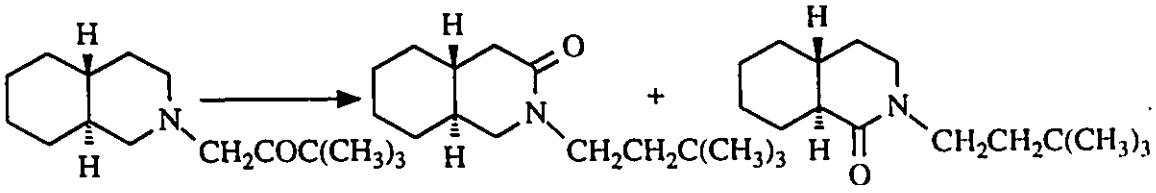
e, n=4, R=Ph e, 92%

The results demonstrate that the novel rearrangement reaction is of general utility, being applicable to heterocycles containing either aliphatic or aromatic ketone side chain groups (i.e., **120a-e**).

The next question was what would happen when two different sites both in the α-position with respect to the N atom are available for the rearrangement. It was unknown whether regioselectivity would be observed, as in the ring expansion carbonylation reaction.

3.2.4 THE REGIOSELECTIVE REARRANGEMENT OF (1-PERHYDRO ISOQUINOLYL)METHYL t-BUTYL KETONE

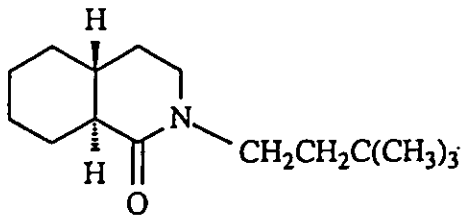
In order to determine whether the rearrangement proceeds with regioselectivity such as that observed in the general ring expansion carbonylation, (1-trans-perhydroisoquinolyl)methyl tert-butyl ketone (**123**) was prepared using the method described in Sec. 2.3.2.4. The compound **123** , on exposure to $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ under carbon monoxide, gave 1-[(3',3'-dimethyl)butyl]-perhydroisoquinolin-3-one (**124**) in 90% yield, with isomeric perhydroisoquinolin-1-one (**125**) isolated in 9% yield :



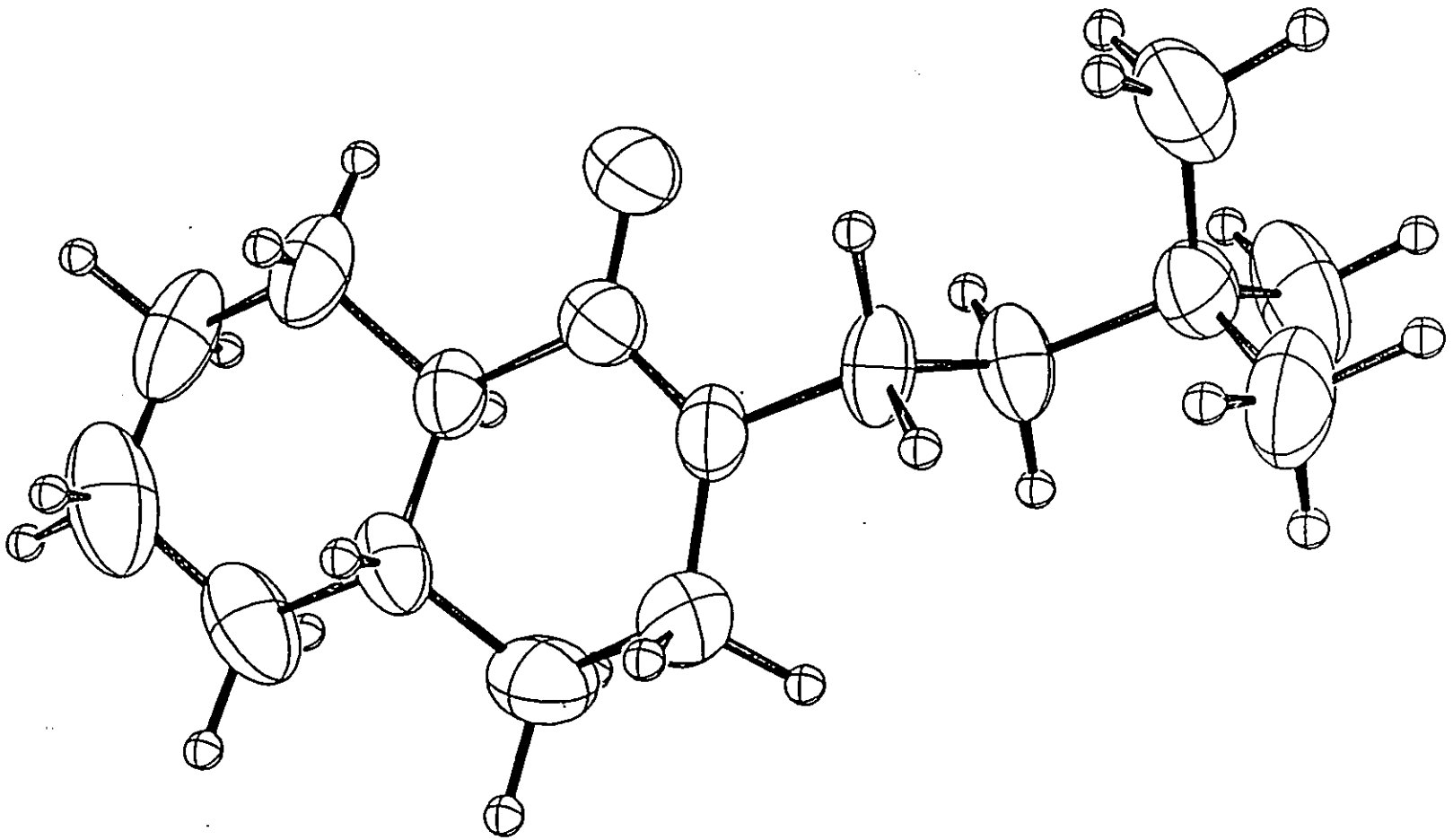
123 **124** **125**

This result demonstrated that the rearrangement process showed considerable site selectivity, namely, the rearrangement occurred mostly at the less sterically hindered site. The other useful feature of this reaction was the possibility of obtaining single crystals from the solid products. While X-ray quality crystals of **124** could not be successfully obtained, crystals of **125** were grown and an X-ray structure determination confirmed the structure which was assigned on the basis of spectral data. From the X-ray analysis data it could be found that the two transfused C-H bonds of **123** were retained in **125**. The ORTEP drawing is shown in **Fig. 1**:

FIGURE 1 :



ORTEP DRAWING OF COMPOUND 125



3.2.5 ANALYSIS OF SPECTRAL DATA OF REARRANGEMENT PRODUCTS

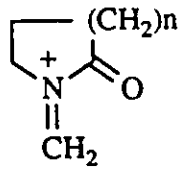
Upon carefully studying the spectral data of these unexpected products, we have found many similarities and trends with change in the structures of starting compounds. A discussion of these similarities and regularities is meaningful even though the final correct structures have already been verified.

3.2.5.1 IR AND MASS SPECTRAL DATA

All the IR ($\nu_{(CO)}$ cm^{-1} in $CDCl_3$) and MS (m/e, EI at 70ev) spectral data obtained from these rearrangement products are listed in Table 5.

The IR spectrum of the rearrangement product shows $\nu_{(CO)}$ at 1656 cm^{-1} ($CDCl_3$) for the five-membered ring lactam; 1626-1630 cm^{-1} for the six-membered ring lactams (products **119b**, **122a-c**); 1622-1628 cm^{-1} for the seven-membered ring (products **119c** and **122d**) systems, and 1622 cm^{-1} for eight-membered rings (products **119d** and **122e**). Thus, when the ring size is smaller than six, the wave number increases with decreasing ring size. But with an increase in ring size, the C=O vibrational frequency decreases. The regularities observed in the IR spectra of lactams are therefore similar to those known for lactones[132].

As in the case of piperidin-2-ones (see Section 2.2), all the parent ions appeared in the mass spectra in various intensities depending on the stability of the molecular ions. In most cases, the iminium ions (**126**) appeared as the most intense peaks.



126

Despite different substituents on the molecule, the spectra of six-membered ring lactams e.g., **119b**, **122a-c** all showed a base peak at m/e = 112, seven-membered ring lactams e.g., **119c**, **122d** at m/e = 126, and eight-membered rings **119d**, **122e** at m/e = 140, the difference being only the number of additional CH_2 groups in the ring. The same trends are also observed in the case of the corresponding starting compounds.

Table 5 IR and MS data of rearrangement products

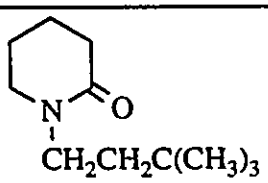
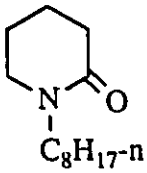
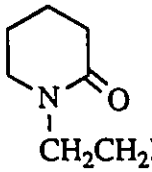
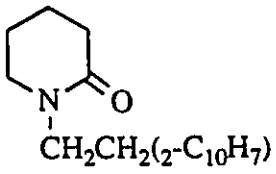
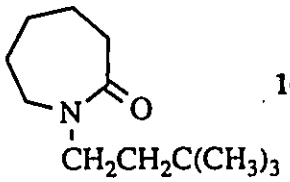
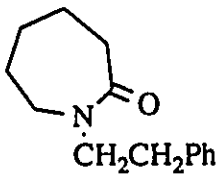
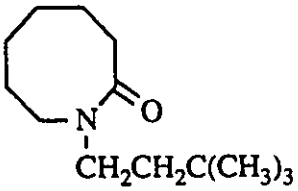
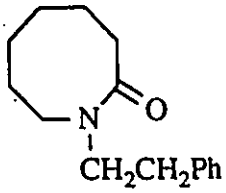
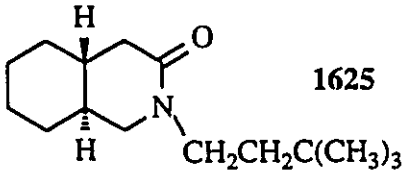
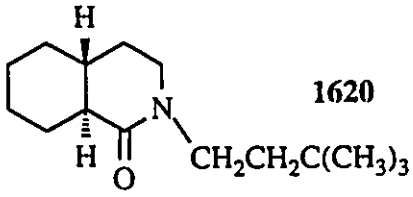
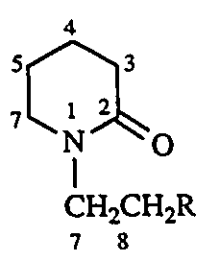
Code of product	Structure of product	IR $\nu_{(CO)}cm^{-1}$	MS (EI) m/e	
			$[M]^+$	Base peak
119b		1630	183	112 $[M-CH_2C(CH_3)_3]^+$
122b		1624	211	112 $[M-C_7H_{15}\text{-}n]^+$
122a		1626	203	112 $[M-CH_2Ph]^+$
122c		1630	253	154 $[CH_2=CH\text{-}2\text{-}C_{10}H_7]^+$
119c		1628	197	126 $[M-CH_2C(CH_3)_3]^+$
122d		1626	217	126 $[M-CH_2Ph]^+$

Table 5 IR and MS data of rearrangement products (cont'd)

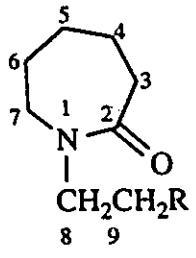
Code of product	Structure of product	IR $\nu_{(CO)}cm^{-1}$	MS (EI) m/e	
			$[M]^+$	Base peak
119d		1622	211	140 $[M-CH_2Ph]^+$
122e		1622	231	140 $[M-CH_2Ph]^+$
124		1625	237	180
125		1620	237	129

3.2.5.2 ^{1}H NMR AND ^{13}C NMR SPECTRAL DATA (HETCOR, COSY)

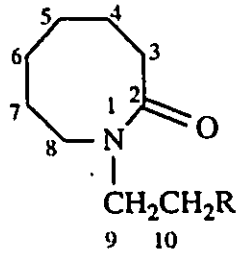
In order to assign the spectral data to exact positions of proton and carbon in each individual molecule, COSY and HETCOR spectra were also run for most of these compounds. For convenience, we numbered the rings as follows:



127



128

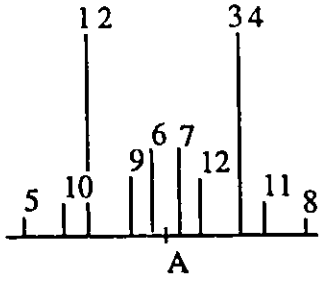


129

The ^{1}H NMR (including COSY and HETCOR) obtained from all the rearrangement products is listed in Table 6.

The most characteristic coupling pattern is the appearance of the AA'XX' coupling pattern at considerably different δ values of the protons on the CH_2CH_2 group of the side chain of compound **119a-d**. The difference in chemical shift value of δ_X and δ_A is between 1.86-1.97 ppm, due to the difference of the chemical environment of these two methylene protons.

An entire AA'XX' spectrum contain 24 lines. the 12 transitions of the A spectrum form a group centrosymmetric about υ_A :



The 1,2 and 3,4 are always degenerate, and together will always contain half the intensity of the A spectrum. The following is one example of this AA'XX' coupling pattern from the proton NMR spectrum of compound **119b (Fig. 2)**.

The AA'XX' coupling patterns disappeared on changing the substituent from a t-butyl (**119b,c,d**) to phenyl (**122b,e**) or naphthyl (**122c**) group, because of the decrease in the chemical shift between the two protons on each of the methylene groups to come AA'BB' coupling patterns.

Table 6 ^{1}H NMR spectral data of rearrangement products

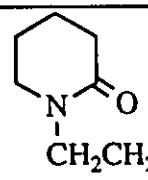
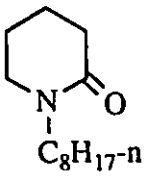
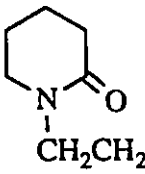
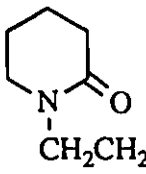
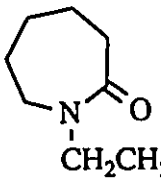
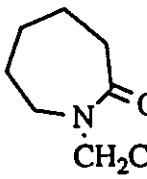
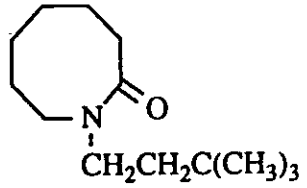
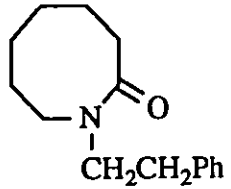
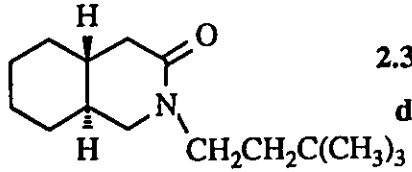
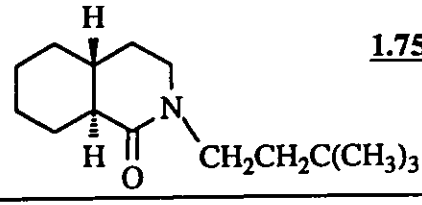
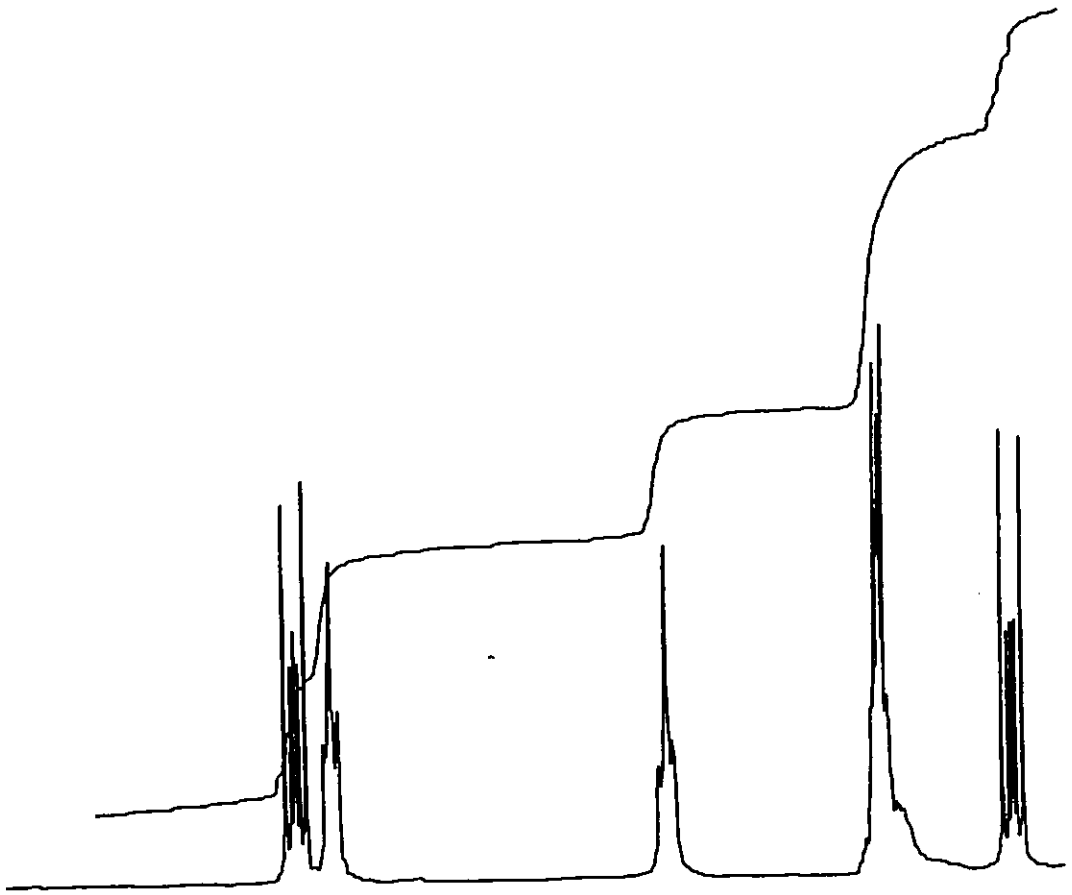
Code of product	Structure of product	^{1}H NMR (ppm) 3	4	5	6	7	8	9	10	R
119b		2.33 t	1.76	1.74 m	3.22 t	3.33 XX'	1.40 AA'			0.91 s CH_3
122b		2.33 t	1.75	1.74 m	3.23 dd	3.30 dd	1.49 m			1.15-1.45 m 0.84 t CH_3
122a		2.34 t	1.68	1.67 m	3.07 t	3.56 AA'	2.84 BB'			7.23 m Ph
122c		2.37 t	1.70	1.65 m	3.08 t	3.63 AA'	3.02 BB'			7.77 (3H) d 7.45 (4H) m
119c		2.46 t	1.62	1.65 m	1.34	3.27 t	3.34 XX'	1.37 AA'		0.90 s CH_3
122d		2.47 t	1.62	1.53 m	1.48	3.24 m	3.54 AA'	2.78 BB'		7.24 m Ph

Table 6 ^{1}H NMR spectral data of rearrangement products (cont'd)

Code of product	Structure of product	^{1}H NMR (ppm)								
		3	4	5	6	7	8	9	10	R
119d		2.40 t	1.72 m	1.45	1.43 m	1.58	3.36 t	3.24 XX'	1.38 AA'	0.86 s CH_3
122e		2.46 t	1.75 m	1.48	1.41 m	1.57	3.31 t	3.49 AA'	2.85 BB'	7.22 m Ph
124		2.38 dd	1.74	1.59	1.41 m	1.32	3.29 dd			2.88 CH m; 1.93 0.90 s CH_3; 3.09 t; 1.72 t
125		1.75	1.63	1.50 m	1.30	1.38	3.26 m			1.37 2.37 CH m; 0.90 s CH_3; 3.38 3.22 m H_a H_b; 1.66 m



VARIAN XL-300
SPECTRAL LINES FOR TH= 8 19
RFL= 2528.6 RFP= 2171.6

INDEX	FREQ	PPM	INTENSITY
01	2172.01	7.241	216.741
02	1006.95	3.357	61.129
03	1002.01	3.341	36.113
04	998.60	3.329	40.684
05	995.12	3.318	36.012
06	990.19	3.301	65.009
07	975.35	3.252	23.313
08	973.69	3.246	22.391
09	969.24	3.231	51.253
10	967.34	3.225	28.191
11	963.19	3.211	28.231
12	703.47	2.345	19.351
13	697.61	2.326	53.383
14	692.13	2.308	22.341
15	532.94	1.777	28.917
16	531.82	1.773	28.621
17	529.52	1.765	84.524
18	525.91	1.753	73.604
19	522.87	1.743	90.479

FIGURE 2 AA'XX' COUPLING PATTERN IN ^{1}H NMR SPECTRUM OF COMPOUND 119b

The ^{13}C NMR spectral data are listed in Table 7.

The range of ^{13}C chemical shifts of the carbon atoms in lactams of various ring size have little effect on their substituents and structures. In six-membered ring lactams the carbonyl carbon resonances at δ 169.09-171.39 ppm, are observed at a higher field than those in seven-membered (δ 174.44-174.62 ppm) and eight-membered ring lactams (δ 175.35-175.58 ppm). Six-membered ring lactams with t-butyl and n-octyl groups show carbonyl carbon resonances at 169.27 and 169.37 ppm respectively. These values are somewhat higher than those observed in ^{13}C spectra of six-membered lactams with phenyl and 2-naphthyl group in the side chain (δ 169.99 and 169.77 ppm respectively). Similar results also appeared in the spectra of seven- and eight-membered lactams. These differences average around 0.2-0.7 ppm.

COSY and HETCOR spectra are most helpful for assigning the correct structures. For COSY and HETCOR spectra of 1-(3',3'-dimethylbutan-1-yl) -piperidin-2-one (**119b**), see **Fig. 3** and **Fig. 4**. From these data the exact assignment of protons and carbon at each position can be achieved.

Table 7 ^{13}C NMR spectral data of rearrangement products

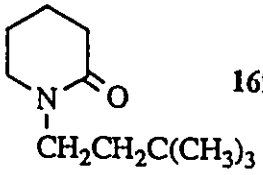
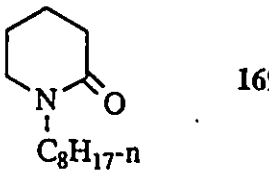
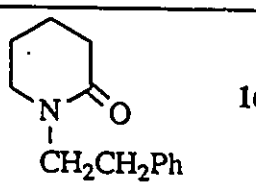
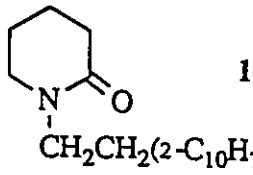
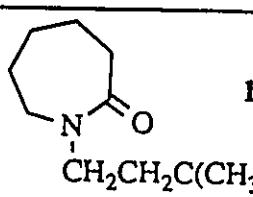
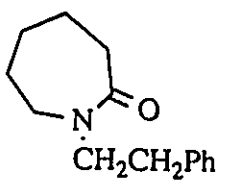
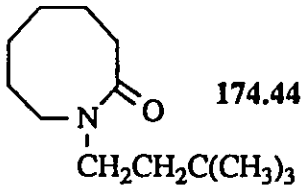
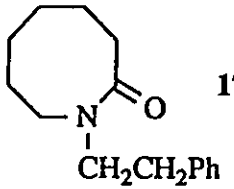
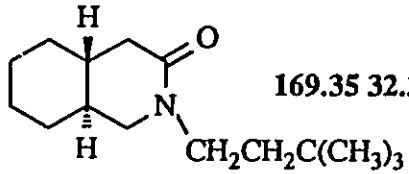
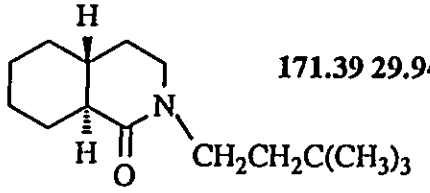
Code of product	Structure of product	^{13}C NMR (ppm) 2	3	4	5	6	7	8	9	10	R
12b	 $CH_2CH_2C(CH_3)_3$	169.29	32.16	23.07	21.19	47.38	43.53	39.90			29.49 qC 29.03 CH_3
14b	 C_8H_{17}-n	169.37	32.25	21.34	23.22	47.70	47.11	26.97			37.71 29.31 29.13 26.86 22.55 9-13 13.99 CH_3
14a	 CH_2CH_2Ph	169.99	32.09	21.01	22.95	48.60	49.31	33.32			139.31 qC 128.82 128.40 Ph-C 126.33
14c	 $CH_2CH_2(2\text{-}C_{10}H_7)$	169.67	32.35	21.12	23.15	48.75	49.29	33.67			136.77 133.51 132.11(qC)127.96 127.93 127.88 127.54 127.38 127.11 125.31
12c	 $CH_2CH_2C(CH_3)_3$	175.35	37.15	23.18	28.56	29.80	49.30	44.73	41.01		29.45 qC 29.06 CH_3
14d	 CH_2CH_2Ph	175.58	37.51	29.89	23.33	28.45	50.41	50.61	34.49		139.26 qC 128.77 128.30 Ph 126.54

Table 7 ^{13}C NMR spectral data of rearrangement products (cont'd)

Code of product	Structure of product	^{13}C NMR (ppm) 2	3	4	5	6	7	8	9	10	R
12d		174.44	33.81	28.36	25.99	24.14	28.46	46.73	41.82	40.69	29.18 qC 29.02 CH_3
14e		174.62	33.92	28.59	26.09	24.21	29.18	47.60	47.62	34.14	(Ph-C:139.42 qC 128.68 128.30 126.09)
16		169.35	32.38	29.84	29.33	28.92	25.18	53.46			36.98 38.32(CH) 43.29 39.87 29.53 qC 29.06 CH_3
17		171.39	29.94	27.14	26.16	25.38	33.20	46.80	43.69	39.91	46.94 38.02(CH) 29.65 qC 29.05 CH_3

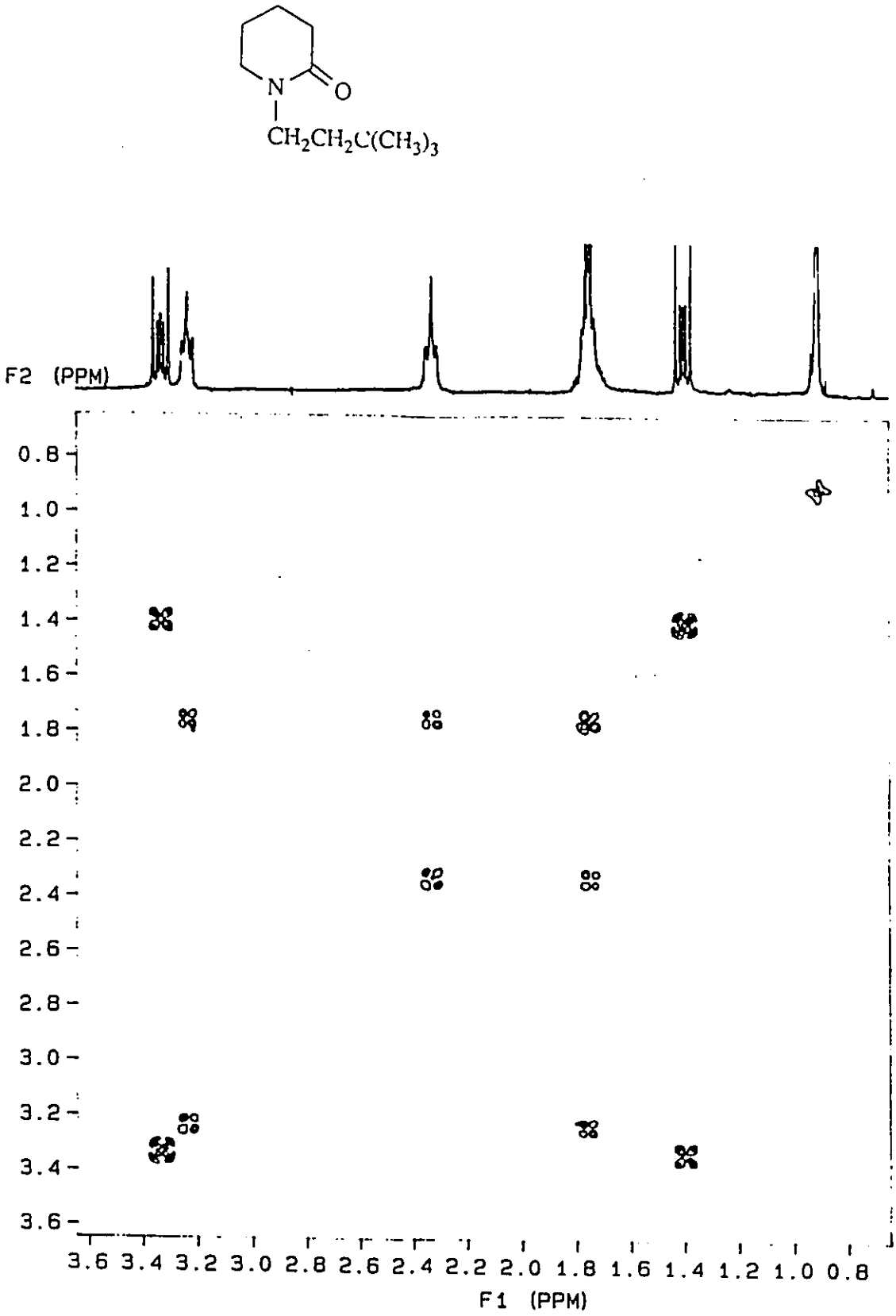


FIGURE 3 COSY SPECTRUM OF COMPOUND 119b

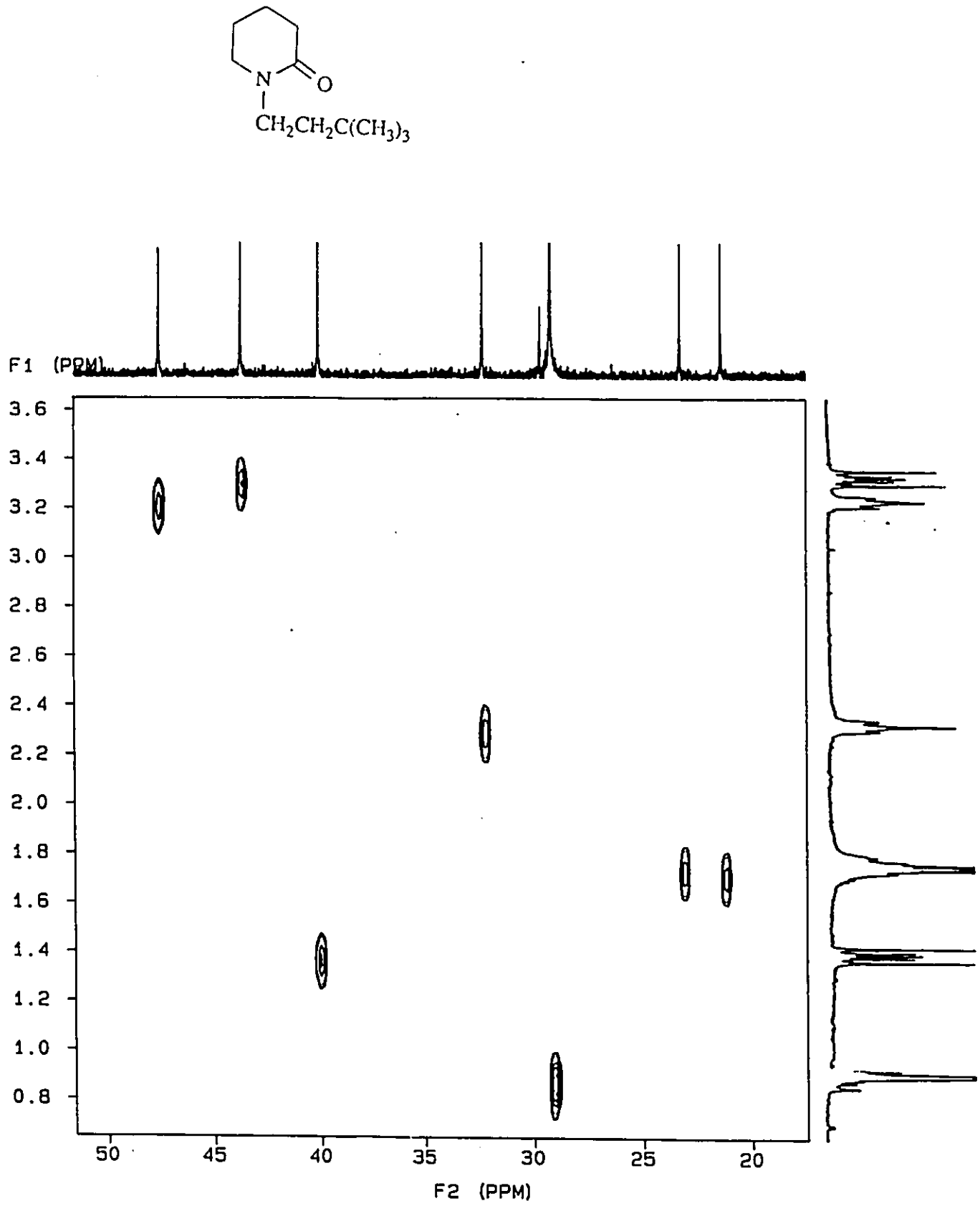


FIGURE 4 HETCOR SPECTRUM OF COMPOUND 119b

3 .2.6 Mechanistic Studies of the Novel Rearrangement

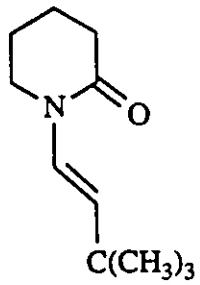
In order to study the mechanism of the novel rearrangement reaction, 1-piperidinyl-2,2-dimethylbutan-2-one (**118b**) was used as a model in the following series of experiments.

3.2.6.1 BLANK REACTION AND REACTION IN THE PRESENCE OF DIFFERENT CATALYSTS

A mixture of 1 mmol of **118b** and 42 mg of undecane (internal standard) in 8 ml of dry benzene was prepared under 600 psi of carbon monoxide and heated at 230-235^{0}C for 3 days. After the reaction was stopped, the mixture was analyzed by GC and GC-MS. Greater than 95% starting material was recovered when the reaction was effected in the absence of a metal complex (neither rearrangement nor ring expansion carbonylation products).

To this unchanged system, $Ru_3(CO)_{12}$ (0.12 mmol) was added and the mixture was kept under the same conditions for 2 days. The reaction mixture was worked up, and 1-(3',3'-dimethylbuten-1-yl)-piperidin-2-one (compound **130**) was isolated in 13% yield.

The remainder of the reaction mixture consisted of unchanged starting material. If cobalt (III) 2 ,4-pentanedionate, $Co(C_5H_7O_2)_3$, was used with $Ru_3(CO)_{12}$ as catalyst, the reaction of **118b** with CO gives **119b** in only 26% isolated yield and many by-products such as 1-formylpiperidine and 1-acetylpiperidine.



130

These results indicate that the novel rearrangement reaction occurs smoothly only in the presence of $Co_2(CO)_8$ and $Ru_3(CO)_{12}$.

3.2.6.2 REACTION WITH LABELLED CARBON MONOXIDE(^{13}CO)

In order to determine whether the carbonyl group of the lactam comes from carbon monoxide via the metal carbonyl complexes or from the carbonyl of the ketone of the side chain, several labelled experiments were undertaken to probe the mechanism of the rearrangement reaction. First, 500 ml of commercial ^{13}C labelled carbon monoxide sealed under 1 atm was condensed into the 45 ml stainless steel autoclave with glass liner using a special procedure (see experimental section) to obtain a pressure of 310 psi. The reaction of **118b** with Co/Ru carbonyl catalysts in a ^{13}CO atmosphere (310 psi) resulted in no incorporation of the label in the product **119b**. This was substantiated by the fact that ^{13}C NMR and MS spectra were identical to those of the unlabelled reaction product **119b**. From this result emerged the question of what would happen using only a nitrogen atmosphere.

3.2.6.3 REACTION UNDER NITROGEN PRESSURE

The reaction mixture of **118b** with Co/Ru carbonyl catalysts was run under identical conditions but using 180 psi of nitrogen yielded less than 5% of the rearrangement product **119b** as determined by GC. Most of the starting material was recovered and the catalyst was isolated as a black precipitate.

In order to confirm that the rearrangement reaction is not stoichiometric, a similar procedure was followed but the mixture was in the ratio **118b** : Co : Ru = 1 : 1 : 0.5, resulting in the formation of only 3% of **119b** and a black precipitate.

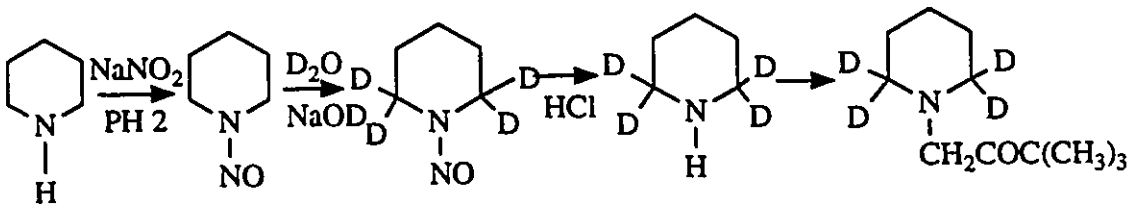
Apparently, carbon monoxide is required to generate and stabilize catalytically active species.

3.2.6.4 REACTION OF 1-(2',2',6',6'-TETRADEUTERIO PIPERIDINYL)-2,2-DIMETHYLBUTAN-2-ONE

In order to determine whether the rearrangement involves positional exchange of one oxygen and two hydrogen atoms or transition of methylene and carbonyl groups, the following labelled experiments were performed.

First, 1-(2',2',6',6'-tetradeuteriopiperidinyl)-2,2 -dimethylbutan-2-one **(134)** was prepared by the following four step procedure (Scheme 7).

Scheme 7



131 **132** **133** **134**

The first three steps followed the reference route.[133]

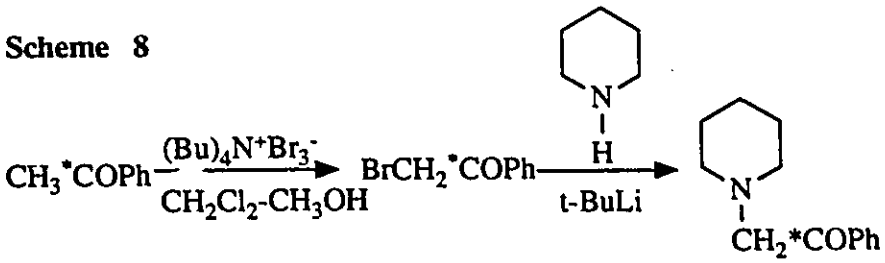
Compound **134** treated with Co/Ru carbonyls under similar reaction conditions gave a mixture of product **119b** with different degrees of deuteration on every hydrogen of the methylene groups in the molecule **119b**, proved by ^{1}H NMR, ^{2}D NMR, ^{13}C NMR and MS (EI and CI). The so-called isotopic "scrambling" phenomenon may be catalyzed by the Co/Ru carbonyls via a procedure similar to that reported in the literature.[134]

3.2.6.5 REACTION OF ^{13}C LABELLED (AT CARBONYL CARBON) 137

While the deuterium labelled experiment was unfruitful, we were gratified with the results obtained with ^{13}C-labelled reactant. The specifically ^{13}C labelled starting compound **137** was synthesized (Scheme 8) by bromination of acetophenone labelled at the carbonyl carbon, using the literature method for the unlabelled analogue.[135] Deprotonation of the α-bromoketone and reaction with piperidine

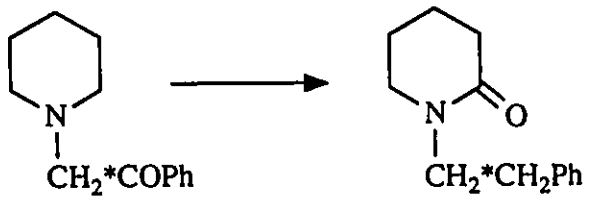
gave **137** in an overall yield of 82%.

Scheme 8



135 **136** **137**

Following the standard procedure compound **137** was used to obtain the rearrangement labelled compound **138** in good yield. The most intense resonance of the ^{13}C-NMR spectrum was at 33.44 ppm of the product **138**, while that of **137** occurred at 196.82.

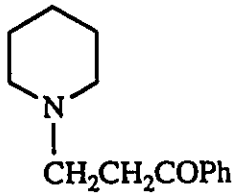


137 **138**

This result clearly provides evidence for the positional exchange of the oxygen and two hydrogen atoms. Our next question was what would happen if there were two methylene groups between the nitrogen atom and the carbonyl group.

3.2.6.6 ATTEMPTED REARRANGEMENT OF PHENYL β-PIPERIDINOETHYL KETONE 139

In order to answer this question, phenyl β-piperidinoethyl ketone (**139**) was prepared in 68% yield by dehydrochlorination of the corresponding hydrochloride.



139

The latter was obtained in 86% yield by the Mannich reaction of acetophenone, paraformaldehyde, and piperidine hydrochloride[136]. No rearrangement took place when compound **139** was treated with CO and Co/Ru carbonyls under standard conditions but decomposition products such as 1-ethylpiperidine, acetophenone, ethyl phenyl ketone were detected by GC-MS. Thus, if one more carbon atom is placed between the nitrogen atom and the carbonyl group, the rearrangement will not occur.

3.2.6.7 REACTION OF 1-(2',2',6',6'-TETRAMETHYL PIPERIDINYL)-2,2-DIMETHYLBUTAN-2-ONE (140)

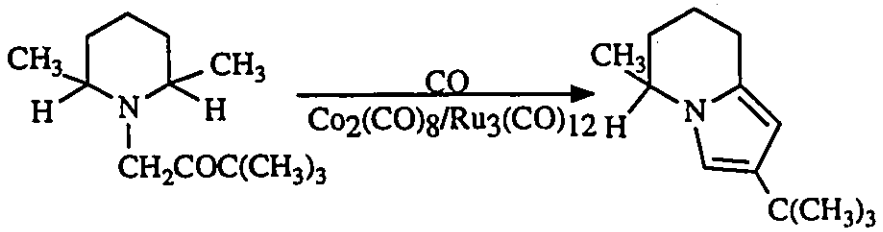
Compound **140** in which all of the hydrogen atoms at the α-carbon atoms of the heterocycle were replaced by methyl groups, was synthesized by a method similar to that in Sec.2.3.2.4. (starting from 2,2,6,6-tetramethylpiperidine).

Compound **140**, treated using the standard procedure, gave no rearrangement product, providing more evidence for the positional exchange of the oxygen and two hydrogen atoms.

What would happen if only one of the hydrogen atoms at an α-carbon atom was replaced by an alkyl group? The reaction could perhaps be stopped at some intermediate step, and it might be possible to separate these species.

3.2.6.8 REACTION OF 1-(2',6'-DIMETHYLPIPERIDINYL)-2,2-DIMETHYLBUTAN-2-ONE (141)

Compound (**141**) was prepared according to the procedure in Sec. 2.3.2.4. Surprisingly, the ketone **141** gave the bicyclic product **142** under the rearrangement conditions. The structure of **142** was determined by spectral data (see Experimental Section).



141 **142**

The studies performed on this unique cyclization reaction will be discussed in detail in Chapter 4.

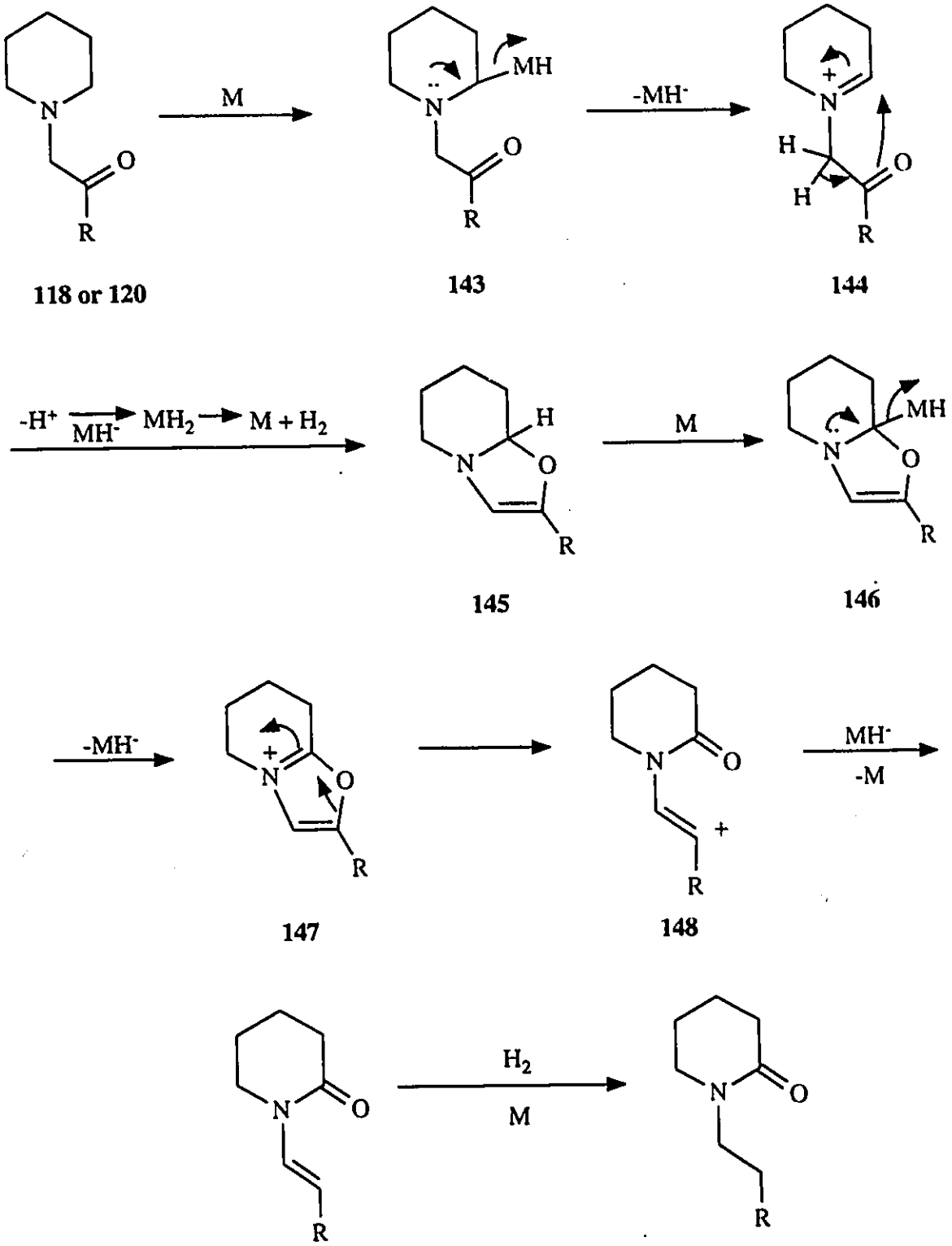
3.2.6.9 A POSSIBLE MECHANISM FOR THE REARRANGEMENT REACTION

Based on the results of the studies on the rearrangement process, a possible mechanism is outlined in Scheme 9 for **118** or **120**, n=2.

Insertion of the metal into the ring C-H bond of **118** or **120**, n=2, would give **143**. Elimination of the anionic metal hydride (to form **144**) and subsequent cyclization of the iminium salt would afford **145**. Repetition of the C-H bond insertion process (**145-146**) followed by loss of MH^- would form **147**. Ring cleavage of **147** to the vinyl cation **148** and then reaction with MH^- would afford the enamide **130**. The product would then result by metal catalyzed hydrogenation of **130**, the hydrogen having been generated during the conversion of **144** to **145**.

Evidence for this pathway comes from the $Ru_3(CO)_{12}$ catalyzed reaction of **118b**. While, as noted previously, no reaction usually occurs with $Ru_3(CO)_{12}$ as the only metal catalyst in the rearrangement reaction, **118b** did react to a limited extent, affording **130** (R = $C(CH_3)_3$) in 13% yield.

Scheme 9



118 or 120 143 144

145 146

147 148

In conclusion, the mixed-metal system $Co_2(CO)_8/Ru_3(CO)_{12}$ catalyzes the rearrangement of alkyl(aryl) (N-heteryl)methyl ketones to the corresponding N-[β-aryl(alkyl)ethyl]lactams in high yields. The rearrangement is most likely an intramolecular positional exchange process involving one oxygen from the ketone and two hydrogen atoms from the α-carbon of nitrogen heterocycle. Since $Ru_3(CO)_{12}$ was recovered after the rearrangement reaction of **118b** (The recovered red-orange crystal structure was proved by IR, MS and X-ray analysis. No Ru-Co mixed clusters were formed), the most probable explanation for this finding may be that some of the individual steps are catalyzed by ruthenium and others more effectively by cobalt (e.g. cobalt may be more effectively responsible for the last hydrogenation, due to separating the compound **113** when $Ru_3(CO)_{12}$ was the only catalyst).

If one hydrogen atom on the α-carbon of the nitrogen heterocycle is replaced by a methyl group, a unique cyclization takes place instead of rearrangement to give substituted 5,6,7,8-tetrahydroindolizine.

3.3 Experimental Section

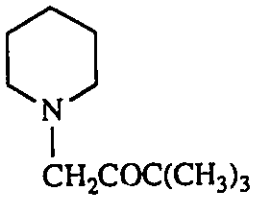
3.3.1 GENERAL COMMENTS

The general comments of Chapter 2 are applicable here.

Special pieces of equipment made by Dr. Regent Dutrisac working in Dr. Keith Preston's lab at the National Research Council, Canada, were used to transfer the commercial 500 ml of ^{13}C labelled carbon monoxide gas at 1 atm to a 45 ml autoclave and to bring the pressure to 300 psi for the purpose of reaction of 1-piperidyl-2,2-dimethylbutan-2-one **118b** under standard rearrangement conditions (See section **3.3.4.1**).

3.3.2 GENERAL PROCEDURE FOR PREPARATION OF REACTANT KETONES

The general procedure of Chapter 2, Section 2.3.2.4 is also applicable for the preparation of starting ketones such as **118b-d** and **120a,c,d,e.**

118b : 

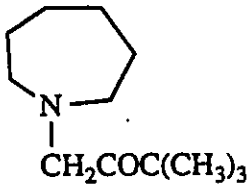
88% yield; bp 100-102^{0}C/1.0 mmHg;

IR ($CDCl_3$) ν (CO) 1715 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H, $C(CH_3)_3$); 1.31-1.49 (m, 6H, protons at C3, C4, C5); 2.28 (m, 4H, protons at C2, C6 of piperidine); 3.21 (s, 2H, NCH_2CO);

MS (EI) m/e 183 $[M]^+$, 98 $[M\text{-}COC(CH_3)_3]$ base peak.

118c :

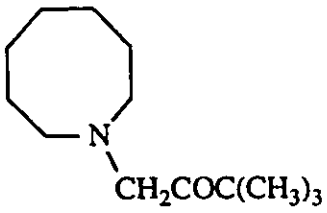


91% yield; bp 115-117^{0}C/4 mmHg;

IR ($CDCl_3$) ν (CO) 1712 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H, $C(CH_3)_3$); 1.50-1.75 (m, 8H, protons at C3-C6); 2.72 (m, 4H, protons at C2, C7); 3.59 (s, 2H, NCH_2CO);

MS (EI) m/e 197 $[M]^+$, 112 $[M\text{-}COC(CH_3)_3]^+$ base peak.

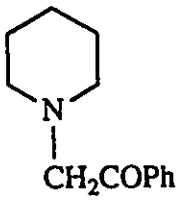
118d : 

91% yield; bp 118-119^{0}C/3.5 mmHg);

IR ($CDCl_3$) ν (CO) 1710 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, $C(CH_3)_3$); 1.53-1.68 (m, 10H, protons at C3-C7); 2.63 (m, 4H, protons at C2, C8); 3.59 (s, 2H, NCH_2CO);

MS (EI) m/e 211 $[M]^+$, 126 $[M\text{-}COC(CH_3)_3]^+$ base peak.

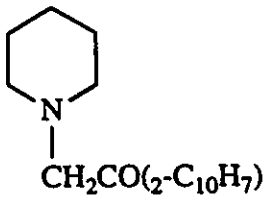
120a : 

94% yield; bp 110-112 ^{0}C/0.4 mmHg;

IR ($CDCl_3$) ν (CO) 1686 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.43-1.61 (m, 6H, protons at C3, C4, C5 of piperidine); 2.49 (m, 4H, protons at C2, C6); 3.72 (s, 2H, NCH_2CO); 7.43 (m, 3H, meta and para protons of phenyl); 7.90 (m, 2H, ortho protons);

MS (EI) m/e 203 $[M]^+$, 98 $[M\text{-}COPh]^+$ base peak.

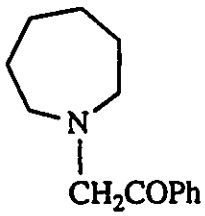
120c : 

85% yield; bp 160-162^{0}C/0.4 mmHg;

IR ($CDCl_3$) ν (CO) 1677 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.56-1.71 (m, 6H, protons at C3, C4, C5 of piperidine); 2,65 (m, 4H, protons at C2, C6); 3.96 (s, 2H, NCH_2CO); 7.51-8.40 (m, 7H, $C_{10}H_7$);

MS (EI) m/e 253 $[M]^+$, 98 $[M\text{-}CO(2\text{-}C_{10}H_7)]^+$ base peak.

120d : 

93% yield; bp 118-120^{0}C/0.4 mmHg;

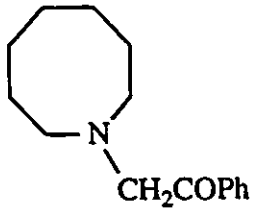
IR ($CDCl_3$) ν (CO) 1680 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.49-1.72 (m, 8H, protons at C3-C6 of azepine); 2.78 (m, 4H, protons at C2, C7 of azepine); 3.95 (s, 2H, NCH_2CO); 7.38 (m, 3H, meta

and para protons of C_6H_5); 8.01 (m, 2H, ortho protons of C_6H_5);

MS (EI) m/e 217 $[M]^+$, 112 $[M\text{-}COPh]^+$ base peak.

120e :



91% yield; bp 135-136^{0}C/0.4 mmHg;

IR ($CDCl_3$) ν (CO) 1675 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.50-1.68 (m, 10H, protons at C3-C7 of azocane); 2.68 (m, 4H, protons at C2, C8 of azocane); 3.87 (s, 2H, NCH_2CO); 7.36 (m, 3H, meta and para protons of C_6H_5); 7.95 (m, 2H, ortho protons of C_6H_5);

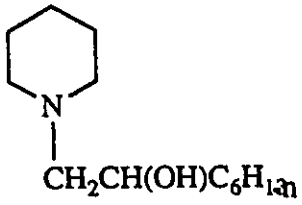
MS (EI) m/e 231 $[M]^+$, 126 $[M\text{-}COPh]^+$ base peak.

When certain 1-bromomethyl ketones were not available or the starting ketone yields were not satisfactory after using the general procedure described in Section 2.3.2.4., such as in the case of **120b**, the second procedure was used to prepare starting materials. The second process involved deprotonation and reaction with an epoxide followed by oxidation (used for the preparation of **120b**).

After generation of the anion as described in the first step of the general

procedure in Section 2.3.2.4. (1), the solution was added dropwise to a solution of 11mmol of 2-n-hexyloxirane in ether (30ml). Workup as described for procedure a afforded the alcohol (**121**) :

121 :



Oxidation of the alcohol to the requisite ketone was effected by known methodology with chromium trioxide.[131]

compound **121** :

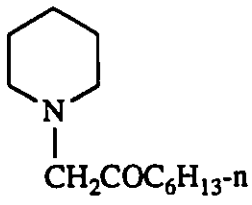
95% yield; bp 116-118^{0}C/0.4 mmHg;

IR ($CDCl_3$) ν (CO) 3413.43 cm^{-1} (OH), 2934.02 cm^{-1} (CH);

^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, CH_3); 1.17-1.48 (m, 12H, $6CH_2$); 1.57 (m, 4H, $2CH_2$); 2.30-2.48 (m, 4H, protons at C2, C6 of piperidine); 2.54 (m, 2H, NCH_2CH); 3.61 (m, 1H, CHOH);

MS (EI) m/e 213 $[M]^+$, 212 $[M-H]^+$, 98 $[M-CH(OH)C_6H_{13}\text{-n}]^+$ base peak.

120b :



67% yield; bp 115-117^{0}C/8 mmHg;

IR ($CDCl_3$) ν (CO) 1718 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.81 (t, 3H, CH_3); 1.18-1.57 (m, 14H, $CH_3(CH_2)_4$, protons at C3-C5 of piperidine); 2.20 (t, 2H, $COCH_2C_5H_{11}$); 2.32 (m, 4H, protons at C2, C6 of piperidine); 3.08 (s, 2H, NCH_2CO);

MS (EI) m/e 211 $[M]^+$, 98 $[M\text{-}COC_6H_{13}]^+$ base peak.

3.3.3 GENERAL PROCEDURE FOR REARRANGEMENT REACTION OF REACTANT KETONES

A mixture of the (N-heteryl)methyl ketone (**118** or **120**), dicobalt octacarbonyl (0.103 g, 0.30 mmol), triruthenium dodecacarbonyl (0.895 g, 0.14 mmol), and dry benzene (10 ml) was placed in an autoclave containing a glass liner and stirring bar. The autoclave was purged several times with carbon monoxide and pressurized to 54 atm. The reaction mixture was stirred at 200-220^{0}C for 3 days. The cooled autoclave was opened, and after standing in air, the mixture was filtered through Celite and the filtrate was concentrated by rotary evaporation. Purification of the resulting crude material was carried out by column chromatography (neutral aluminium oxide) with dichloromethane-hexane (10 % to 30 %) and then ethyl acetate as the eluant.

Only yields and analytical data for the products are presented as the spectral data have been listed in previous tables (see Sec.3.2.5).

119b : 86% yield;

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64

Found: C, 71.92; H, 11.28; N, 7.46.

119c : 85% yield

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10

Found: C, 73.41; H, 11.81; N, 6.73.

119d : 87% yield

Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63

Found: C, 74.28; H, 11.57; N, 6.46.

122a : 91% yield

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89

Found: C, 76.89; H, 8.66; N, 7.01.

122b : 79% yield

Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63

Found: C, 74.12; H, 12.24; N, 6.65.

122c : 88% yield

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53

Found: C, 80.56; H, 7.61; N, 5.81.

122d : 93% yield

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45

Found: C, 77.51; H, 8.52; N, 6.42.

122e : 92% yield

Anal. Calcd for $C_{15}H_{21}NO$: C, 78.05; H, 9.15; N, 6.06

Found: C, 77.81; H, 9.34; N, 5.71.

124 : 90% yield

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.895; H, 11.465; N, 5.90

Found: C, 76.70; H, 11.89; N, 6.23.

125 : 9% yield

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.895; H, 11.465; N, 5.90

Found: C, 76.42; H, 11.73; N, 6.20.

The view of **125** showing the atom-numbering scheme is in Figure 5. Crystal data collection and refinement information are listed in Table 8. The atomic parameters x, y, z and B_{iso} of **125** are in Table 9. Tables 10 and 11 will show the interatomic distances (in angstroms) and angles (in degrees) of **125** respectively.

FIGURE 5 VIEW OF COMPOUND 125 SHOWING THE ATOMIC-NUMBERING SCHEME

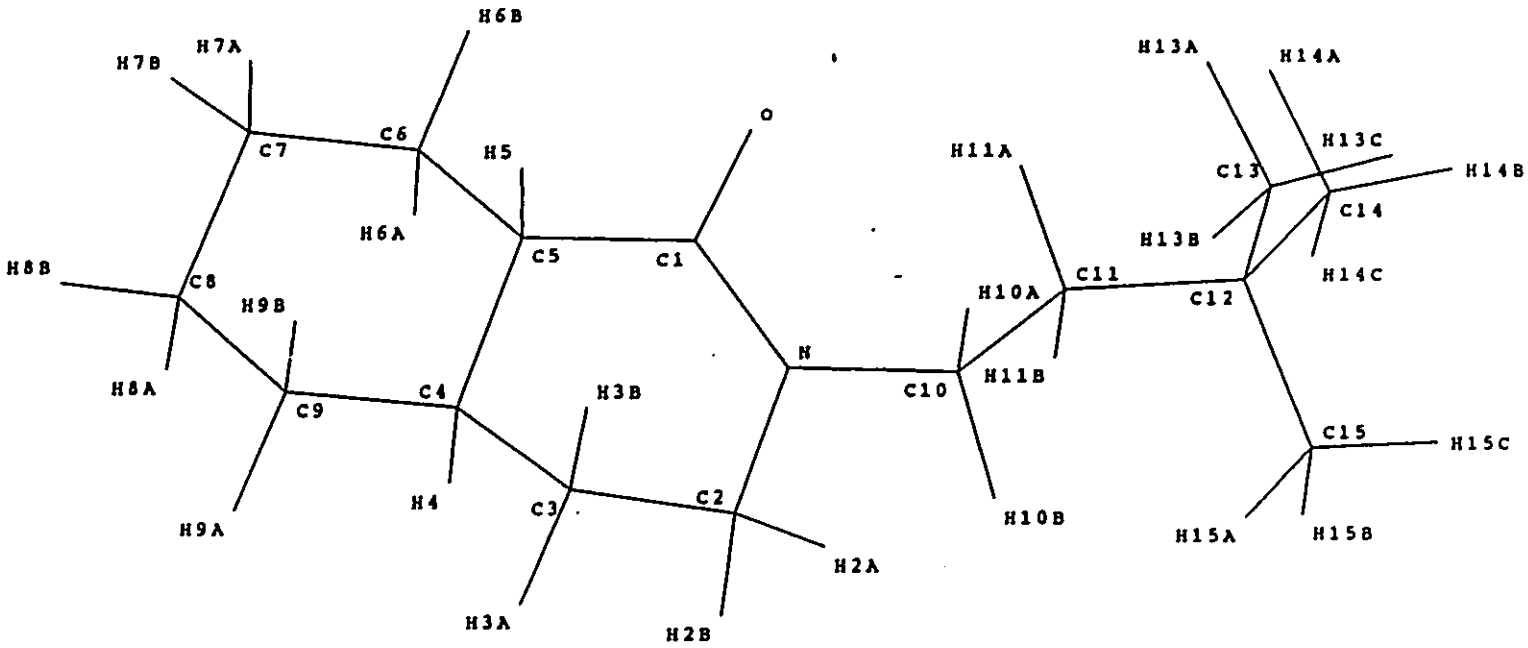


TABLE 8 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR COMPOUND 125

Empirical formula	NOC15H27
Formula weight	237.38
Crystal shape	PLATE
Crystal dimensions	.3,.2,.3
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 40,47
Lattice parameters	a= 6.001(6) b= 9.4868(17) c= 26.197(3)
Space group	P 21/n
Z value	4
Dcalc	1.06
F(000)	659.91
mu	.08
No of reflection measured	2459
No of reflection unique	2219
No of reflection observed	1186
No of atoms	44
No of variables	155
Rf (sign refl)	.099
Rw (sign refl)	.070
Rf (all refl)	.168
Rw (all refl)	.070
Goodness of fit	7.98
Last difference fourier map	
max peak	.260
min peak	-.280

TABLE 9 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 125

Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
O	0.3047(8)	0.6293(6)	0.21901(18)	5.90(23)
N	-0.0163(9)	0.7335(6)	0.18875(18)	4.39(23)
C 1	0.1381(11)	0.6987(7)	0.22664(22)	4.2 (3)
C 2	-0.2259(11)	0.8070(8)	0.1941 (3)	5.3 (3)
C 3	-0.2315(13)	0.8822(8)	0.2458 (3)	5.8 (3)
C 4	-0.1387(11)	0.7856(7)	0.28794(24)	4.7 (3)
C 5	0.1049(11)	0.7559(7)	0.28048(21)	4.0 (3)
C 6	0.2114(13)	0.6563(8)	0.32165(25)	5.7 (4)
C 7	0.1927(17)	0.7229(9)	0.3745 (3)	7.5 (5)
C 8	-0.0479(19)	0.7552(10)	0.3829 (3)	8.4 (5)
C 9	-0.1579(15)	0.8519(9)	0.3411 (3)	6.7 (4)
C10	0.0172(12)	0.6810(8)	0.13605(22)	5.0 (3)
C11	0.1438(12)	0.7934(8)	0.10735(24)	5.0 (3)
C12	0.1968(12)	0.7503(8)	0.05291(24)	5.1 (3)
C13	0.3384(15)	0.6197(9)	0.0534 (3)	6.9 (4)
C14	0.3275(18)	0.8716(10)	0.0317 (3)	8.4 (5)
C15	-0.0159(16)	0.7275(13)	0.0197 (3)	8.6 (6)
H 2A	-0.258	0.881	0.162	5.9
H 2B	-0.365	0.730	0.191	5.9
H 3A	-0.400	0.920	0.252	5.9
H 3B	-0.125	0.979	0.245	5.9
H 4	-0.237	0.687	0.285	5.2
H 5	0.194	0.856	0.285	4.5
H 6A	0.125	0.557	0.318	6.0
H 6B	0.386	0.641	0.314	6.0
H 7A	0.289	0.819	0.378	7.9
H 7B	0.259	0.649	0.404	7.9
H 8A	-0.141	0.658	0.383	8.3
H 8B	-0.053	0.804	0.421	8.3
H 9A	-0.328	0.876	0.348	6.8
H 9B	-0.065	0.955	0.342	6.8
H10A	0.111	0.583	0.139	5.5
H10B	-0.145	0.660	0.115	5.5
H11A	0.300	0.819	0.130	5.7
H11B	0.044	0.891	0.104	5.7
H13A	0.493	0.640	0.082	8.0
H13B	0.259	0.530	0.068	8.0
H13C	0.404	0.599	0.018	8.0
H14A	0.480	0.894	0.059	8.3
H14B	0.384	0.850	-0.005	8.3
H14C	0.230	0.968	0.031	8.3
H15A	-0.117	0.645	0.036	8.5
H15B	-0.113	0.823	0.016	8.5
H15C	0.020	0.693	-0.018	8.5

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

TABLE 10 ATOMIC BONDS IN ANGSTROMS OF 125

O-C(1)	1.226(8)	C(8)-H(8A)	1.081(9)
N-C(1)	1.345(8)	C(8)-H(8B)	1.091(8)
N-C(2)	1.454(9)	C(9)-H(9A)	1.077(8)
N-C(10)	1.496(8)	C(9)-H(9B)	1.123(8)
C(1)-C(5)	1.539(8)	C(10)-C(11)	1.540(10)
C(2)-C(3)	1.534(11)	C(10)-H(10A)	1.082(8)
C(2)-H(2A)	1.096(7)	C(10)-H(10B)	1.096(7)
C(2)-H(2B)	1.108(8)	C(11)-C(12)	1.541(9)
C(3)-C(4)	1.508(10)	C(11)-H(11A)	1.098(7)
C(3)-H(3A)	1.096(7)	C(11)-H(11B)	1.102(7)
C(3)-H(3B)	1.120(8)	C(12)-C(13)	1.501(11)
C(4)-C(5)	1.517(9)	C(12)-C(14)	1.522(11)
C(4)-C(9)	1.542(9)	C(12)-C(15)	1.503(11)
C(4)-H(4)	1.108(7)	C(13)-H(13A)	1.163(9)
C(5)-C(6)	1.535(9)	C(13)-H(13B)	1.062(9)
C(5)-H(5)	1.091(6)	C(13)-H(13C)	1.057(7)
C(6)-C(7)	1.534(10)	C(14)-H(14A)	1.132(11)
C(6)-H(6A)	1.074(8)	C(14)-H(14B)	1.056(8)
C(6)-H(6B)	1.086(8)	C(14)-H(14C)	1.087(10)
C(7)-C(8)	1.509(15)	C(15)-H(15A)	1.098(11)
C(7)-H(7A)	1.078(9)	C(15)-H(15B)	1.077(11)
C(7)-H(7B)	1.089(8)	C(15)-H(15C)	1.087(8)
C(8)-C(9)	1.536(14)		

TABLE 11 ATOMIC ANGLES IN DEGREES OF 125

C(1)-N-C(2)	126.7(5)	C(9)-C(8)-H(8A)	108.2(8)
C(1)-N-C(10)	117.6(5)	C(9)-C(8)-H(8B)	110.4(8)
C(2)-N-C(10)	115.4(5)	H(8A)-C(8)-H(8B)	108.6(7)
O-C(1)-N	122.3(5)	C(4)-C(9)-C(8)	110.0(6)
O-C(1)-C(5)	120.3(6)	C(4)-C(9)-H(9A)	112.6(7)
N-C(1)-C(5)	117.3(5)	C(4)-C(9)-H(9B)	108.1(6)
N-C(2)-C(3)	112.8(6)	C(8)-C(9)-H(9A)	111.0(7)
N-C(2)-H(2A)	109.6(5)	C(8)-C(9)-H(9B)	108.3(8)
N-C(2)-H(2B)	109.1(6)	H(9A)-C(9)-H(9B)	106.5(7)
C(3)-C(2)-H(2A)	111.2(6)	N-C(10)-C(11)	109.1(5)
C(3)-C(2)-H(2B)	107.6(6)	N-C(10)-H(10A)	109.7(5)
H(2A)-C(2)-H(2B)	106.3(6)	N-C(10)-H(10B)	109.8(6)
C(2)-C(3)-C(4)	109.4(6)	C(11)-C(10)-H(10A)	110.3(6)
C(2)-C(3)-H(3A)	111.4(7)	C(11)-C(10)-H(10B)	109.7(5)
C(2)-C(3)-H(3B)	108.2(6)	H(10A)-C(10)-H(10B)	108.1(6)
C(4)-C(3)-H(3A)	112.7(6)	C(10)-C(11)-C(12)	114.5(6)
C(4)-C(3)-H(3B)	109.5(7)	C(10)-C(11)-H(11A)	109.0(5)
H(3A)-C(3)-H(3B)	105.5(6)	C(10)-C(11)-H(11B)	109.3(6)
C(3)-C(4)-C(5)	108.8(5)	C(12)-C(11)-H(11A)	109.1(6)
C(3)-C(4)-C(9)	111.4(6)	C(12)-C(11)-H(11B)	108.0(6)
C(3)-C(4)-H(4)	107.9(6)	H(11A)-C(11)-H(11B)	106.6(6)
C(5)-C(4)-C(9)	109.5(6)	C(11)-C(12)-C(13)	111.6(6)
C(5)-C(4)-H(4)	110.4(5)	C(11)-C(12)-C(14)	106.8(6)
C(9)-C(4)-H(4)	108.7(5)	C(11)-C(12)-C(15)	110.3(6)
C(1)-C(5)-C(4)	112.3(5)	C(13)-C(12)-C(14)	108.6(7)
C(1)-C(5)-C(6)	110.5(5)	C(13)-C(12)-C(15)	109.9(7)
C(1)-C(5)-H(5)	107.4(5)	C(14)-C(12)-C(15)	109.6(7)
C(4)-C(5)-C(6)	112.1(5)	C(12)-C(13)-H(13A)	107.1(7)
C(4)-C(5)-H(5)	107.0(5)	C(12)-C(13)-H(13B)	113.1(7)
C(6)-C(5)-H(5)	107.2(5)	C(12)-C(13)-H(13C)	113.1(7)
C(5)-C(6)-C(7)	108.9(6)	H(13A)-C(13)-H(13B)	104.8(7)
C(5)-C(6)-H(6A)	108.1(6)	H(13A)-C(13)-H(13C)	105.2(7)
C(5)-C(6)-H(6B)	108.1(6)	H(13B)-C(13)-H(13C)	112.7(8)
C(7)-C(6)-H(6A)	111.4(6)	C(12)-C(14)-H(14A)	109.0(7)
C(7)-C(6)-H(6B)	110.7(7)	C(12)-C(14)-H(14B)	113.3(8)
H(6A)-C(6)-H(6B)	109.5(7)	C(12)-C(14)-H(14C)	110.8(8)
C(6)-C(7)-C(8)	110.8(7)	H(14A)-C(14)-H(14B)	107.3(9)
C(6)-C(7)-H(7A)	110.1(7)	H(14A)-C(14)-H(14C)	105.2(8)
C(6)-C(7)-H(7B)	108.4(7)	H(14B)-C(14)-H(14C)	110.8(8)
C(8)-C(7)-H(7A)	109.4(8)	C(12)-C(15)-H(15A)	110.3(7)
C(8)-C(7)-H(7B)	109.2(7)	C(12)-C(15)-H(15B)	110.6(9)
H(7A)-C(7)-H(7B)	109.0(7)	C(12)-C(15)-H(15C)	110.7(8)
C(7)-C(8)-C(9)	112.3(6)	H(15A)-C(15)-H(15B)	108.3(8)
C(7)-C(8)-H(8A)	108.9(9)	H(15A)-C(15)-H(15C)	107.6(10)
C(7)-C(8)-H(8B)	108.4(8)	H(15B)-C(15)-H(15C)	109.1(7)

3.3.4 EXPERIMENTS TO PROBE THE REACTION MECHANISM

3.3.4.1 THE REACTION OF 118B WITH ^{13}CO

A mixture of **118b** (247 mg, 1.32 mmol), $Co_2(CO)_8$ (103 mg, 0.30 mmol) and $Ru_3(CO)_{12}$ in 12 ml dry benzene was placed in an autoclave, which was purged with unlabelled CO (4 times) and closed. The autoclave was connected to the special pieces of equipment in the system (See Figure 6) designed and built by Dr. Regent Dutrisac of Dr. Keith Preston's lab. The exact procedure may be described as follows:

(1) The mixture was solidified by cooling down the autoclave **1** using liquid N_2, ensuring that **a** was closed.

(2) The system was degassed for several minutes by opening **b**, **c**, **d**, **e** and **f**.

(3) **d** and **f** were closed. **2** (previously packed with a known amount of molecular sieves, type 13X) was cooled down. **A** was opened and ^{13}CO gas was condensed in **2** and absorbed.

(4) **E** was closed, **f** was opened and **1** was cooled. **2** was warmed in order to transfer ^{13}CO from **2** to **1**. After 10-20 minutes, **f** was closed.

(5) The cooling system was removed and the presure of the autoclave **1** at room temperature was allowed to reach 310 psi.

The autoclave was heated in an oil bath at 210-220^{0}C for 72h. The reaction mixture, worked-up using the general procedure followed by column chromatography (neutral alumina oxide) with 30% dichloromethane-hexane and ethyl acetate as eluant, afforded the product (205 mg, 85% yield). The product was identifided by IR, MS, ^1H NMR and especially ^{13}C NMR as being identical to the unlabelled **119b**. No incorporation of labelling to the product was found.

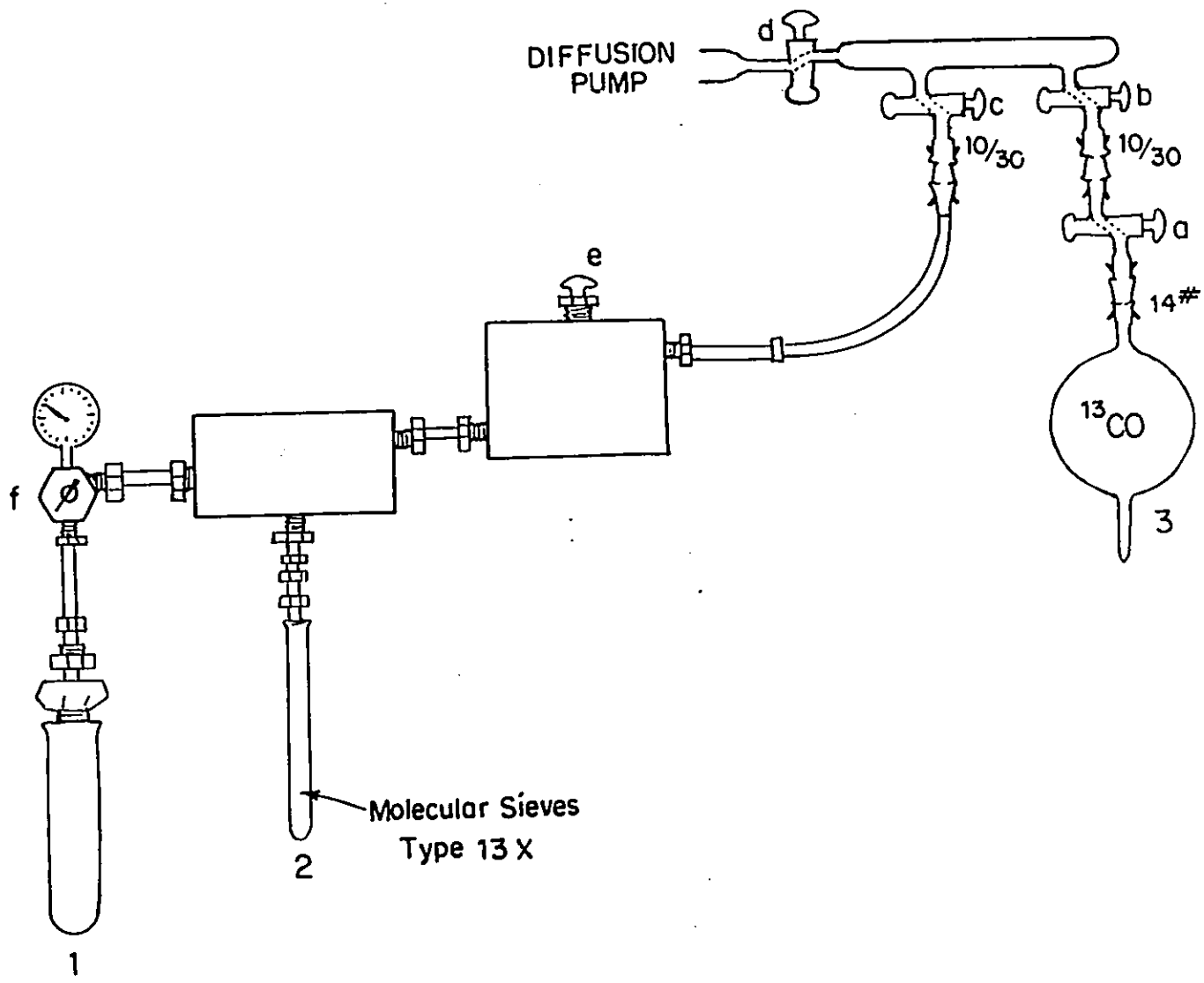
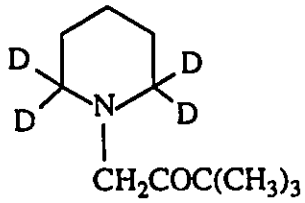


FIGURE 6 SCHEMATIC DIGRAM OF THE APPARATUS FOR TRANSFERING 1atm ^{13}CO TO AN AUTOCLAVE

3.3.4.2 THE 2,2,6,6-TETRADEUTERIOPIPERIDINYL KETONE (134)

1-Nitrosopiperidine was prepared by reacting piperidine with sodium nitrite in an acidic medium[130] and was obtained in 92 % yield, bp 170^{0}C/20mmHg (reference data: only for 1-nitrosopyrrolidine: 60%, bp 99^{0}C/15mmHg). 1-Nitrosopiperidine readily underwent base-catalyzed exchange with D_2O under reflux for 24hr to afford 1-nitroso-2,2,6,6-tetradeuteriopiperidine (**132**) in 71 % yield, bp 63-65^{0}C/0.3 mmHg with 85 % H-D exchange ratio checked by MS and ^{1}H NMR. Hydrolysis with hydrochloric acid, gave 2,2,6,6-tetradeuteriopiperidine (**133**) in 27 % yield. Compound **133** was deprotonated by t-butyllithium and reacted with 1-bromo-3,3-dimethylbutan-2-one, following the general procedure of Sec. 2.3.2.4., to give **134** in 80 % yield, bp 54-56^{0}C/1.1 mmHg.

compound **134** :



^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $C(CH_3)_3$); 1.38-1.54 (m, 6H, protons at C3, C4, C5 of piperidine); 2.32 (m, 0.6H, protons at C2, C6); 3.28(s, 2H, NCH_2CO);

MS (EI) m/e 187 $[M]^+$,186,185,184, 102 $[M\text{-}COC(CH_3)_3]^+$, 101, 100 base peak.

Compound **134** underwent the standard reaction to give the rearrangement product in 84 % yield, but NMR and MS spectral data showed that it was a mixture of different levels of deuteration at all positions of CH_2 groups in the molecule.

3.3.4.3 ^{13}C LABELLED (CARBONYL CARBON)PIPERIDIN-1-YL ACETOPHENONE (137)

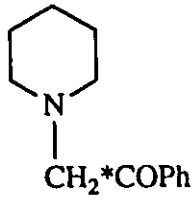
Treatment of 1g of commercial $CH_3{}^*COPh$ with tetrabutylammonium tribromide (4.40 g, 9.16 mmol) in 100 ml dichloromethane and 40 ml methanol at room temperature overnight, and work up following the literature procedure,[132] gave 1.534 g of labelled 2-bromoacetophenone in 91% yield, mp 48-50^{0}C (ref. 78% yield, mp 49-59^{0}C), and reaction of the latter with piperidine and tert-butyllithium in ether gave **137** in 89% yield.

$BrCH_2{}^*COPh$ (**136**):

IR ($CDCl_3$) ν (CO) 1648 cm^{-1};

^1H NMR ($CDCl_3$) δ 4.42 [d($J_{H\text{-}13C}$ 11.2Hz), 2H, $NCH_2{}^{13}CO$); 7.55 (m, 3H, meta and para protons of phenyl); 7.95 (m, 2H, meta protons of phenyl);

^{13}C NMR ($CDCl_3$) δ 30.66 [d($J_{C\text{-}13C}$ 86Hz), $BrCH_2$]; 128.38 (5C of phenyl), 134.10 (q-C of phenyl), 191.87 (^{13}CO, intense).

137 : 

bp 105-107^{0}C/0.3 mmHg;

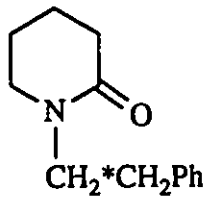
IR ($CDCl_3$) ν (CO) 1656 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.42-1.59 (m, 6H, protons at C3, C4, C5 of piperidine); 2.48 (m, 4H, protons at C2, C6); 3.72 (d, 2H, $^2J_{HC-13C}$=10.1 Hz, NCH_2CO); 7.43 (m, 3H, meta and para protons); 7.94 (m, 2H, ortho protons);

^{13}C NMR δ 23.99 (C4 of piperidine), 25.79 (C3, C5), 51.84 (C2, C6), 65.27 (NCH_2^*CO), 128.08, 128.30, 128.47, 133.06 (aromatic), 196.82 (^{13}CO, intense signal);

MS (EI) m/e 204 $[M]^+$, 98 $[M-^{13}COPh]^+$ base peak.

When **137** was subjected to rearrangement using conditions identical to those for **118** or **120**, the rearrangement product **138** was obtained in 90 % yield, with the label remaining at the carbon atom adjacent to the phenyl group.

138 : 

IR ($CDCl_3$) ν (CO) 1626 cm^{-1}; mp 38-40^{0}C

^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4H, protons at C4, C5 of piperidine); 2.32 (t, 2H, CH_2CO); 2.88 (dd, 2H, $^{13}CH_2Ph$); 3.08 (t, 2H, NCH_2ring); 3.54 (dd, 2H, NCH_2); 7.25 (m, 5H, Ph)

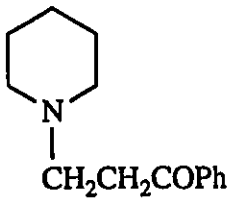
^{13}C NMR ($CDCl_3$) δ 21.07 (C4 of piperidinone), 23.09 (C5), 32.14 (CH_2CO), 33.44 ($^{13}CH_2Ph$, intense signal), 48.68 (NCH_2, ring), 49.38 (NCH_2), 126.22, 128.39, 128.80, 139.30 (aromatic), 169.92 (CO)

MS (EI) m/e 204 $[M]^+$, 112 $[M-^{13}CH_2Ph]^+$ base peak, 92 $[Ph^{13}CH_2]^+$.

3.3.4.4 COMPOUNDS 139, 140 AND 141

Phenyl β-piperidinoethyl ketone (**139**) was prepared in 85 % yield by the known Mannich reaction of acetophenone, paraformaldehyde, and piperidine hydrochloride following the literature procedure.[133] Then dehydrochlorination of the hydrochloride gave **139** in 68% yield.

139 :



mp 27-29^{0}C; (mp of the chloride : 186-189^{0}C, lit.: 185-189^{0}C);

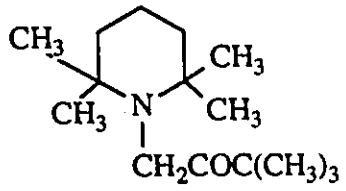
IR ($CHCL_3$) ν (CO) 1681 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.42-1.55 (m, 6H, protons at C3-C5 of piperidine); 2.41 (m, 4H, NCH_2ring); 2.75 (m, 2H, CH_2COPh); 3.12 (m, 2H, NCH_2); 7.44 (m, 3H,

protons at meta and para positions of Ph); 7.95 (m, 2H, ortho protons of Ph);

MS (CI) m/e 218 $[M+1]^+$.

140 :



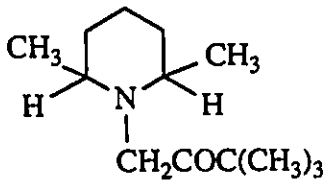
Compound **140** was synthesized in a manner similar to that outlined in Sec.2.3.2.4. in 11 % yield, bp 50-51^{0}C/0.25 mmHg.

IR ($CHCl_3$) ν (CO) 1717 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.10 (S, 9H, $C(CH_3)_3$); 1.19, 1.21 (s, 12H, CH_3); 1.21-1.40 (m, 6H, CH_2ring); 4.07 (s, 2H, NCH_2CO);

MS (EI) m/e 239 $[M]^+$.

131 :



bp 60-62^{0}C/0.2mmHg, yield : 30%;

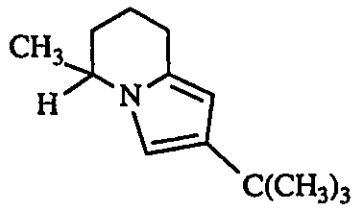
IR ($CDCl_3$) ν (CO) 1710 cm^{-1};

^1H NMR ($CDCl_3$) δ 0.98 (d, 6H, CH_3); 1.12 (s, 9H, $C(CH_3)_3$); 1.18-1.65 (m, 6H, ring CH_2); 3.05 (m, 2H, CHN); 3.81 (s, 2H, NCH_2CO);

MS (EI) m/e 211 $[M]^+$, 126 $[M\text{-}COC(CH_3)_3]^+$ base peak.

When **141** was subjected to rearrangement using conditions identical to those described above for **118** or **120**, surprisingly, the new cyclization product **142** was isolated in 86 % yield, without any by-products (GC conversion of **141** was found to be 100 %). The structure of **142** was supported by analytical and spectral data.

142 :



IR ($CDCl_3$) ν (CH) 2938 cm^{-1}; 1463.73 cm^{-1}, no ν (C=O);

^1H NMR ($CDCl_3$) δ 1.19 (s, 9H, $C(CH_3)_3$); 1.43 (d, 3H, CH_3); 1.56-1.81 (m, 4H, protons at C6, C7 of indolizine); 2.70 (m, 2H, protons at C8); 3.94 (m, 1H, $CHCH_3$); 5.72 (d, 1H, ^4J= 2 Hz, proton at C1); 6.39 (d, 1H, ^4J= 2 Hz, NCH=);

^{13}C NMR ($CDCl_3$) δ 19.51, 23.53 (C6, C7), 22.09 (CH_3), 29.63 ($C(CH_3)_3$), 30.46 (q-C of t-Bu), 32.06 (C8), 50.18 ($CHCH_3$), 102.76 (C1), 111.69 ((C3), 129.10 (C2), 134.85 (C8a);

MS (EI) m/e 191 $[M]^+$, 176 $[M\text{-}CH_3]^+$ base peak.

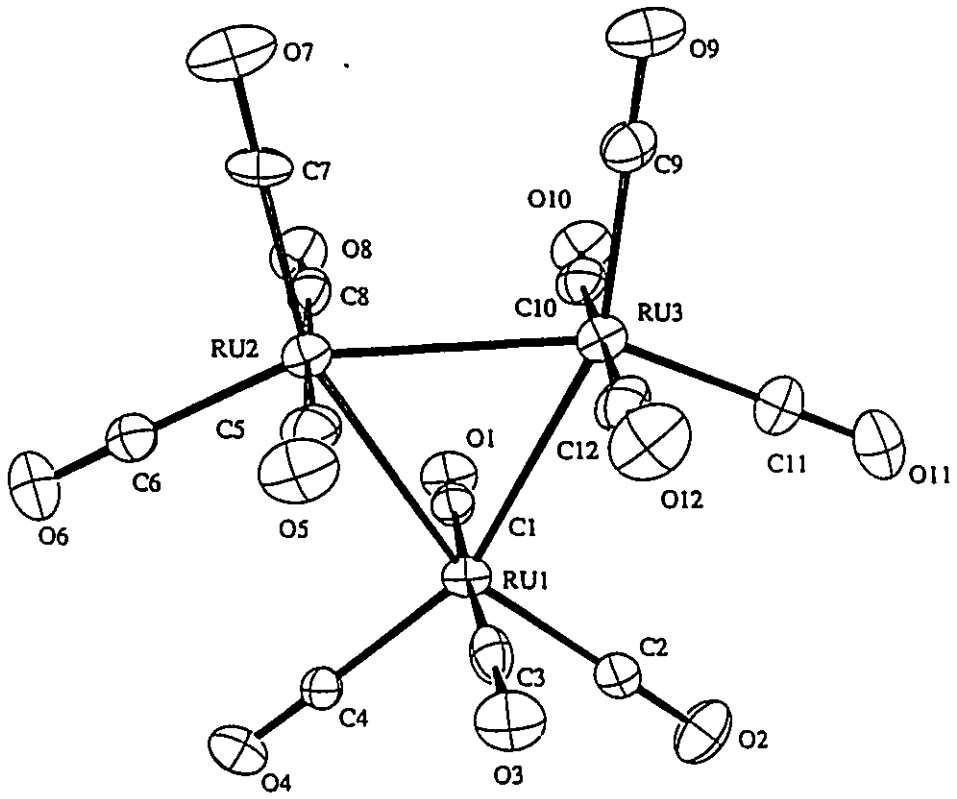
Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32

Found: C, 81.54; H, 10.95; N, 7.25.

3.3.4.5 THE RECOVERED CATALYST

After the rearrangement reaction, the reaction mixture was exposed to air overnight and part of the solvent benzene was removed to give some red-orange metal complex crystals. The structure of these crystals from the reaction of **118b** was shown to be $Ru_3(CO)_{12}$ and analysed by IR, MS and further confirmed by X-ray analysis (ORTEP drawing: Figure 7).

FIGURE 7 THE ORTEP DRAWING OF THE RECOVERED CATALYST

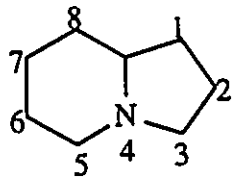


Chapter 4

Metal Catalyzed Cyclization of 2-Methyl(or 2,6-di -Methyl)Piperidinyl Ketones and the Oxidation of 5,6,7,8-Tetrahydroindolizines

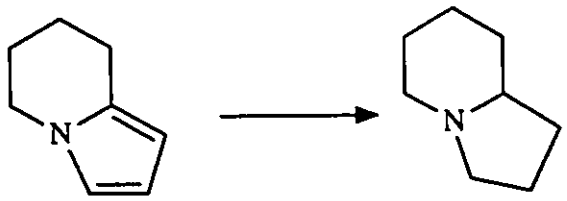
4.1 INTRODUCTION

The indolizidine system **149** is present in many alkaloids isolated from plants, and also from fungal and animal sources.[137]



149

From a synthetic viewpoint, 5,6,7,8-tetrahydroindolizines are synthetic precursors of octahydroindolizines,[138] including a number of natural products. For example the alkaloid δ-coniceine **151** can be derived from **150** by catalytic hydrogenation.[139]



150 **151**

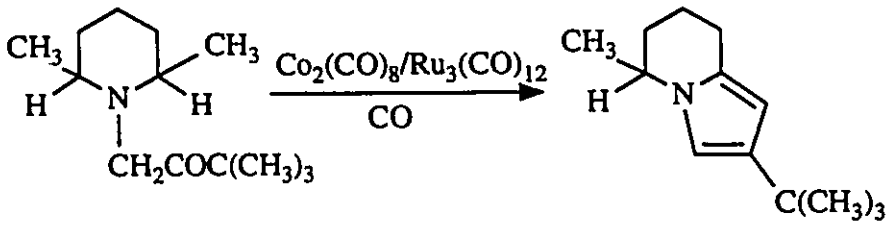
The literature on the syntheses of indolizidine alkaloids has been the subject of some reviews.[137,140-143] A number of general methods have been developed for the syntheses of the basic skeleton of indolizidines and substituted indolizidines. Only a few examples have appeared in the literature for cationic cyclizations in which the terminator is a pyrrole.[144] A method providing 5,6,7,8-tetrahydro indolizines by an exo-tet type of reaction has not been described until 1990.[145] This is likely due to the instability of pyrroles towards oxygen and acids.

This chapter is concerned in part with an unusual cobalt or ruthenium carbonyl catalyzed cyclization reaction of 2-methyl(or 2,6-dimethyl)piperidinyl ketones affording (5-methyl)5,6,7,8-tetrahydroindolizines in 37-94% yields. This reaction was discovered during the pursuit of mechanistic information for the rearrangement reaction (see Chapter 3). Appropriately substituted tetrahydroindolizines and related indolizidine alkaloids are of considerable pharmacological interest.[137,145] During the investigation of a single crystal X-ray structure of 2-phenyl-5,6,7,8-tetrahydroindolizine, a photoassisted catalytic oxidation of 5,6,7,8-tetrahydroindolizines to 8a-hydroxy-2-phenyl -6,7,8,8a-tetrahydro-3(5H)indolizinone s at room temperature under 1 atm of O_2 was discovered and further studied.

4.2 RESULTS AND DISCUSSION

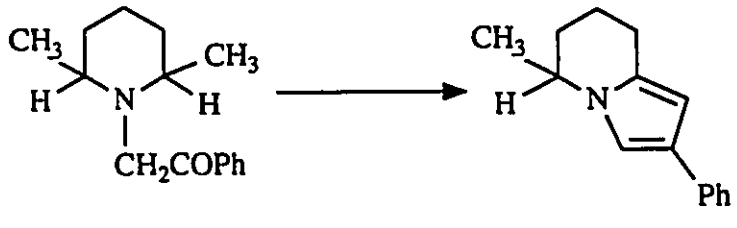
4.2.1 The cyclization of 2,6-dimethylpiperidinyl ketones

As described in Chapter 3, in order to get more information about the unusual rearrangement reaction, a ketone was prepared in which only one of the hydrogen atoms at an α-carbon atom is replaced by an alkyl group. Deprotonation of commercially available 2,6-dimethylpiperidine by n-butyllithium, followed by reaction with 2-bromo-3,3-dimethylbutan-1-one (See Sec. 2.3.2.4) gives the reactant ketone **141**. Exposure of **141** to the reaction conditions utilized for rearrangement resulted in cyclization to form the 5-methyl-2-tert-butyl-5,6,7,8-tetrahydroindolizine **142** in 86% yield.



141 **142**

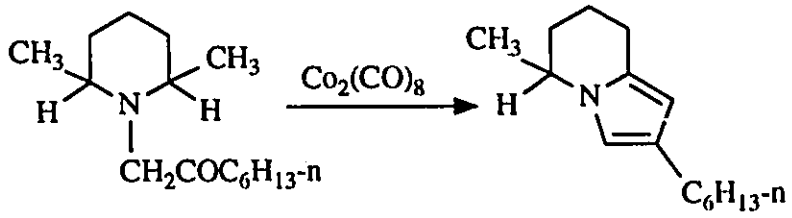
Similarly **152** gives **153** in 94% yield.



152 **153**

152 was prepared via 1-phenyl-2-(2,6-dimethylpiperidinyl) ethanol, obtained in 85% yield from 2-phenyloxirane and lithium 2,6-dimethylpiperidide.

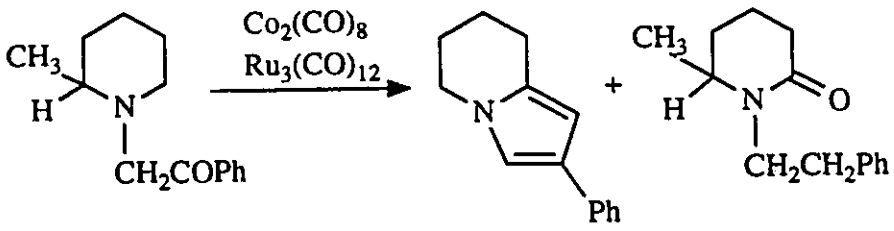
In contrast to the rearrangement process which requires both $Co_2(CO)_{12}$ and $Ru_3(CO)_{12}$ as catalysts, when starting from **152** using $Co_2(CO)_8$ (or $Ru_3(CO)_{12}$) as the only catalyst this unique cyclization reaction affords **153** in high yield (94% for **152** : $Co_2(CO)_8$ = 4 : 1; 84% for **152** : $Ru_3(CO)_{12}$ = 9 : 1). Another 2,6-dimethylpiperidinyl ketone, **154**, was prepared via 1-(2,6-dimethyl piperidinyl)-2-octanol, obtained in 80% yield from 2-n-hexyloxirane and lithium 2,6-dimethylpiperidide (see Experimental Section). Using $Co_2(CO)_8$ as the only catalyst gave **155** in 91% yield by the cyclization reaction of **154**.



154 **155**

4.2.2 The cyclization of 156 in the presence of $Co_2(CO)_8$/$Ru_3(CO)_{12}$

An interesting question arises as to the selectivity, when there is one α-CH_2 capable of undergoing rearrangement and one α-CH which can cyclize using both metal carbonyls as catalysts. For this reason, the 2-methylpiperidinyl ketone **156** was prepared in 63% yield by a similar synthetic method to that described in Section 2.3.2.4. That is, **156** was used to assess the relative facility for rearrangement versus cyclization. Using both $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ as catalysts for the reaction of **156** under carbon monoxide results in 10 : 1 selectivity (77% yield) for cyclization to **157**, compared with rearrangement to **158**.

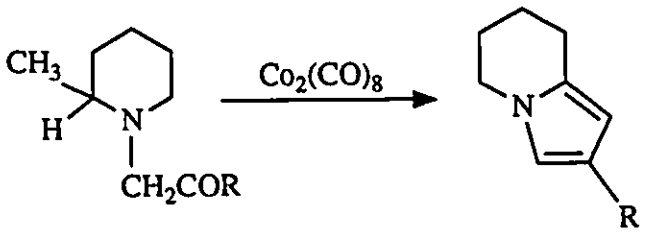


156 **157** **158**

The preference for cyclization may be due to kinetic control. Only cyclization occurs (72% **157**) when $Co_2(CO)_8$ is employed as the catalytic species.

4.2.3 The cyclization of the other 2-methylpiperidinyl ketones in the presence of $Co_2(CO)_8$

Two other 2-methylpiperidinyl ketones **159a,b** were synthesized by the method described in Section 2.3.2.4. Using $Co_2(CO)_8$ as the only catalyst for the reactions of **159a,b** under carbon monoxide gave the cyclization product **160a,b** in 76% and 83% yield, respectively.



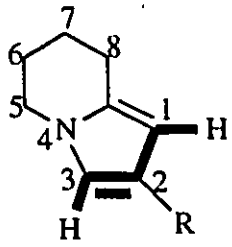
159a,b **160a,b**

a, R = CH_2CH_3 yield a, 76%

b, R = 4-$CH_3C_6H_4$ b, 83%

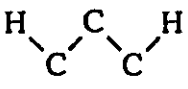
4.2.4 Analysis of spectral data of cyclization products

The structures of the metal catalyzed cyclization reaction products (substituted tetrahydroindolizines) were determined by analytical and spectral data. For example, in all the ^1H NMR spectra of these products the two protons at the C1 and C3 positions of the indolizine ring appear as a doublet at a range of 5.8-7.2 ppm with a coupling constant $^4J_{HH}$ = 1-2Hz due to four-bond W type long-range coupling. The further coupling of C^1H to one of the protons of C^8H_2 by the same 4-bound coupling is usually observed in these ^1H NMR spectra. A part of the ^1H NMR spectrum of compound **153** is shown in Figure 8.



161

The meta (^4J) coupling in aromatics is one example of long-range coupling. These range from ca. 1-3Hz, are always positive,[146] and are very similar to long-range coupling in saturated systems. ^4J Coupling in freely rotating fragments, e.g. $CH_3.C.CH_3$, is very small, but for specific orientations of the bonds the coupling may be appreciable. It is largest (1-2Hz in non-strained systems) if the bonds are in a planar zig-zag orientation, i.e.



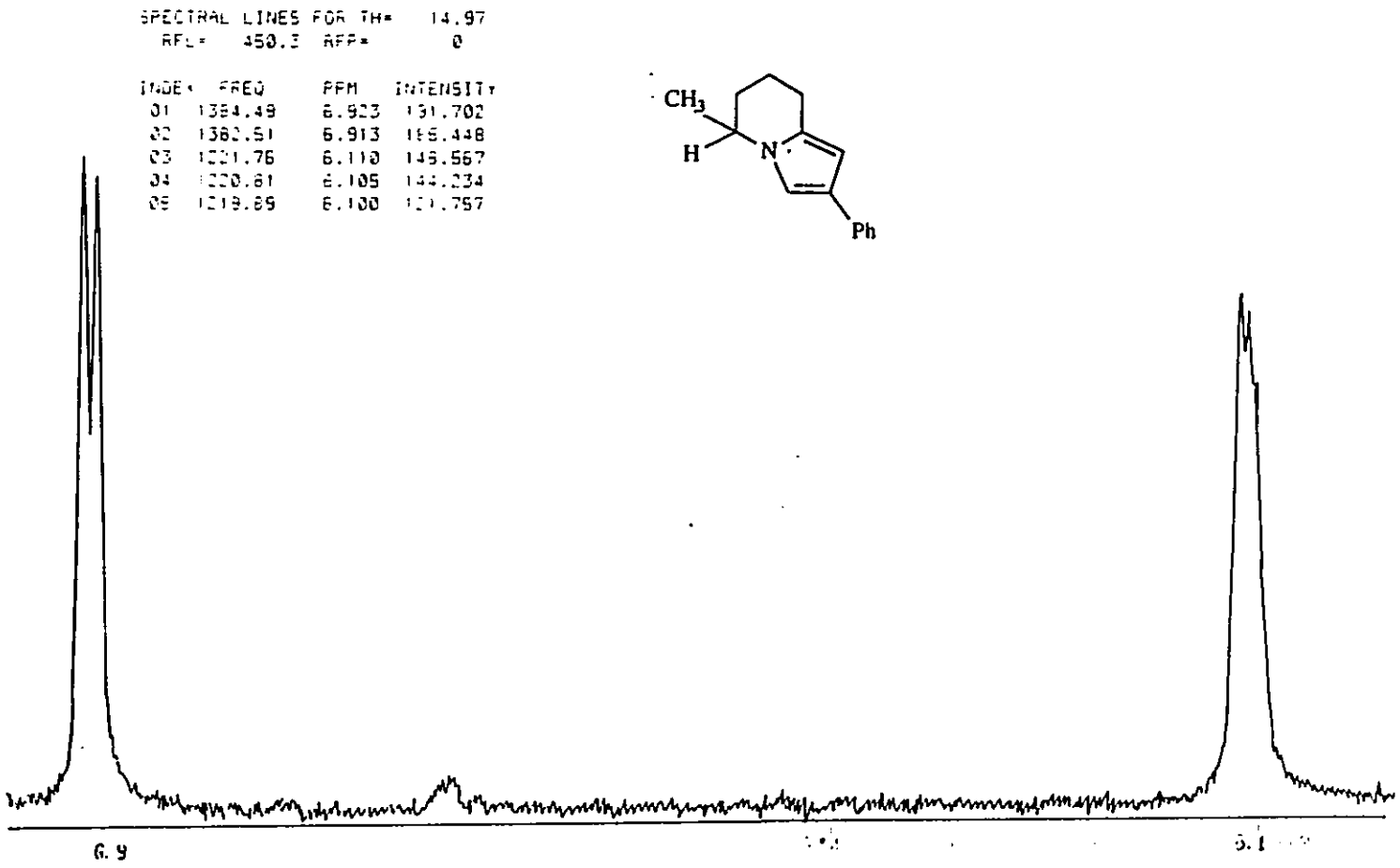
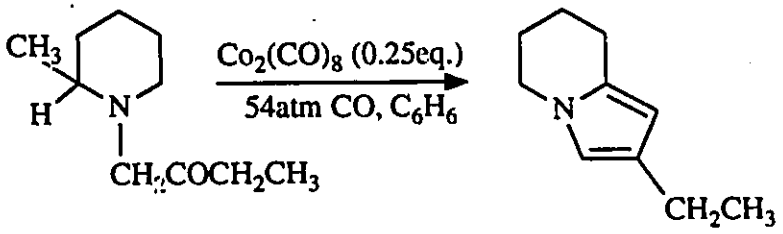


FIGURE 8 A PART OF THE ^{1}H NMR SPECTRUM OF 153

Representative ^{1}H NMR, ^{13}C NMR (including DEPT) spectra (for **155**) are shown in Figures 9, 10, 11.

4.2.5 Variation in reaction conditions

In order to optimize the reaction conditions further experiments, starting from reactant **159a**, at different temperatures and reaction times revealed that the conversion of **159a** to **160a** proceeds with $Co_2(CO)_8$ at a higher reaction rate than the rearrangement process.

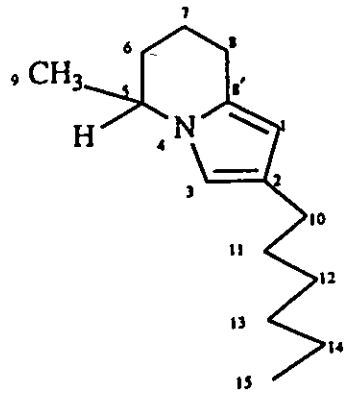


159a **160a**

100-110^{0}C, 3days,	conversion of **159a**: 0%
150-160^{0}C, 60h,	32%
194-196^{0}C, 60h,	82%
200-205^{0}C, 2days,	100%

A reaction temperature around 200^{0}C is necessary for this catalytic cyclization reaction. A blank reaction i.e. without any catalyst, shows no cyclization occurring at all, but only some decomposition of **159a**.

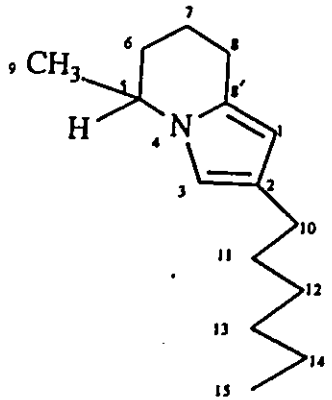
FIGURE 9 ^{1}H NMR SPECTRUM (200 MHz) OF COMPOUND 155



155

SPECTRAL LINES FOR TH= 33.16
RFL= 6108.5 RFP= 0

INDEX	FREQ	PPM	INTENSITY
01	6502.5	129.301	87.132
02	6253.1	124.342	85.714
03	5729.5	113.930	125.263
04	5246.2	104.320	131.270
05	3920.5	77.958	56.942
06	3888.3	77.319	56.948
07	3856.2	76.679	59.065
08	2530.3	50.314	131.525
09	1624.9	32.311	130.110
10	1609.7	32.009	150.620
11	1581.0	31.437	128.088
12	1485.6	29.620	139.966
13	1381.0	27.461	123.833
14	1195.7	23.776	124.414
15	1148.7	22.842	144.937
16	1127.2	22.414	124.818
17	1013.9	20.161	122.567
18	718.1	14.280	135.108



155

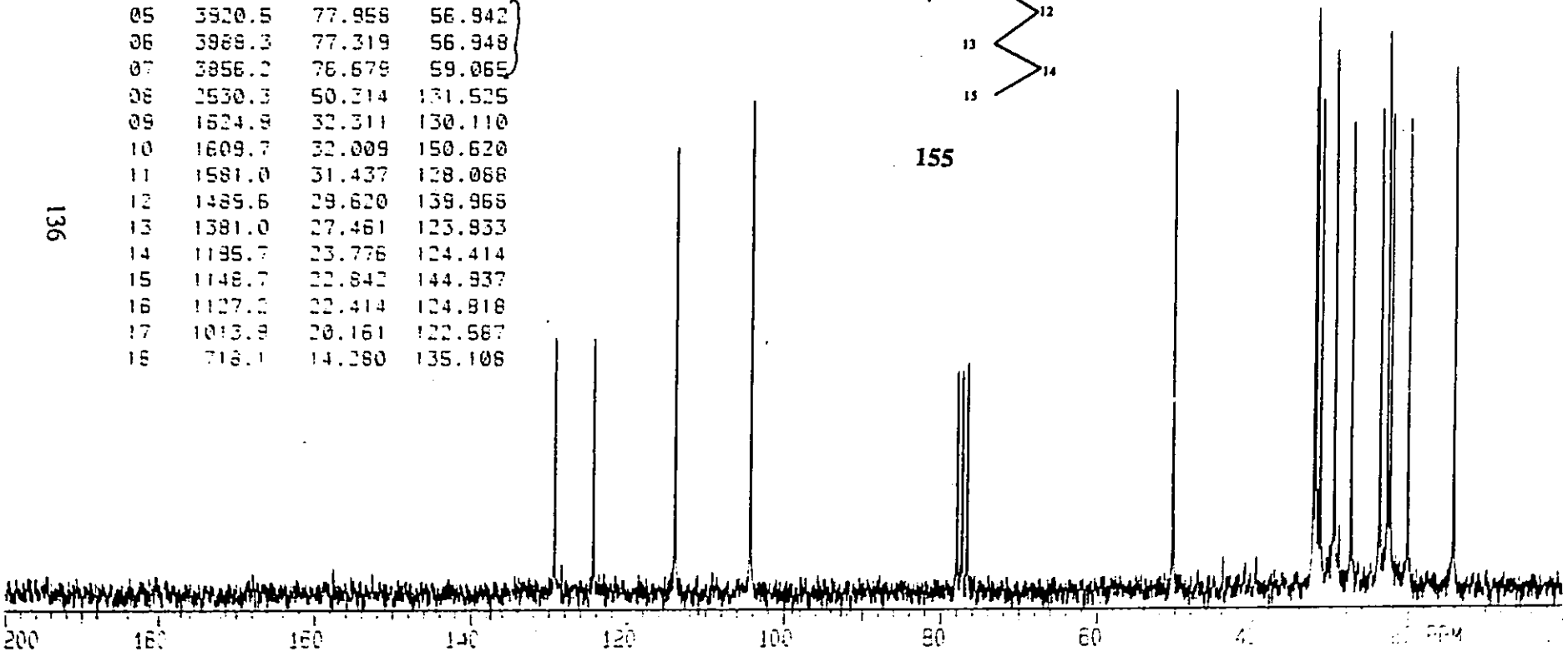


FIGURE 1 0 ^{13}C NMR SPECTRUM (50.4MHz) OF COMPOUND 155

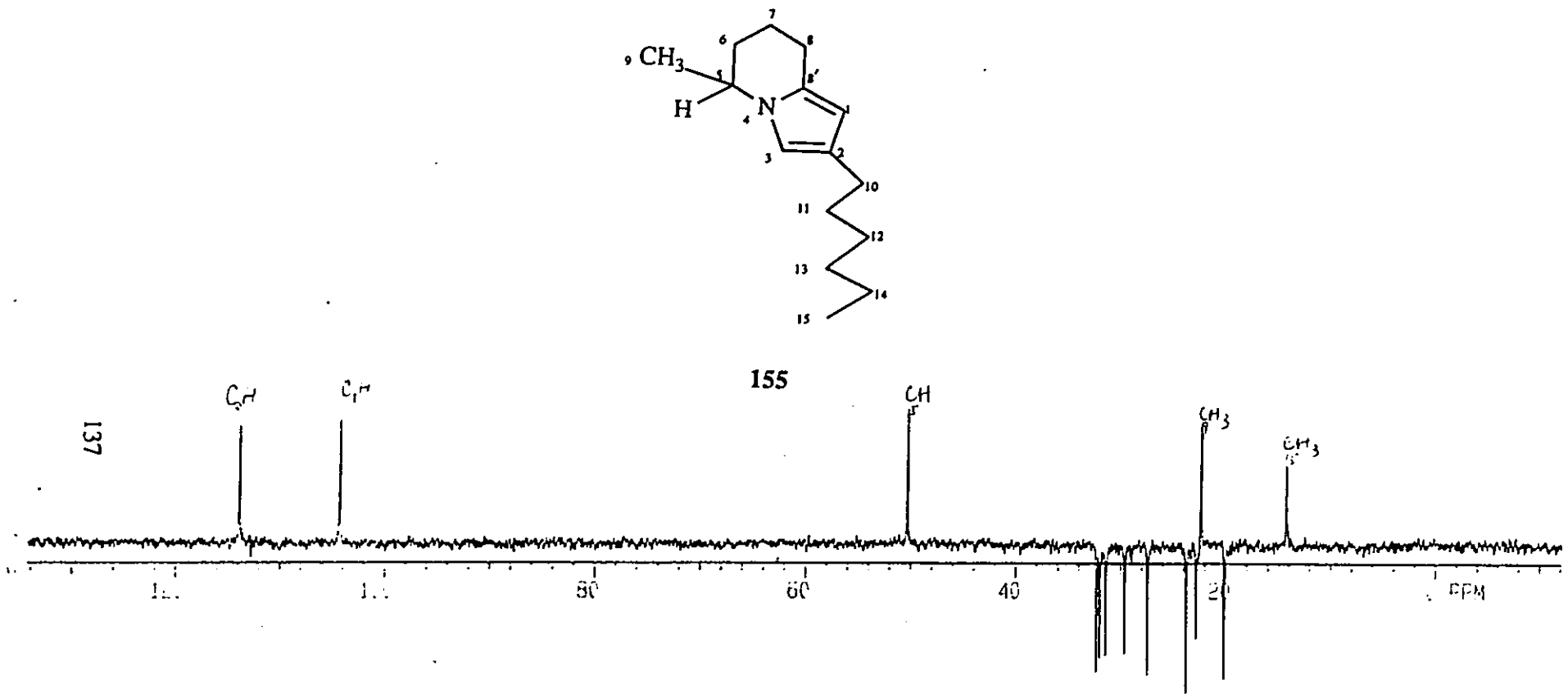
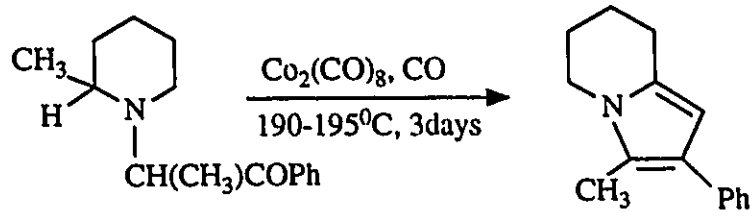


FIGURE 11 DEPT OF ^{13}C NMR SPECTRUM (50.4 MHz) OF COMPOUND 155

Finally, in order to determine what would happen if one hydrogen of the NCH_2 fragment chain of the reactant ketone is replaced by an alkyl group such as methyl, 2-methylpiperidinyl ketone **161** was prepared from 2-bromopropytophenone and 2-methylpiperidide in 39% yield. The cyclization reaction of **161** gave the 2,3-disubstituted-5,6,7,8-tetrahydroindolizine **162** in 54% yield.



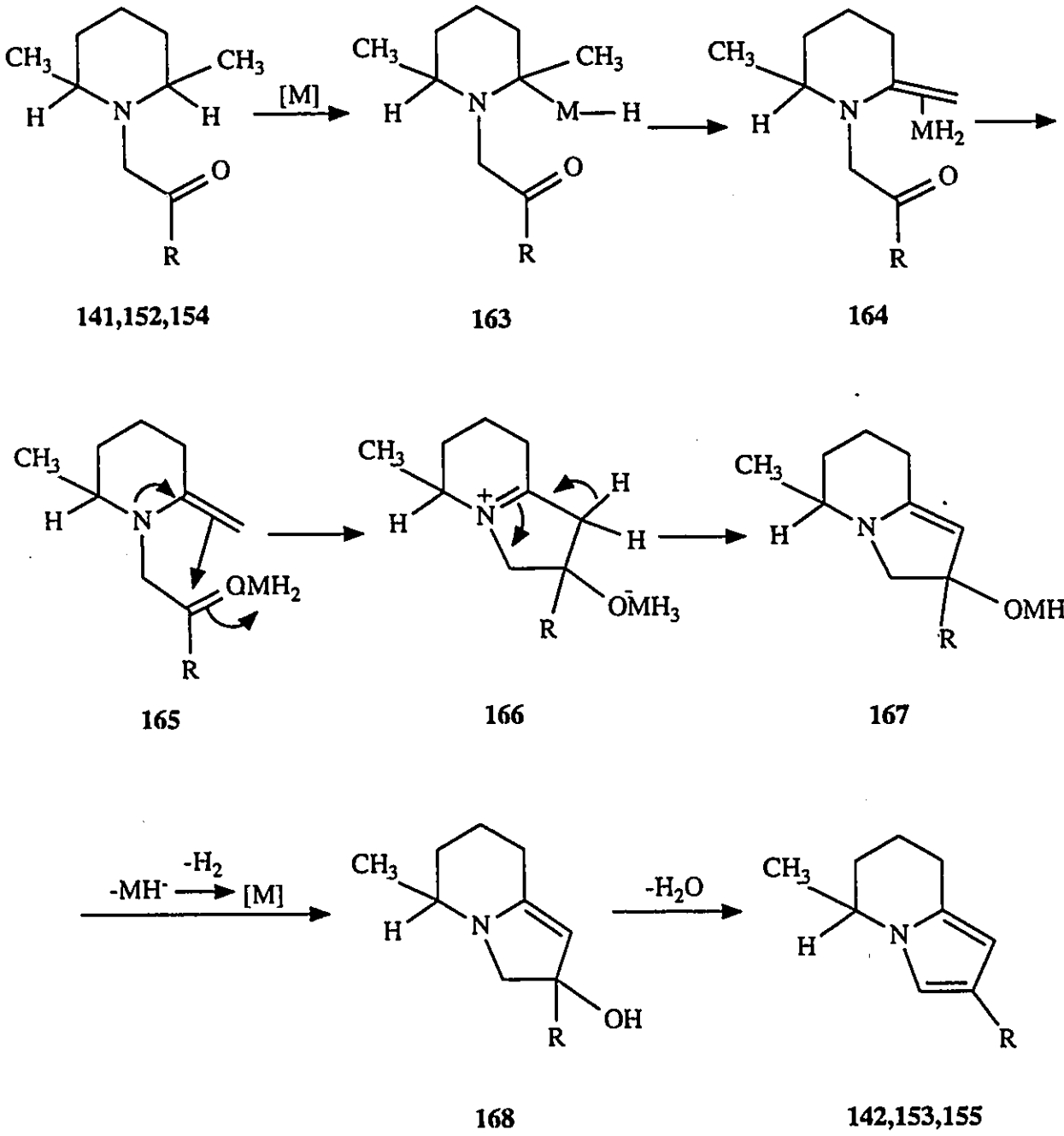
161 **162**

4.2.6 A possible mechanism for the cyclization reaction

A possible mechanism for the cyclization reaction is outlined in Scheme 10.

The initial step (**141, 152, 154** or **156, 159a,b**) in the conversion of 2,6-dimethyl(or 2-methyl)piperidinyl ketones to 5,6,7,8-tetrahydroindolizines is likely the same as that for the rearrangement process. Hydrogen transfer from the methyl group to the metal (β-elimination process) would form **164** which can collapse to the monodentate complex **165**. Cyclization to **166** followed by conversion to **167** and subsequent reductive elimination of MH_2 would result in the formation of **168**. The 5,6,7,8-tetrahydroindolizine would then be produced by dehydration. Note that **164** can alternatively undergo decomplexation to give the enamino ketone (uncomplexed analogue of **165**) which can, by an analogous reaction sequence, be converted to the 5,6,7,8-tetrahydroindolizines. Nevertheless, in the presence of a metal complex which can function as a Lewis acid, intramolecular addition to the carbonyl group of **164** occurred to give 5,6,7,8-tetrahydroindolizine.

Scheme 10



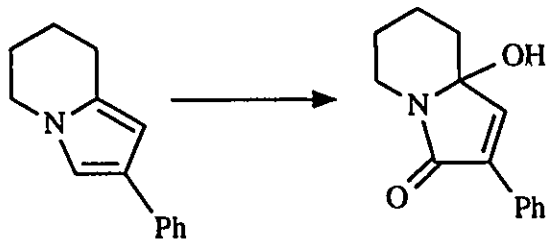
141,152,154 163 164

165 166 167

168 142,153,155

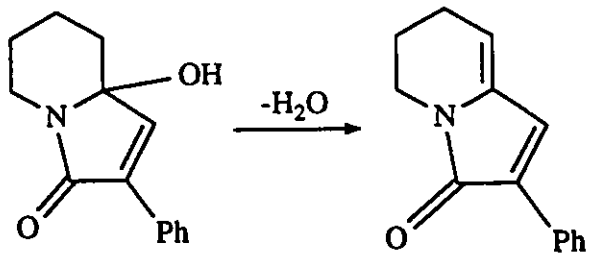
4.2.7 The oxidation of 5,6,7,8-tetrahydroindolizines with singlet oxygen

A crystal sample of 2-phenyl-5,6,7,8-tetrahydroindolizine **157** was grown in a small vial by dissolving in CH_2Cl_2 and keeping at room temperature for about 30 days, and the single crystals were sent for X-ray analysis. Surprisingly, the structure solution and refinement shows a new compound **169** with good Rf = 0.34, and Rw = 0.21 data (see Experimental Section). The ORTEP drawing is shown in Fig. 12. Further all the spectral data e.g. ^1H NMR, MS, GC (RT data) were consistent with the structure of **169** but not with **157** (see Experimental Section).



157 **169**

Compound **169**, in crystalline form, is very stable to air, moisture and light. A crystalline sample of **169** was dissolved in a solvent such as CH_2Cl_2, CH_3OH or $CDCl_3$. After several months, the solvent had evaporated and the sample remained in powdered form. ^1H NMR, COSY and HMQC (500 MHz) spectra of this powder (**170**) showed that it was a completely dehydrated form of **169** (See Figure 13, 14, 15, 16).



169 **170**

Figure 13 shows the unchanged ^1H NMR spectrum (200 MHz, in $CDCl_3$) of the crystalline sample **169** after standing in air, exposed to light and at room temperature for three months. Figure 14 shows the ^1H NMR spectrum (500 MHz, in CD_3OD) of the powdered sample **170** after 10 months. Compared with the ^1H NMR of **169**, the ^1H NMR spectrum of **170** shows the new absorption signal arising at 5.83 ppm, due to the proton attached at sp^2 carbon C^8 (different from the original two protons at sp^3 carbon C^8 at about 2.4 ppm). Figure 15, the COSY spectrum of **170**, clearly shows the correlation between the protons at each position. Figure 16 is the HMQC spectrum of **170** and shows the correlation between the protons and the attached carbon.

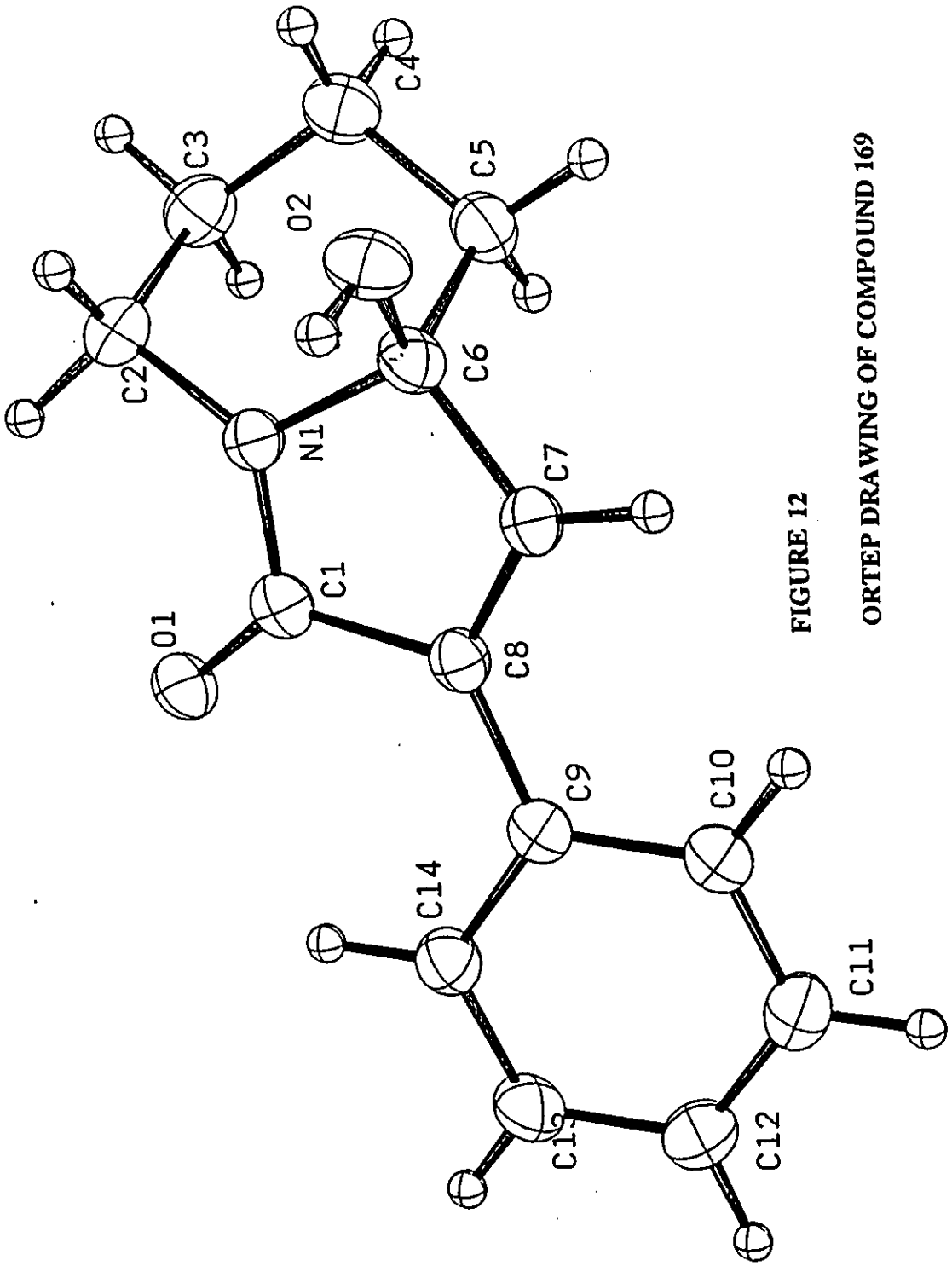
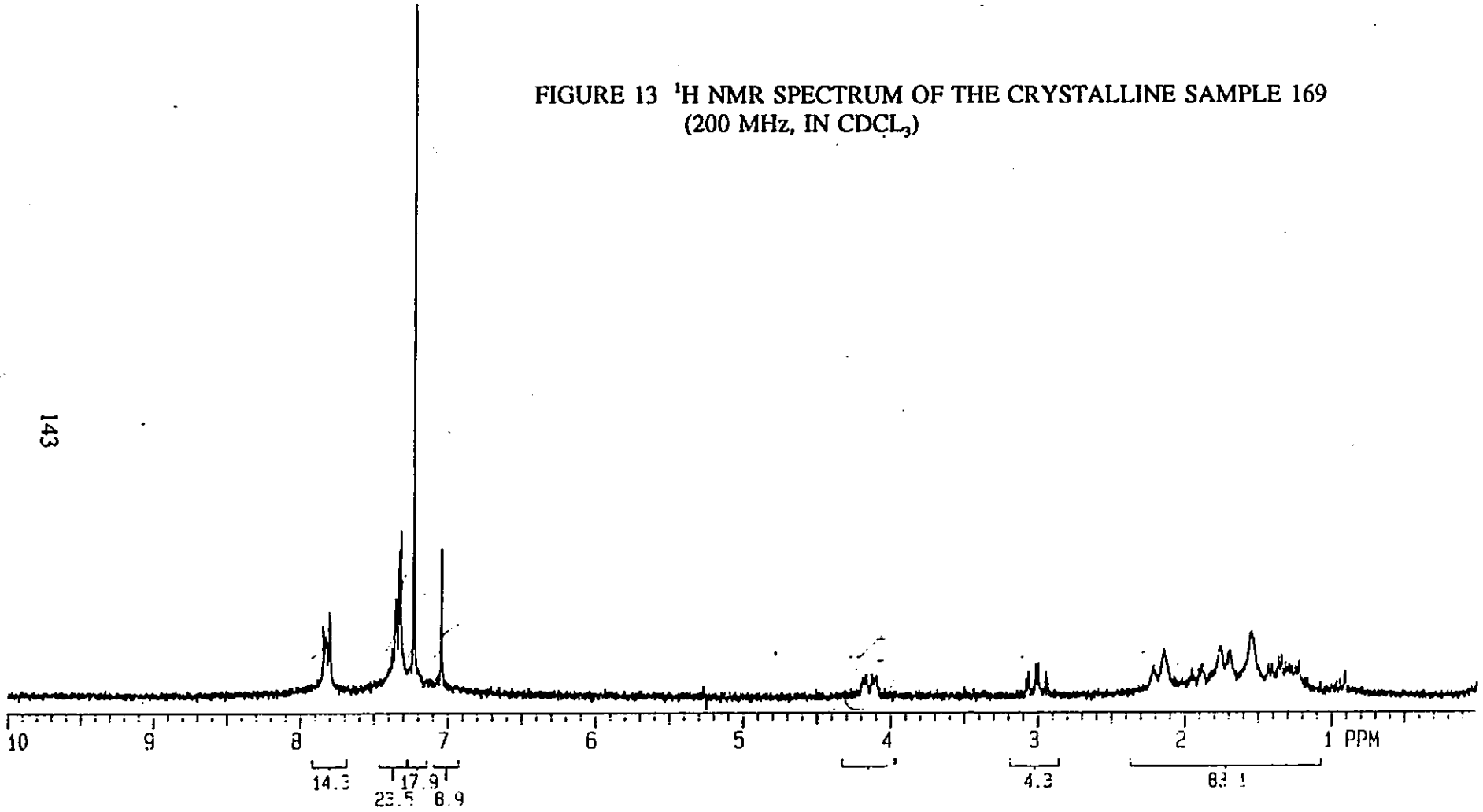


FIGURE 12

ORTEP DRAWING OF COMPOUND 169

FIGURE 13 ^{1}H NMR SPECTRUM OF THE CRYSTALLINE SAMPLE 169
(200 MHz, IN $CDCL_3$)



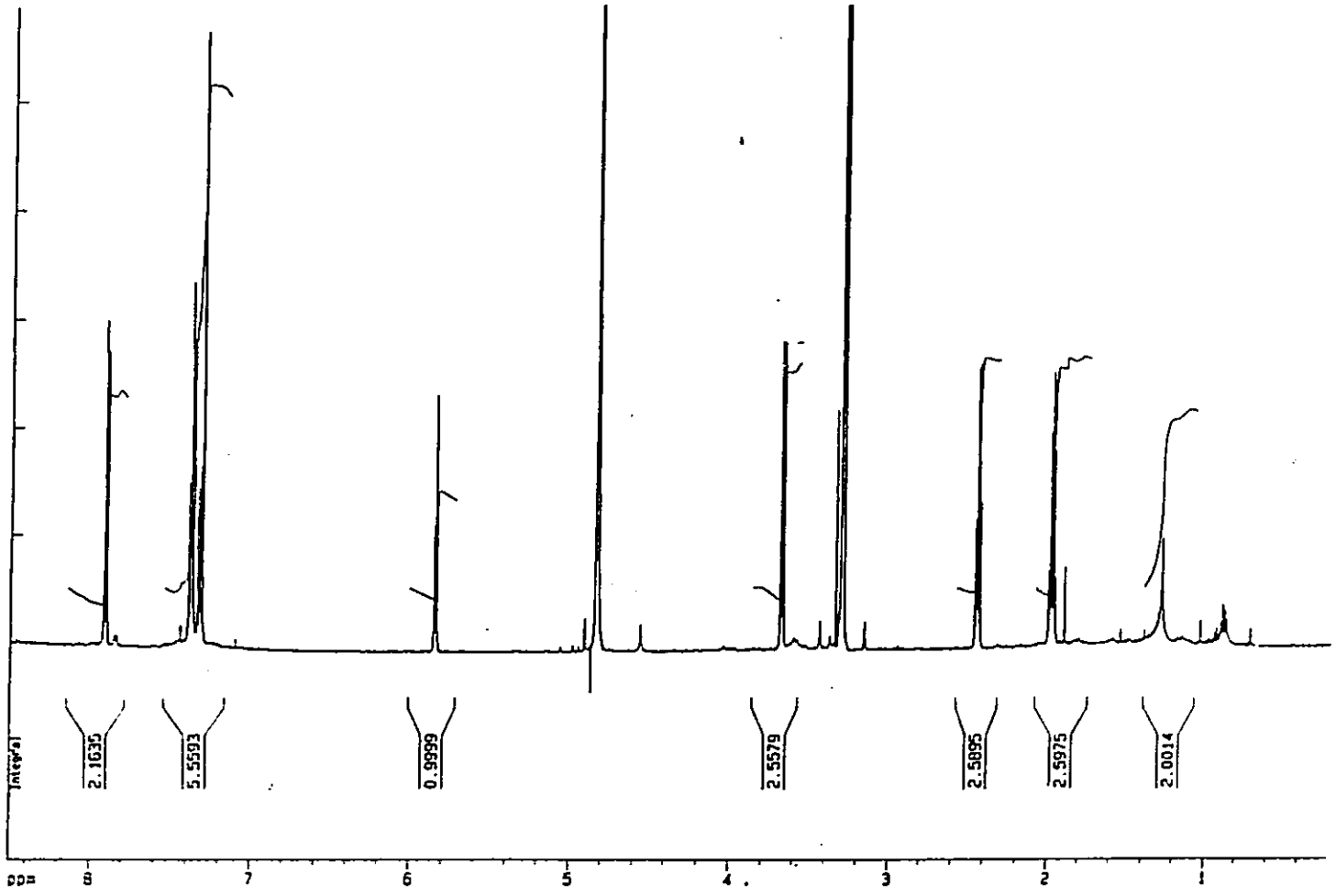


FIGURE 14 ^{1}H NMR (500MHz, CD_3OD) OF THE POWDER SAMPLE 170

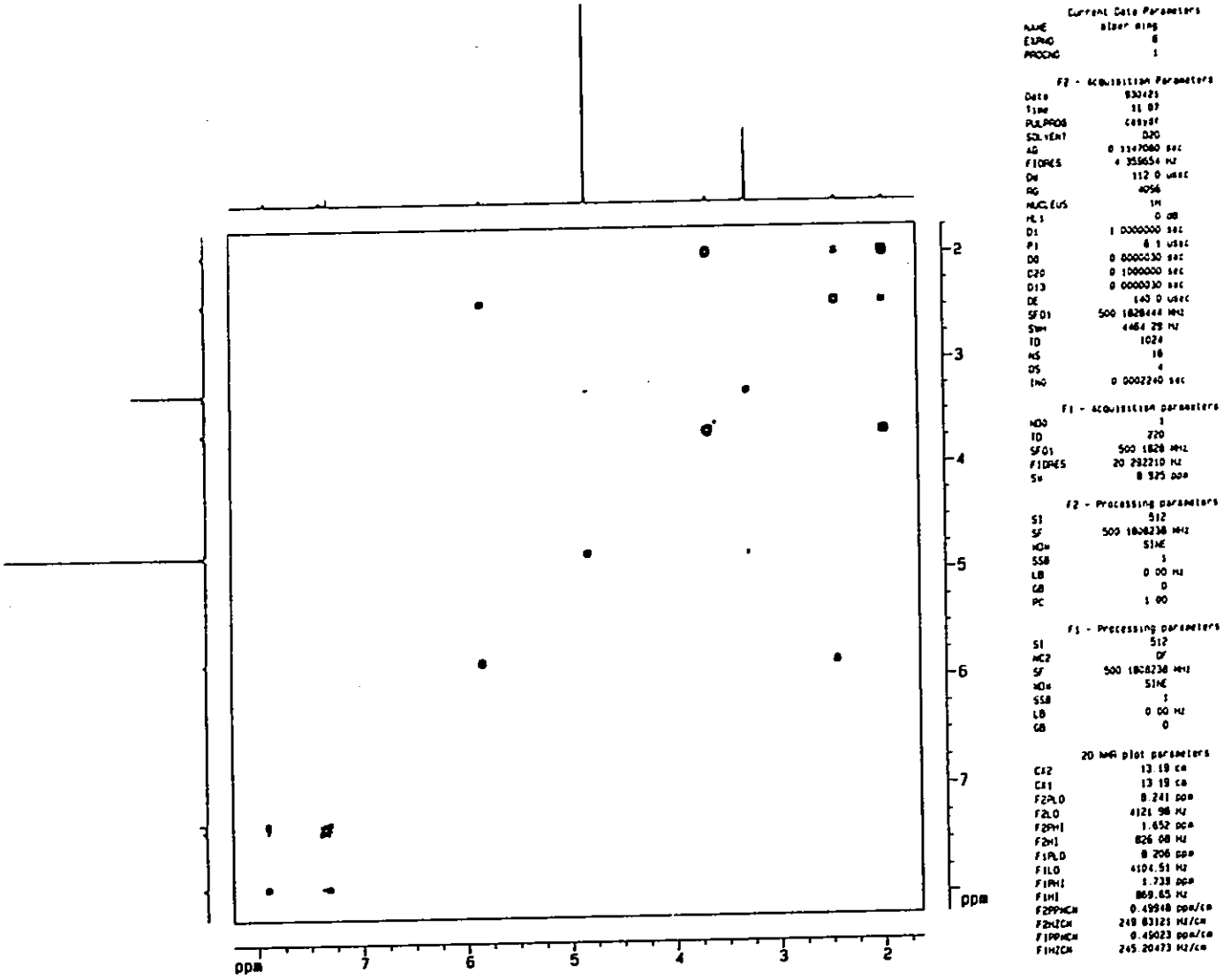


FIGURE 15 COSY SPECTRUM OF 170 (500 MHz, IN CD_3OD)

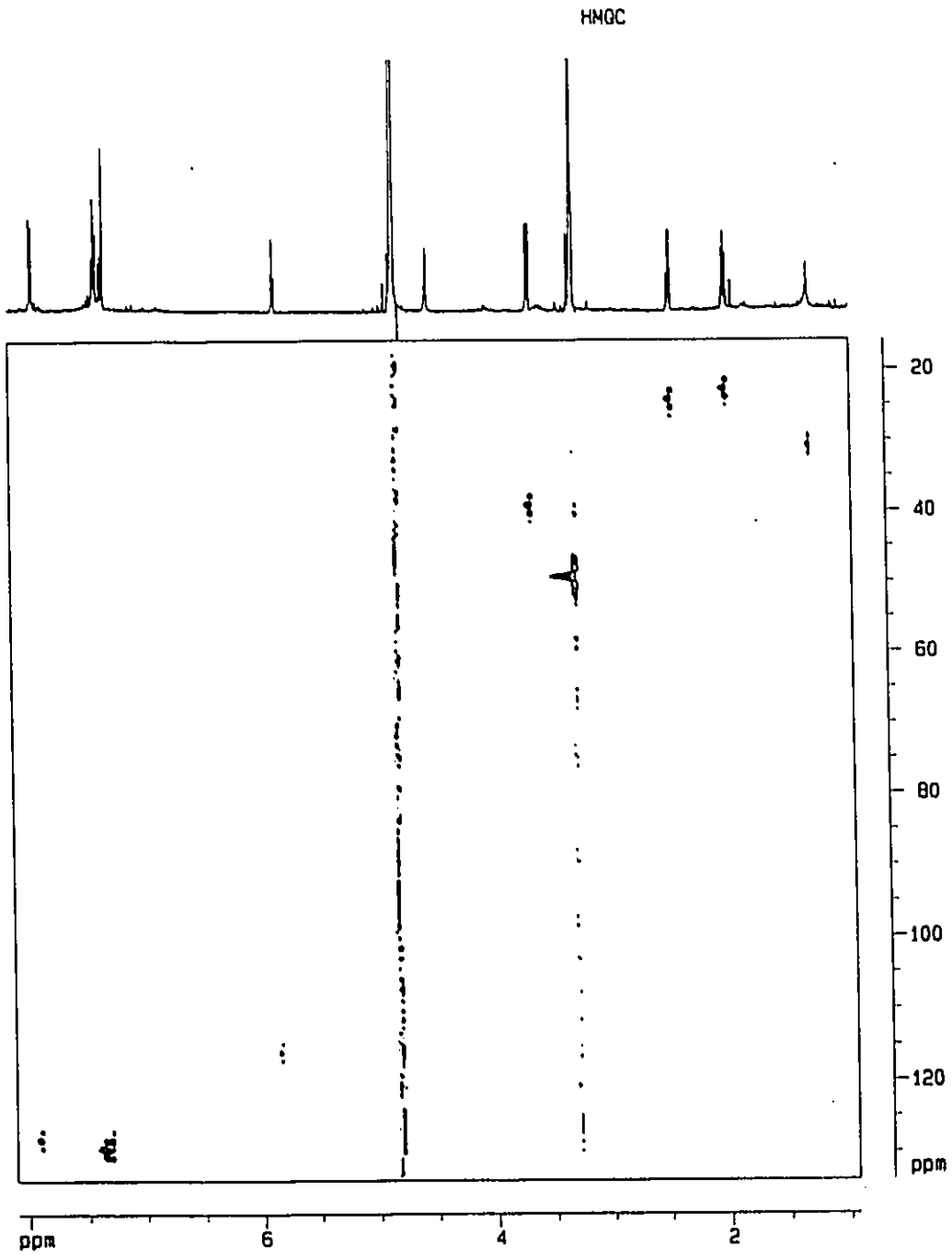
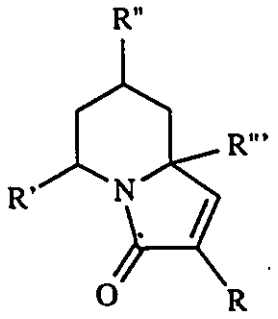


FIGURE 16 HMQC SPECTRUM OF 170 (500 MHz, IN CD_3OD)

To our knowledge, there are no examples of 8a-hydroxy-6,7,8,8a-tetrahydro-3(5H)indolizinone. Recently, Gilbert and Blackburn[147] have developed a synthetic method via N,N-disubstituted-2-oxopropanamides with diethyl (diazomethyl)phosphonate under basic conditions to give 3-pyrrol-2-ones including alkyl substituted 6,7,8,8a-tetrahydro-3(5H)-indolizinones **171** in 63-70% yield.



171 a-d

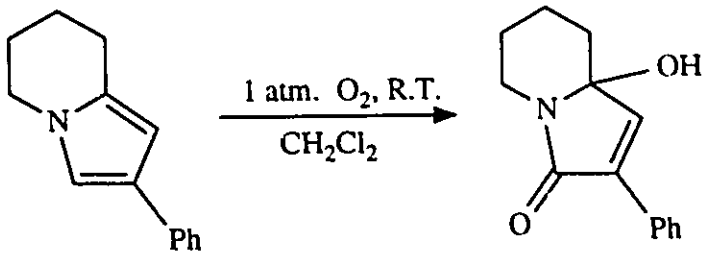
a, $R = CH_3$, $R' = R'' = R''' = H$

b, $R = CH_3$, $R' = CH_3$, $R'' = R''' = H$

c, $R = CH_3$, $R' = R'' = H$, $R''' = CH_3$

d, $R = CH_3$, $R' = R''' = H$, $R'' = t\text{-}Bu$

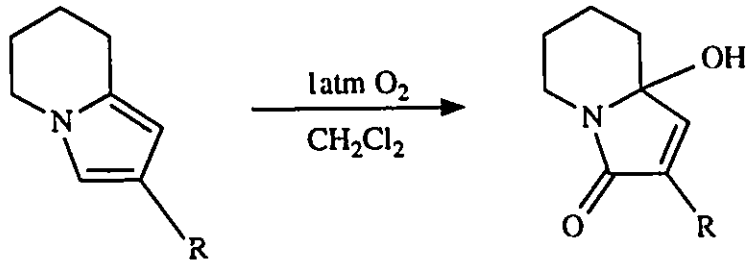
The transformation of compound **157** to **169** seems to proceed via an oxidative reaction by oxygen in air. In order to prove this, compound **157**, prepared by the cyclization reaction of **156**, was reacted with oxygen bubbled at 1 atm in CH_2Cl_2. after 6 hours, the conversion of **157** was 92% (GC yield) and after work-up, the isolated yield of **169** was 63%.



157 **169**

Side reactions are complicated and resulted in several low yield by-products of unproved structure.

Oxidation of other 2-alkyl-5,6,7,8-tetrahydroindolizines (e.g. 2-ethyl 5,6,7,8-tetrahydroindolizine), gave analogous **172a** but in lower yield than **169** and **172b**.



160a,b **172a,b**

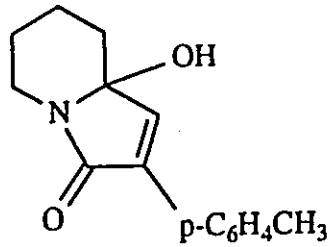
a, R = CH_2CH_3 yield: 21%*

b, R = 4-$CH_3C_6H_4$ 68%

(* GC yield)

The structure of the oxidation product **172b** was also proven by single crystal X-ray analysis data and IR, ^1H NMR, ^{13}C NMR, and MS (see Experiment Section). The ORTEP drawing of **172b** is shown in Fig.17.

172b :



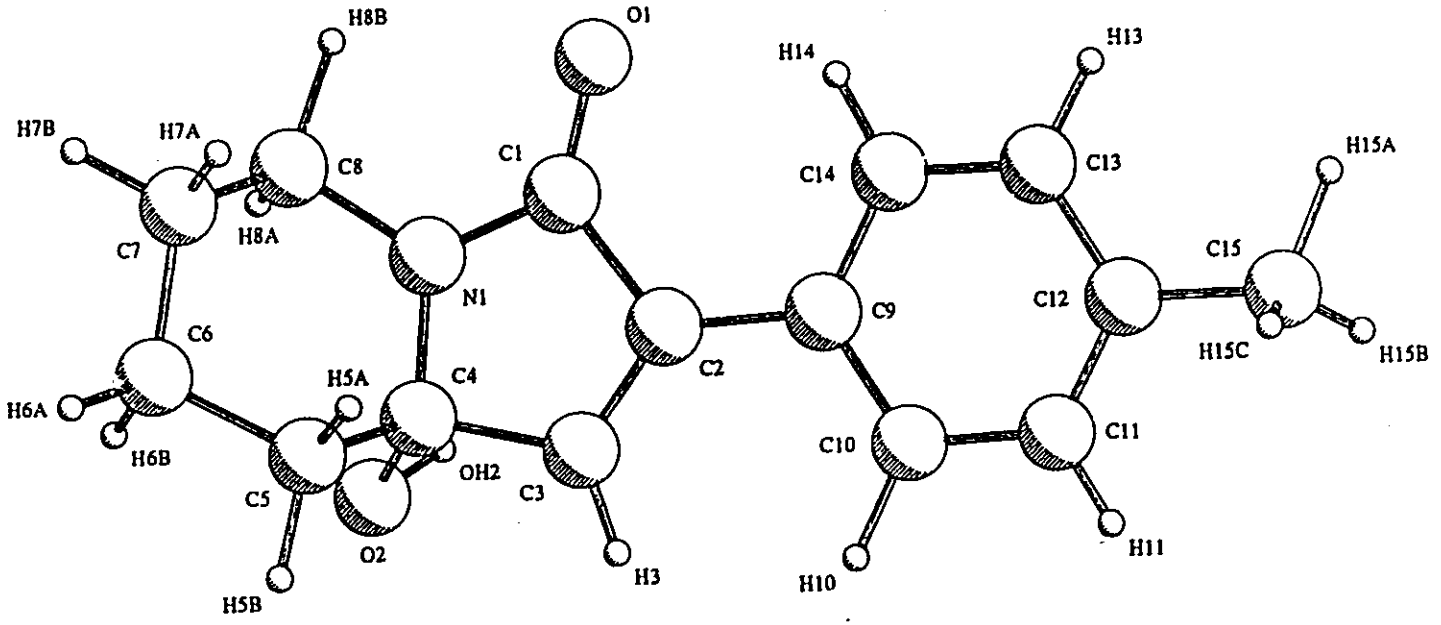
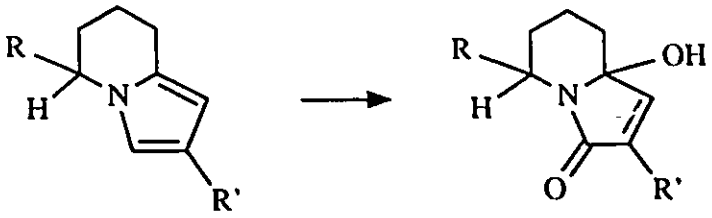


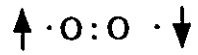
FIGURE 17 ORTEP DRAWING OF COMPOUND 172b

One representative compound **155** of 5-methyl-2-substituted 5,6,7,8-tetrahydroindolizine undergoing an oxidation reaction under the same mild conditions, converted to **173a** in 10% (by GC-MS) and several other products.



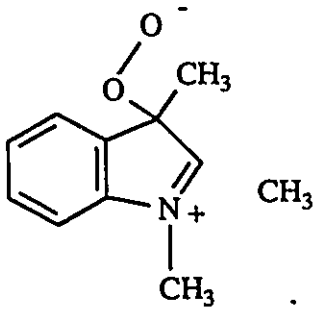
155 R=CH_3, R'=C_6H_{13}-n **173** 10%

The results of this oxidation reactions show that oxygen is the oxidizing agent for these transformations. Air, the cheapest oxidant, is used only rarely without irradiation and without catalysts for such oxidation reactions. Examples of oxidations by air alone are the conversion of aldehydes into carboxylic acids (autoxidation) and the oxidation of acyloins to α-diketones.[148] Usually, exposure to light, irradiation with ultraviolet light, or catalysts are needed. Under such circumstances, oxygen is in an excited state (singlet oxygen) with two odd electrons possessing antiparallel spins:



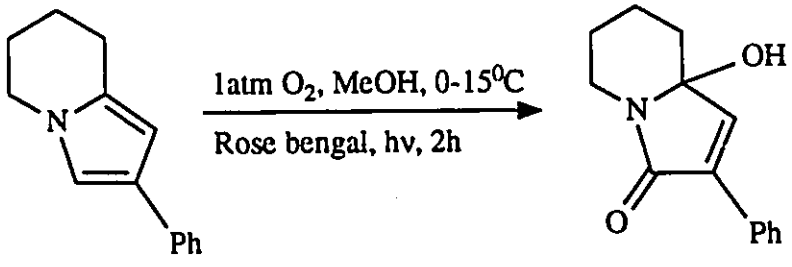
In the presence of sensitizers that absorb the light of a particular wavelength, e.g. benzophenone, rose bengal, methylene blue, etc., under irradiation of gaseous

oxygen, singlet oxygen forms and reacts with organic compounds in the same way as singlet oxygen generated chemically.[148] For example, singlet oxygen (produced by dye-sensitized irradiation) forms the same type of peroxide but probably by electrophilic attack at C-3 of indoles, since the zwitterionic intermediate **174** to be expected for such an attack on 1,3-dimethylindole has been detected.[149]



174

In order to know whether singlet oxygen was involved in these oxidation reactions, **157** was treated with singlet oxygen generated in situ, using rose bengal as a sensitizer by irradiation of oxygen by a 450-W high-pressure mercury immersion lamp (Hanovia 679 A36, cooled by running water) with a pyrex filter.[150] After 2 hours of irradiation and left to stand at room temperature in the dark over night, **169** was obtained in 71% yield.

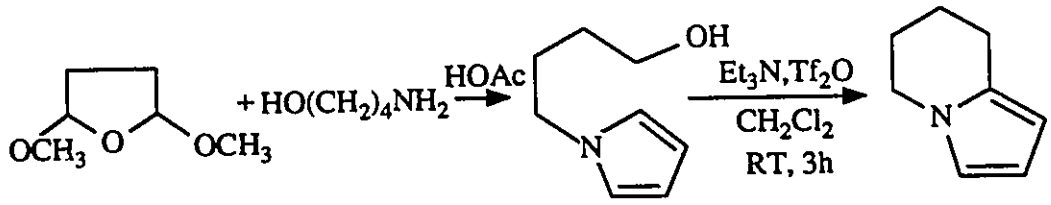


157 **169**

Apparently, the transformation of 5,6,7,8-tetrahydroindolizines to 8a-hydroxy-6,7,8,8a-tetrahydro-3(5H)-indolizinones can proceed by a singlet oxygen mechanism process. But the question arises why in our case the oxidation reaction could occur without irradiation (but exposure to light) and without any sensitizer. There must be some catalytic species to make this reaction possible. Because oxidations with oxygen are free-radical reactions, free radicals should be good initiators. In practice many oxidations are catalyzed by transition metals, such as platinum,[151,152] or, more often, metal oxides and salts, especially salts soluble in organic solvents. Cobalt[153,154] is one of the many favored catalysts.[148] Some transition metal complexes have been shown to be effective as catalysts for the selective oxidation of organic substrates in combination with oxidizing agents such as hydroperoxides[155] or amine oxides.[156] While such procedures are of obvious utility, they do require the consumption of expensive organic oxidants. Clearly the ability to use molecular oxygen in a procedure which selectively oxidizes organic compounds under mild conditions would be more desirable. Examples include the homogeneous $PdCl_2$-NaOAc catalyzed oxidation of secondary alcohols to ketones[157] by molecular oxygen at room temperature or H_2PtCl_6 and $CuCl_2$ catalyzed selective oxidation of both aliphatic and allylic primary alcohols to aldehydes without over-oxidation to the carboxylic acid[158] under 1 atm and visible light.

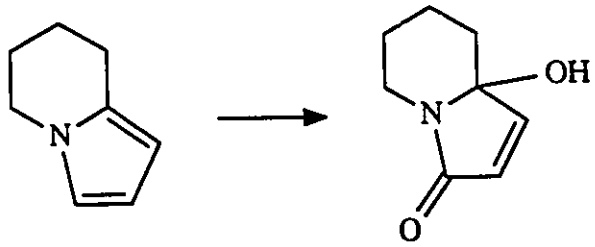
Since the reactants, such as **157,160a,b** are prepared by $Co_2(CO)_8$ catalyzed cyclization reactions, and then used in the next oxidation reaction, it is possible that a trace amount of oxidized cobalt complex such as cobalt oxide or hydroxide participated in the oxidation reaction with **157** or **160a,b**. In order to check this possibility, the following synthetic methods were used to prepare the analogue of **157**, i.e. 5,6,7,8-tetrahydroindolizine **150**.[159,145] In this way, the presence of any

trace amonts transition metal in the reaction can be avoided.



175 **150**

4-(1-pyrrolyl)butal **175** was prepared in 54% yield by the reaction of 2,5-dimethoxytetrahydrofuran with 4-aminobutanol in glacial acetic acid following the literature procedure.[159] Treatment of **175** with Tf_2O/Et_3N yielded **150** in 50% yield.[145] **150** is now a model compound. A solution of **150** in CH_2Cl_2 was bubbled with oxygen gas (exposed to the light in a fumehood) and the reaction was monitored by GC. After 3 days more than 95% of unchanged **150** was recovered (a colour change to brown as compared to the original colourless was observed). However, treatment of **150** with 3% $Co_2(CO)_8$ (which had oxidized to a blue colour) and 1 atm O_2 for 12h, about 20% of **176** (8a-hydroxy-5,6,7,8-tetrahydro-3(5H)-indolizine was produced.



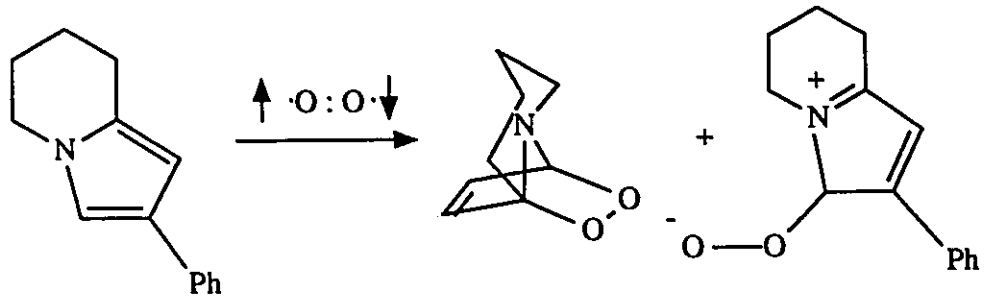
150 **176**

If 5% $CoCl_2$ was used as a catalyst, the similar results were obtained. The photoreaction of **150** in the presence of rose bengal as sensitizer afforded about 25% (GC yield) of **176**. During all the oxidation reactions of **150** with singlet oxygen and following work-up procedure, some decomposition and polymerization were observed. It was probably due to the lack of an electron withdrawing group (e.g. phenyl at 2-position) to stabilize some transition states. Nevertheless, the results show that the transformation of 5,6,7,8-tetrahydroindolizines to 8a-hydroxy-6,7,8,8a-tetrahydro-3(5H)-indolizinones does need singlet oxygen whether generated under photo- or catalysis circumstances.

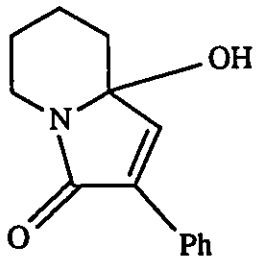
It is known that, heterocyclic systems such as furans, oxazoles and imidazoles undergo photooxidation reactions to afford useful oxidation products. However, very little use has been made of them in pyrrole systems because of normally low yields and multiple product formation along with considerable decomposition. One piece of work performed in the Wasserman group in 1991 involved reactions of singlet oxygen with 3-methoxy-2-carbalkoxypyrroles. The reactions lead to the 2,5-oxygenation product in 45% yield; if pyridine (10%) is present, the yield was enhanced to 80%. In that event, the irradiation in the presence of a photosensitizer, e.g. methylene blue or rose bengal, is necessary. Our results involving O_2 based catalytic oxidation (or alternatively photooxidation) of 5,6,7,8-tetrahydroindolizines to give 8a-hydroxy-6,7,8,8a-tetrahydro-3(5H)-indolizinones under very mild conditions (1 atm, room temperature) may also have some potential synthetic uses. This is especially true, when there is a phenyl group at the 2-position, where the yield of 8a-hydroxy-2-phenyl-6,7,8,8a-tetrahydroindolizinones can be as high as 63% (**169**) and 68% (**172b**).

The transformation of 5,6,7,8-tetrahydroindolizines to 8a-hydroxy-6,7,8,8a -tetrahydro-3(5H)-indolizinones in the presence of singlet oxygen preceeds the formation of oxides or endooxides from conjugated dienes by 1,4-addition (Diels-Alder reaction). The formation of 8a-hydroxy-6,7,8,8a-tetrahydro -3(5H)-indolizinones are in accord with the expected decomposition of an intermediate 3,8a-transannular peroxide **177** by a β-elimination or from the formed zwitterion **178** (Scheme 11).

Scheme 11



157 **177** **178**



169

4.3 Experimental Section

4.3.1 GENERAL COMMENTS

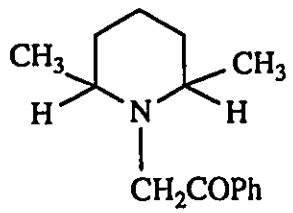
The general comments of Chapter 2 are applicable here.

A 450-W high-pressure mercury immersion lamp (Hanovia 679 A36, cooled by running water) with a Pyrex filter were used for the photoreaction of 2-phenyl-5,6,7,8-tetrahydroindolizine (**157**) or 5,6,7,8-tetrahydroindolizine (**150**) with oxygen (1atm) in the presence of rose bengal as a sensitizer.

4.3.2 GENERAL PROCEDURE FOR THE PREPARATION OF REACTANT KETONES

The general procedure of Chapter 2, Section 2.3.2.4, is also applicable for the preparation of starting ketones such as **152**, **154**, **159a** (method b), **156** **159b** and **161** (method a).

152 :



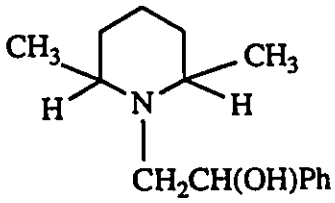
69% yield;

IR ($CDCl_3$) ν (CO) 1689cm^{-1};

^1H NMR ($CDCl_3$) δ 1.03 (d, 6H, CH_3); 1.28-1.53 (m, 6H, protons at C3-C5); 3.03 (m, 2H, $2NCHCH_3$); 4.20 (s, 2H, NCH_2CO); 7.45 (m, 3H, meta and para protons of Ph); 7.93 (m, 2H, ortho protons of Ph);

MS (EI) m/e 231 $[M]^+$.

152 was prepared via 1-phenyl-2-(2,6-dimethylpiperidinyl)ethanol:



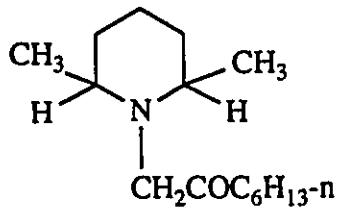
85% yield; bp 125-128^{0}C/0.4mmHg;

IR ($CDCl_3$) ν (OH) 3385cm^{-1};

^1H NMR ($CDCl_3$) δ 1.16 (d, 6H, CH_3 at C2, C6); 1.30-1.72 (m, 6H, protons at C3-C5); 2.61 (m, 4H, NCH_2 and 2NCH); 4.56 (m, 1H, CHPh); 7.27 (m, 5H, Ph);

MS (EI) m/e 215 $[M-H_2O]^+$.

154 :



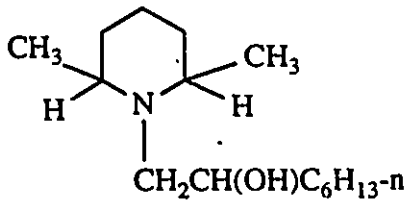
90% yield; bp 108-109^{0}C/0.3mmHg;

IR ($CHCl_3$) ν (CO) 1712cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3CH_2); 0.98 (d, 6H, CH_3 at C2, C6); 1.23-1.54 (m, 14H, $CH_3(CH_2)_4$ and C3-C5 of ring); 2.39 (t, 2H, $COCH_2$); 2.72 (m, 2H, protons at C2, C6 of ring); 3.39 (s, 2H, NCH_2CO);

MS (EI) m/e 224 $[M\text{-}CH_3]^+$.

154 was prepared via 1-(2,6-dimethylpiperidinyl)-2-octanol:

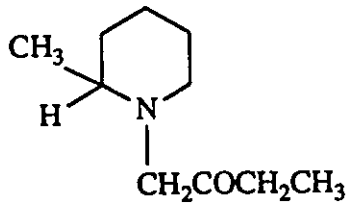


80%; bp 103-106^0/0.4mmHg;

IR ($CHCl_3$) ν (OH) 3385cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, CH_3); 1.01 (d, 6H, CH_3 at C2, C6); 1.20-1.60 (m, 16H, $CH_3(CH_2)_5$, protons at C3-C5 of ring); 2.49 (m, 4H, NCH_2 and 2NCH); 3.49 (m, 1H, CHOH);

MS (EI) m/e 208 $[M\text{-}H_2O\text{-}CH_3]^+$.

159a: 

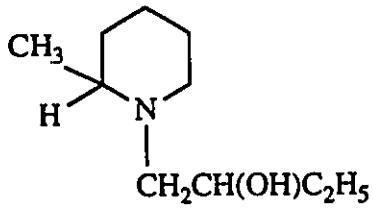
yield 87%; pale yellow liquid;

IR (neat) ν (CO) 1717cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.99 (d, 3H, CH_3CH); 1.02 (t, 3H, CH_3CH_2); 1.30-1.51 (m, 6H, C3-C5 ring); 2.33 (m, 2H, NCH_2 ring); 2.43 (q, 2H, CH_2CH_3); 2.72 (m, 1H, CH); 2.99 (d $^2J_{HaHb}$=19Hz, 1H, H_a of NCH_2); 3.41 (d $^2J_{HaHb}$=19Hz, 1H, H_b of NCH_2);

MS (EI) m/e 154 $[M-CH_3]^+$, 112 $[M-C_2H_5CO]^+$ base peak.

159a was prepared via 1-(2-methylpiperidinyl)-2-butanol:



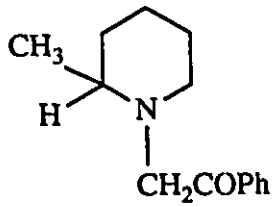
75% yield; bp 63-65^{0}C/0.2mmHg;

IR ($CDCl_3$) ν (OH) 3364cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, CH_3CH_2); 0.99 (d, 3H, CH_3CH); 1.25-1.67 (m, 6H, protons at C3-C5 ring); 2.01 (dq, 2H, CH_2CH_3); 2.52 (m, 4H, 2 NCH_2); 2.89

(m, 1H, $CHCH_3$); 3.45 (m, 1H, CH(OH)); 3.80 (br, 1H, OH);

MS (EI) m/e 153 $[M-H_2O]^+$.

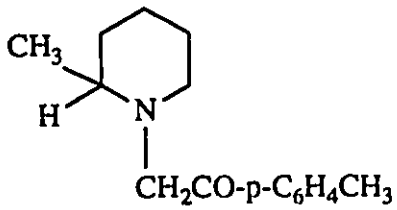
156 : 

63% yield; bp 114-116^{0}C/0.45mmHg;

IR ($CDCl_3$) ν (CO) 1683cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3H, CH_3); 1.23-1.83 (m, 6H, protons at C3-C5 of piperidine ring); 2.79 (m, 2H, NCH_2 ring); 3.40 (m, 1H, $CHCH_3$); 4.00 (m, 2H, NCH_2CO); 7.35 (m, 3H, meta and para protons of Ph); 8.01 (m, 2H, ortho protons of Ph);

MS (EI) m/e 112 $[M-PhCO]^{+\cdot}$ 105 $[PhCO]^+$.

159b : 

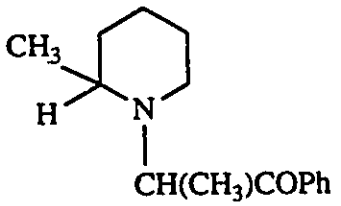
50% yield; bp 107^{0}C/0.1mmHg;

IR (neat) ν (CO) 1684cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.08 (d, 3H, CH_3CH); 1.26-1.69 (m, 6H, protons at C3-C5 ring); 2.33 (s, 3H, Ph-CH_3); 2.85 (m, 2H, CH_2N ring); 3.05 (m, 1H, CH); 3.75 (d ^{2}J= 20Hz, 1H, H_a of CH_2N chain); 4.09 (d ^{2}J= 20Hz, 1H, H_b of CH_2N chain); 7.22 (dd, 2H, meta-protons of Ph); 7.88 (dd, 2H, ortho-protons of Ph);

MS (EI) m/e 231 $[M]^+$, 112 $[M\text{-}COC_6H_4CH_3]^+$ base peak.

161 :



39% yield; bp 143-145^{0}C/0.55mmHg;

IR (neat) ν (CO) 1684cm^{-1};

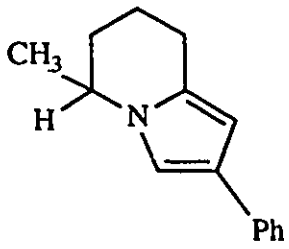
^{1}H NMR ($CDCl_3$) δ 1.12 (d, 3H, CH_3CHring); 1.24 (d, 3H, CH_3CHchain); 1.35-1.68 (m, 6H, protons at C3-C5 ring); 2.54 (m, 2H, NCH_2); 2.97 (m, 1H, CH ring); 4.54 (q, 1H, CH chain); 7.28-7.65 (m, 5H, Ph);

4.3.3 GENERAL PROCEDURE FOR THE $Co_2(CO)_8$ AND/OR $Ru_3(CO)_{12}$ CATALYZED CYCLIZATION REACTION OF 2-METHYL(OR 2,6-DIMETHYL)PIPERIDINYL KETONES

Application of the "rearrangement" procedure (Chapter 3, Experiment Section) to **152**, **154**, **156** resulted in exclusive cyclization to **153**, **155** while **156**

afforded the cyclized heterocycle **157** as the predominant product, with the rearranged ketone **158** obtained as a minor product. Note that the cyclization of **152** to **153** occurs in almost in high yield using only $Co_2(CO)_8$ or $Ru_3(CO)_{12}$ rather than both metal catalysts. Yields and characterization data for the bicyclic heterocycles **153** and **155** as well as rearranged **158**, are as follows.

153 :



94% yield; (84% using $Ru_3(CO)_{12}$ only);

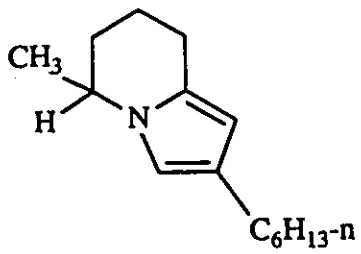
^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3H, CH_3); 1.81-2.01 (m, 4H, $CH_3CHCH_2CH_2$); 2.76 (m, 2H, CH_2C=); 4.09 (m, 1H, $CHCH_3$); 6.11 (d $^4J_{H1H3}$= 2Hz, 1H, proton at C1); 6.92 (d $^4J_{H3H1}$= 2Hz, 1H, proton at C3); 7.28-7.46 (m, 5H, Ph);

^{13}C NMR ($CDCl_3$) δ 19.69, 22.30 ($CH_3CHCH_2CH_2$), 22.31 (CH_3), 31.89 (CH_2C=), 50.56 ($CHCH_3$), 102.12 (C1), 113.64 (C3), 124.87, 125.00, 128.40, 129.05 (aromatic CH), 130.66, 136.17 (q-C);

MS (EI) m/e 211 $[M]^+$;

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26% H, 8.11% N, 6.63%

Found: C, 84.86% H, 8.32% N, 6.57%

155 : 

91% yield;

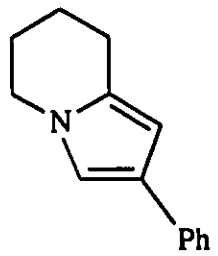
^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3CH_2); 1.25-1.68 (m, 11H, $CH_3(CH_2)_4$ and CH_3CH); 1.78-1.91 (m, 4H, $CH_3CHCH_2CH_2$); 2.39 (t, 2H, $CH_3(CH_2)_4CH_2$); 2.71 (m, 2H, CH_2C=); 3.98 (m, 1H, $CHCH_3$); 5.56 (d $^4J_{H1H3}$= 2Hz, 1H, proton at C1); 6.56 (d $^4J_{H3H1}$= 2Hz, 1H, proton at C3);

^{13}C NMR ($CDCl_3$) δ 14.17 (CH_3CH_2), 19.99, 23.63 ($CH_3CHCH_2CH_2$), 22.30 (CH_3CH), 22.67, 27.29, 29.49, 31.23, 31.83 ($CH_3(CH_2)_5$), 32.13 (CH_2C=), 50.49 ($CHCH_3$), 104.08 (C1), 113.82 (C3), 124.27 (C2), 129.34 (C8a);

MS (EI) m/e 219 $[M]^+$;

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13% H, 11.49% N, 6.385%

Found: C, 81.79%, H, 11.11%, N, 6.18%

157 : 

73% yield;

^{1}H NMR ($CDCl_3$) δ 1.73-2.08 (m, 4H, protons at C6, C7); 2.78 (m, 2H, CH_2C=), 3.80 (m, 2H, CH_2N); 6.15 (d $^4J_{H1H3}$= 2Hz, 1H, proton at C1); 6.86 (d $^4J_{H3H1}$= 2Hz, 1H, proton at C3); 7.35 (m, 5H, Ph);

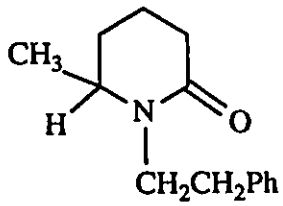
^{13}C NMR ($CDCl_3$) δ 21.39, 23.30 (C6, C7), 29.26 (CH_2C=), 45.42 (NCH_2), 102.12 (C1), 115.45 (C3), 124.94, 125.21, 128.33, 128.77 (aromatic CH), 130.47 (C2), 137.10 (C8a);

MS (EI) m/e 197 $[M]^+$;

Anal. Calcd for $C_{14}H_{15}N$: C, 85.24% H, 7.66% N, 7.10%

Found: C, 84.89%, H, 7.27, N, 6.98%

158 :



7% yield;

IR ($CHCl_3$) ν (CO) 1628cm^{-1};

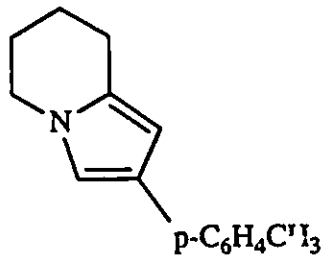
^{1}H NMR ($CDCl_3$) δ 1.35 (d J=6Hz, 3H, CH_3CH); 1.69 (m, 4H, protons at C4, C5 ring); 2.32 (t, 2H, CH_2CO); 2.81 (AA'BB', 2H, CH_2Ph); 3.36 (AA'BB', 2H, NCH_2); 3.81 (m, 1H, $CHCH_3$); 7.28 (m, 5H, Ph);

MS (EI) m/e 217 $[M]^+$.

This metal catalized cyclization reaction contrasts to the rearrangement process which requires both $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ as catalysts. For example, the

cyclization of **152** to **153** occurs in high yield using only $Co_2(CO)_8$ or $Ru_3(CO)_{12}$ rather than both metal catalysts. Cyclization products **160a,b**, and **162** are produced by the reactions of **159a,b**, **161** using $Co_2(CO)_8$ as only catalyst.

160b :

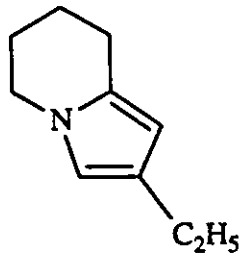


83% yield;

^1H NMR ($CDCl_3$) δ 1.67-1.94 (m, 4H, protons at C6,C7); 2.51 (s, 3H, CH_3); 2.72 (m, 2H, CH_2C=); 3.86 (m, 2H, CH_2N); 6.06 (d $^4J_{H1H3}$= 1.5Hz, 1H, proton at C1); 6.72 (d $^4J_{H3H1}$= 1.5Hz, 1H, proton at C3); 7.12 (m, 2H, meta-protons of Ph); 7.79 (m, 2H, ortho-protons of Ph);

^{13}C NMR ($CDCl_3$) δ 21.06 (CH_3), 21.58, 23.30 (C6, C7), 26.85 (C8), 45.32 (C5), 102.22 (C1), 115.10 (C3), 124.83, 128.30, 128.41, 129.21 (Ph-CH), 130.03, 133.85, 134.67, 143.79 (qC);

MS (EI) m/e 211 $[M]^+$

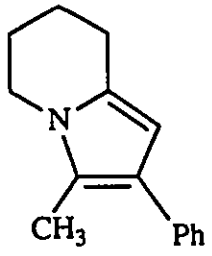
160a : 

76% yield;

^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, CH_3CH_2); 1.55-1.91 (m, 4H, protons at C6, C7); 2.45 (q, 2H, CH_2CH_3); 2.71 (t, 2H, CH_2C=); 3.84 (t, 2H, CH_2N); 5.685 (d $^4J_{H1H3}$= 1.5Hz, 1H, proton at C1); 6.28 (d $^4J_{H3H1}$= 1.5Hz, 1H, proton at C3);

^{13}C NMR ($CDCl_3$) δ 15.44 (CH_3), 20.23, 21.65, 23.36, 24.01 (C6-C8 and CH_2 at chain), 45.105 (C5), 103.89 (C1), 115.32 (C3), 125.91 (C2), 129.03 (C8a);

MS (EI) m/e 149 $[M]^+$, 134 $[M-CH_3]^+$.

162 : 

54% yield;

^{1}H NMR ($CDCl_3$) δ 1.87-2.10 (m, 4H, protons at C6, C7); 2.34 (s, 3H, CH_3); 2.85 (t, 2H, CH_2C=); 3.83 (t, 2H, CH_2N); 6.08 (s, 1H, proton at C1); 7.25-7.65 (m, 5H, Ph);

^{13}C NMR ($CDCl_3$) δ 10.51 (CH_3), 21.16, 23.70, 23.795 (C6-C8), 43.04 (C5),

103.88 (C1), 124.92, 125.30, 128.29, 128.60 (PhC), 129.70, 132.92, 137.75 (qC of C2, C8a and PhC).

MS (EI) m/e 211 $[M]^+$.

4.3.4 PREPARATION OF 5,6,7,8-TETRAHYDROINDOLIZINE 150

5,6,7,8-tetrahydroindolizine **150** was prepared from 1-(4-hydroxybutyl)pyrrole **175** following the literature methods.[159,145] Compound **175** (1.41 g, b.p 63-67^{0}C/0.02mmhg), thus obtained from the reaction of 4-aminobutanol (5.00 g, 56.1 mmol) with 2,5-dimethoxytetrahydrofuran (2.51g, 19.0 mmol), in glacial HOAc solution (10 ml) in 54% yield (ref. b.p 69%). The reaction of **175** (1.41 g, 10.1 mmol), triethylamine (1.025 g, 10.15 mmol) and trifluomethanesulfonic anhydride [1.71 ml (d=1.677), 10.144 mmol] in 30 ml CH_2Cl_2 at room temperature for 3h afforded **150** (0.615 g, b.p 22-24^{0}C/0.03 mmhg) in 50% yield.

150 : colourless liguid;

^{1}H NMR ($CDCl_3$) δ 1.72-1.98 (m, 4H, protons at C6, C7); 2.78 (t, 2H, protons at C8); 3.92 (t, 2H, protons at C5); 5.82 (m, 1H, proton at C1); 6.10 (dd, 1H, proton at C2); 6.49 (dd, 1H, proton at C3);

MS (EI) m/e 121 $[M]^+$, 120 $[M-H]^+$ base peak.

4.3.5 VARIATION IN CYCLIZATION REACTION CONDITIONS

In order to optimize the reaction conditions for the cyclization, experiments with **159a** were carried out and followed by GC using undecane as the internal

standard.

A mixture of 106mg (0.64mmol) of **159a**, 55mg (0.16mmol) of $Co_2(CO)_8$ and 5ml of dry, freshly distilled benzene and 39mg of undecane was placed in a autoclave with glass liner, and pressurized to 54atm CO. When the stirred reaction was run at 100-110^{0}C after 3days, no conversion of **159a** occurred. If the temperature was increased to 150-160^{0}C for 60h, the conversion increased to 32%, while at 194-196^{0}C for 60h the conversion rose to 82%. If the reaction temperature reached to 200-205^{0}C for 2days, the complete conversion of **159a** was obtained.

4.3.6 BLANK REACTION

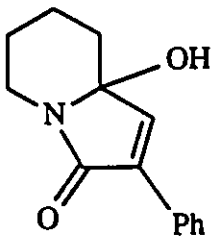
A mixture of 60mg (0.26mmol) of **152** and 21mg of undecane (internal standard) in 3.5ml of dry benzene was placed in a autoclave with a glass liner under 54 atm of carbon monoxide and heated at 205-210^{0}C for 60h without any catalyst. The cooled mixture was analyzed by GC and GC-MS. No cyclization product **153** appeared at all, but decomposed fragments of starting materal **152** appeared, such as acetophenone.

4.3.7 GENERAL PROCEDURE FOR THE OXIDATION OF 2-SUBSTITUTED 5,6,7,8-TETRAHYDROINDOLIZINES WITH OXYGEN

A mixture of 120mg (0.6 mmol) of 2-phenyl-5,6,7,8-tetrahydroindolizine **157** (as a model compound) and 3ml dry freshly distilled CH_2Cl_2 was bubbled with oxygen gas. The reaction was followed by GC, and after 6h bubbling of O_2 the conversion of **157** reached 95%. The reaction mixture was then allowed to stand over night, followed by rotary evaporation of the solvent. Dry ether (20 ml) was

carefully added, and filtration gave 87mg (0.38mmol) of **169** as a brownlish solid, mp 123-125^{0}C. When CH_2Cl_2 as solvent was added into the residue and kept in a small vial with loosely capped, at room temperature for several days, colourless crystals of **169** were grown and some of these crystals were subjected by crystallographic examination.

169 :



63% yield; mp 123-125^{0}C;

IR ($CDCl_3$) ν (OH) 3625cm^{-1}, ν (CO) 1687cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.65-2.24 (m, 6H, protons at C6-C8); 3.02 (dt, J=3Hz, 14Hz, 1H, H_a of NCH$\mathcal{H}$CH$_2$); 4.16 (dd, J= 6Hz, 14Hz, 1H, H_e of NCH$\mathcal{H}$CH$_2$); 7.04 (s, 1H, proton at C1); 7.32 (m, 3H, meta and para-protons at Ph); 7.83 (m, 2H, ortho-protons at Ph).

MS (EI) m/e 229 $[M]^+$, 211 $[M-H_2O]^+$ base peak.

The single crystal X-ray analysis data including description of experimental procedures, listing of atomic parameters, bond lenths and angles for **169** are shown as following Table 12-15.

TABLE 12 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR 169

Empirical formula	NO2C14H15
Formula weight	229.28
Crystal shape	losange
Crystal dimensions (mm)	.2,.1,.3
Crystal system	triclinic
No. Reflection used for unit cell dimension (2theta range)	25 40,50
Lattice parameters	a=8.383(3) b=10.638(4) c=6.5937(15) alpha=100.333(23) beta=94.117(22) gamma=85.38(3)
Space group	P -1
Z value	2
Dcalc (g.cm-3)	1.323
F(000)	244.10
mu (mm-1)	.09
No of reflection measured	2165
No of reflection unique	2015
No of reflection observed	1648
No of atoms	32
No of variables	215
Rf (sign refl)	.034
Rw (sign refl)	.021
Rf (all refl)	.046
Rw (all refl)	.021
Goodness of fit	3.58
Last difference fourier map	
max peak	.180
min peak	-.170

TABLE 13 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 169

Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
O1	0.31947(15)	0.40067(10)	0.15180(16)	2.35(6)
O2	0.36781(18)	0.68617(12)	-0.27195(20)	2.52(6)
N1	0.29361(17)	0.57436(13)	-0.01449(20)	1.95(7)
C1	0.30726(20)	0.44723(16)	-0.0089 (3)	1.96(9)
C2	0.26404(24)	0.67599(18)	0.1629 (3)	2.34(9)
C3	0.0918 (3)	0.73387(20)	0.1389 (3)	2.72(9)
C4	0.0594 (3)	0.77510(20)	-0.0716(3)	2.84(10)
C5	0.09116(25)	0.66242(19)	-0.2474 (3)	2.47(9)
C6	0.26141(22)	0.60007(16)	-0.2261 (3)	2.11(8)
C7	0.28110(23)	0.46749(16)	-0.3504 (3)	2.17(9)
C8	0.30236(21)	0.37816(16)	-0.22978(24)	1.88(8)
C9	0.30976(21)	0.23724(16)	-0.2933 (3)	1.95(8)
C10	0.27134(25)	0.18542(17)	-0.4994 (3)	2.59(9)
C11	0.2683 (3)	0.05440(18)	-0.5633 (3)	3.30(10)
C12	0.3052 (3)	-0.02803(18)	-0.4235 (3)	3.09(10)
C13	0.3457 (3)	0.02171(18)	-0.2203 (3)	2.77(9)
C14	0.34797(23)	0.15295(17)	-0.1542 (3)	2.36(9)
H2A	0.3400 (19)	0.7396 (14)	0.1638 (22)	2.0 (4)
H2B	0.2881 (20)	0.6316 (15)	0.3098 (24)	3.8 (4)
H3A	0.0165 (20)	0.6648 (15)	0.1552 (23)	3.2 (4)
H3B	0.0690 (19)	0.8087 (14)	0.2541 (22)	2.8 (4)
H4A	0.1254 (20)	0.8467 (15)	-0.0829 (23)	2.7 (4)
H4B	-0.0550 (21)	0.8098 (15)	-0.0877 (24)	3.0 (4)
H5A	0.0153 (19)	0.5962 (14)	-0.2475 (22)	2.3 (4)
H5B	0.0744 (19)	0.6891 (13)	-0.3918 (22)	2.3 (4)
H7	0.2801 (17)	0.4561 (12)	-0.5040 (21)	1.6 (3)
H10	0.2503 (19)	0.2414 (14)	-0.5985 (22)	2.3 (4)
H11	0.2428 (20)	0.0207 (14)	-0.7104 (23)	3.0 (4)
H12	0.3035 (20)	-0.1242 (15)	-0.4666 (23)	3.4 (4)
H13	0.3732 (20)	-0.0343 (14)	-0.1241 (21)	2.7 (4)
H14	0.3728 (18)	0.1880 (13)	-0.0063 (21)	1.9 (4)
OH2	0.464 (3)	0.6588 (21)	-0.258 (3)	7.0 (8)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

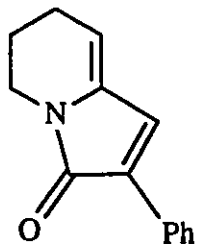
TABLE 14 ATOMIC BONDS IN ANGSTROMS OF 169

C6-O2-OH2	111.9(16)	O2-C6-N1	111.41(14)
C1-N1-C2	125.16(14)	O2-C6-C5	107.29(14)
C1-N1-C6	112.05(13)	O2-C6-C7	114.26(15)
C2-N1-C6	120.32(13)	N1-C6-C5	109.27(14)
O1-C1-N1	124.63(15)	N1-C6-C7	101.36(13)
O1-C1-C8	128.40(15)	C5-C6-C7	113.16(15)
N1-C1-C8	106.97(14)	C6-C7-C8	111.85(15)
N1-C2-C3	108.73(15)	C6-C7-H7	119.4(8)
N1-C2-H2A	107.6(9)	C8-C7-H7	128.7(8)
N1-C2-H2B	107.7(7)	C1-C8-C7	107.20(14)
C3-C2-H2A	110.8(9)	C1-C8-C9	124.64(14)
C3-C2-H2B	113.0(8)	C7-C8-C9	128.04(15)
H2A-C2-H2B	109.0(12)	C8-C9-C10	118.99(15)
C2-C3-C4	110.92(17)	C8-C9-C14	122.81(15)
C2-C3-H3A	107.2(9)	C10-C9-C14	118.17(16)
C2-C3-H3B	111.1(9)	C9-C10-C11	120.93(17)
C4-C3-H3A	110.7(9)	C9-C10-H10	119.4(9)
C4-C3-H3B	110.5(8)	C11-C10-H10	119.6(9)
H3A-C3-H3B	106.2(12)	C10-C11-C12	120.31(18)
C3-C4-C5	111.11(16)	C10-C11-H11	119.0(9)
C3-C4-H4A	110.8(9)	C12-C11-H11	120.7(9)
C3-C4-H4B	110.2(9)	C11-C12-C13	119.37(18)
C5-C4-H4A	110.2(9)	C11-C12-H12	121.7(9)
C5-C4-H4B	108.9(9)	C13-C12-H12	118.9(9)
H4A-C4-H4B	105.4(13)	C12-C13-C14	120.82(17)
C4-C5-C6	111.71(16)	C12-C13-H13	119.9(9)
C4-C5-H5A	110.2(9)	C14-C13-H13	119.3(9)
C4-C5-H5B	112.4(8)	C9-C14-C13	120.40(16)
C6-C5-H5A	107.9(9)	C9-C14-H14	119.4(8)
C6-C5-H5B	108.5(9)	C13-C14-H14	120.2(8)
H5A-C5-H5B	105.9(12)		

TABLE 15 ATOMIC ANGLES IN DEGREES OF 169

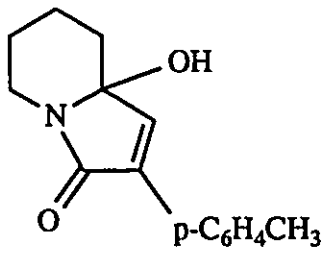
O1-C1	1.2421(20)	C5-H5A	0.986(16)
O2-C6	1.4126(23)	C5-H5B	1.038(15)
O2-OH2	0.839(22)	C6-C7	1.5016(24)
N1-C1	1.3549(21)	C7-C8	1.3380(24)
N1-C2	1.4641(22)	C7-H7	0.998(14)
N1-C6	1.4715(21)	C8-C9	1.4798(23)
C1-C8	1.5085(22)	C9-C10	1.3967(24)
C2-C3	1.532(3)	C9-C14	1.3984(24)
C2-H2A	0.965(16)	C10-C11	1.384(3)
C2-H2B	1.150(16)	C10-H10	0.959(15)
C3-C4	1.529(3)	C11-C12	1.386(3)
C3-H3A	1.031(17)	C11-H11	0.986(15)
C3-H3B	1.013(15)	C12-C13	1.378(3)
C4-C5	1.532(3)	C12-H12	1.012(16)
C4-H4A	0.992(17)	C13-C14	1.387(3)
C4-H4B	1.005(17)	C13-H13	0.951(15)
C5-C6	1.533(3)	C14-H14	0.993(14)

The compound **169** in $CDCl_3$ was capped in a NMR tube for a long-term, e.g. 10 months. The solvent was gradually evaporated and the sample remained as powder form which ^1H NMR spectrum showed a completely transformation from **169** to **170.**

170 : 

^1H NMR (500MHz, CD_3OD) δ 1.976 (m, 2H, CH_2 at C6); 2.447 (m, 2H, CH_2 at C7); 3.516 (m, 2H, CH_2 at C5); 5.846 (t, J=4.7Hz, 1H, CH at C8); 7.307 (s, 1H, CH at C1); 7.339 (m, 3H, meta and para protons at phenyl ring); 7.971 (m, 2H, ortho protons at phenyl ring);

^{13}C NMR information from HMQC spectrum (126 MHz, CD_3OD) δ 22.5 (C6), 23.5 (C7), 38.5 (C5), 117.0 (C8), 128.0 (C1), 127.0-130.0 (carbon at phenyl ring).

172b : 

68% yield; mp 166-167^{0}C;

IR (CH_2Cl_2) ν(OH) 3691cm^{-1}, ν(CO) 1698cm^{-1};

^1H NMR (CD_3OD, 500MHz) 1.28 (m, 1H, axial H at C6); 1.35 (m, 1H, equatorial H at C8); 1.72 (m, 2H, 2H at C_{6e} and C_{7a}); 1.93 (m, 1H, H at C_{7e}); 2.14 (bd, 1H, H at C_{8e}); 2.32 (s, 3H, CH_3); 3.06 (m, 1H, H at C_{5a}); 4.07 (m, 1H, H at

C_{5e}); 7.20 (s, 1H, H at C1); 7.21 (m, 2H, meta H at Ph); 7.77 (m, 2H, ortho H at Ph);

^{13}C NMR (CD_3OD, 126 MHz) δ 21.317 (CH_3), 20.324, 26.301, 36.139 (C6-C8), 37.489 (C5), 86.354 (C8a), 128.231, 129.831 (CH at Ph), 136.335, 140.765 (qC), 144.194 (C1), 168.274 (CO).

MS (EI) m/e 243 $[M]^+$, 225 $[M-H_2O]^+$ base peak.

The ^1H NMR, COSY (500MHz, CD_3OD) spectrum of **172b** is showed in Figure 18, 19). The Table 16-19 will list crystal X-ray analysis data for **172b**.

4.3.8 SENSITIZED PHOTOOXIDATION OF 2-PHENYL-5,6,7,8-TETRAHYDRO INDOLIZINE 157 WITH 1 ATM OXYGEN

A mixture of 97mg (0.49mmol) of **157**, and 4.5mg of rose bengal (sodium salt) in 10ml dry distilled methanol was placed in a quartz tube. Oxygen was bubbled through the solution for 5 min, the mixture was cooled with ice and water to 15^0C and irradiated with a 450-W high-pressure mercury immersion lamp (Hanovia 697 A36, cooled by running water) with a Pyrex filter. the passage of oxygen was continued for 2h, and after standing over night at room temperature in the dark, the solvent was evaporated at reduced pressure, the residue was purified by column chromatography (Al_2O_3 neutral) to afford 81mg of white powder, mp: 123-124^0C.

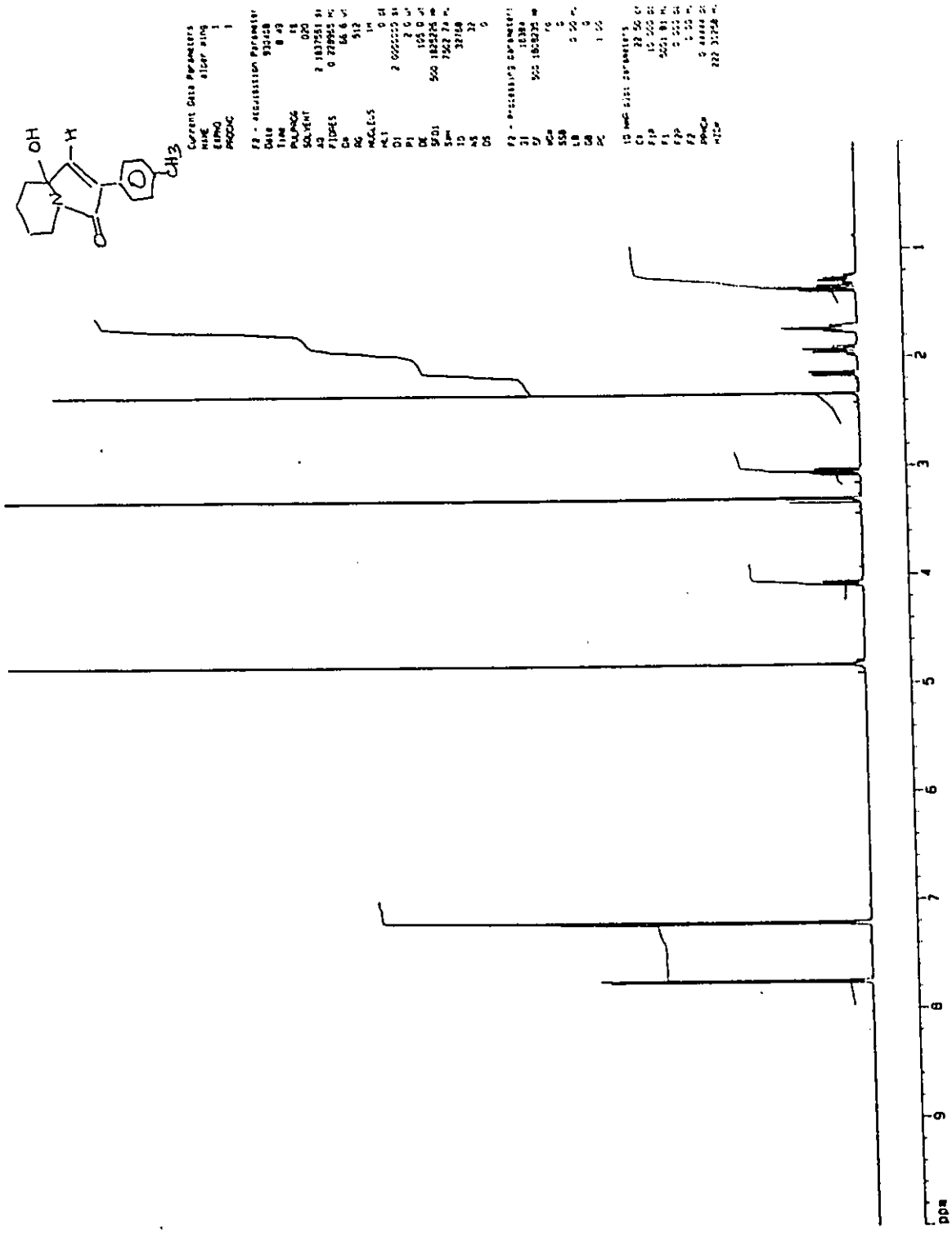


FIGURE 18 ^{1}H NMR (500MHz, CD_3OD) SPECTRUM OF 172b

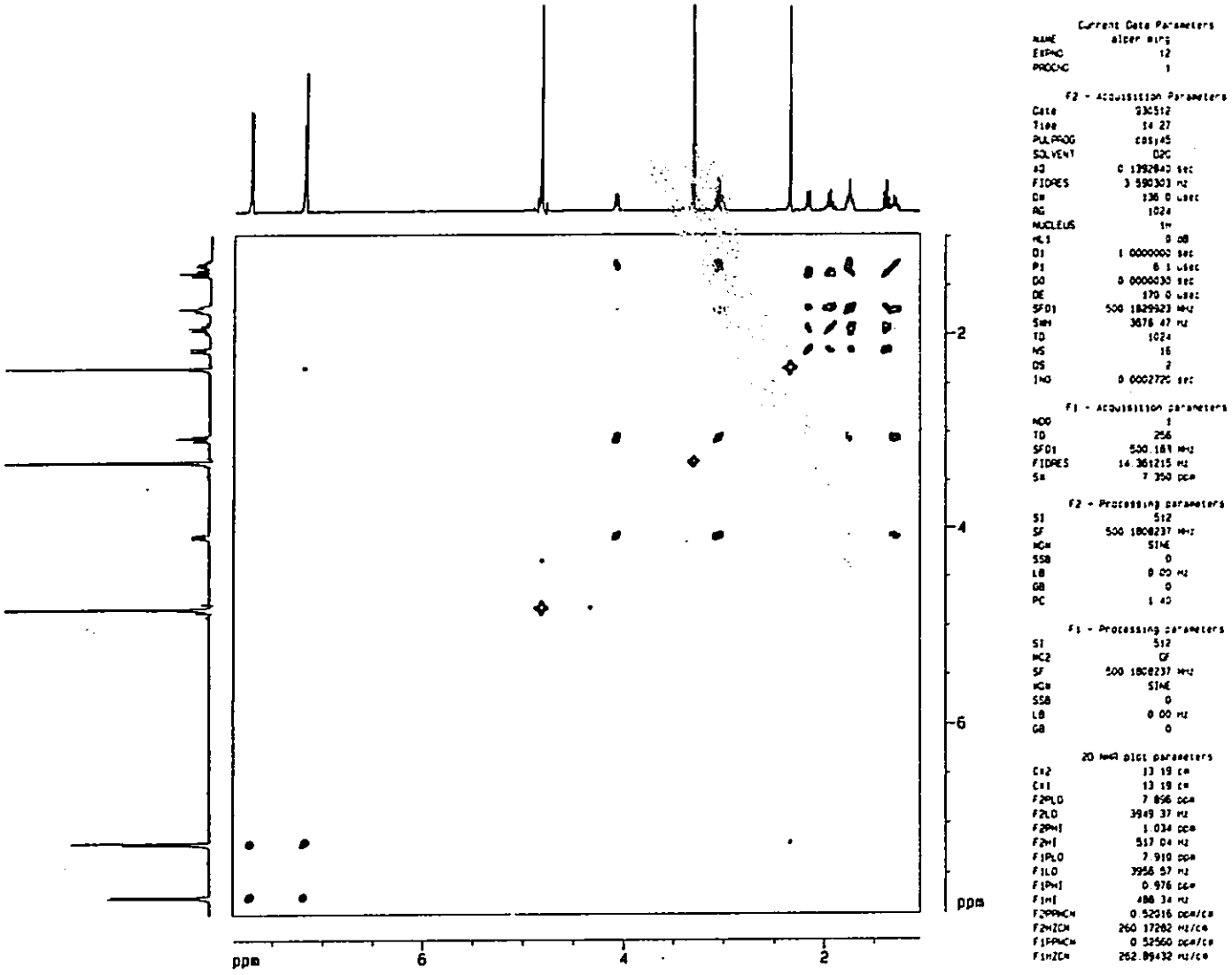


FIGURE 19 COSY (500MHz, CD_3OD) SPECTRUM OF 172b

TABLE 16 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR 172b

Empirical formula	O2NC15H17
Formula weight	243.30
Crystal shape	cube
Crystal dimensions (mm)	.2,.2,.2
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 40-50
Lattice parameters	a=13.781(7) b=10.102(1) c=18.414(4) beta=99.49(3)
Space group	C 2/c
Z value	8
Dcalc (g.cm-3)	1.278
F(000)	1040.40
mu (mm-1)	0.08
No of reflection measured	2312
No of reflection unique	2217
No of reflection observed	1763
No of atoms	35
No of variables	232
Rf (sign refl)	.065
Rw (sign refl)	.042
Rf (all refl)	.083
Rw (all refl)	.042
Goodness of fit	6.52
Last difference fourier map	
max peak	.270
min peak	-.250

TABLE 17 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 172b

Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
O1	0.78235(15)	0.43762(21)	0.95282(11)	2.85(11)
O2	0.91985(16)	0.09625(21)	1.08904(11)	3.00(11)
N1	0.87691(19)	0.31087(24)	1.04018(13)	2.45(13)
C1	0.83863(23)	0.3442 (3)	0.97085(16)	2.34(15)
C2	0.87770(23)	0.2440 (3)	0.92140(16)	2.40(15)
C3	0.93806(24)	0.1650 (3)	0.96439(17)	2.75(16)
C4	0.94704(23)	0.2031 (3)	1.04516(16)	2.58(16)
C5	1.04856(24)	0.2476 (3)	1.07951(17)	3.01(17)
C6	1.0458 (3)	0.3248 (4)	1.15215(18)	3.64(20)
C7	0.9736 (3)	0.4386 (3)	1.13851(18)	3.61(18)
C8	0.87138(25)	0.3929 (3)	1.10508(17)	2.99(17)
C9	0.85573(23)	0.2436 (3)	0.84031(16)	2.39(16)
C10	0.88554(25)	0.1349 (3)	0.80201(17)	3.18(18)
C11	0.8688 (3)	0.1346 (3)	0.72548(17)	3.27(18)
C12	0.82416(24)	0.2389 (3)	0.68472(17)	2.78(16)
C13	0.79316(24)	0.3457 (3)	0.72291(17)	2.91(16)
C14	0.80816(24)	0.3475 (3)	0.80005(16)	2.81(17)
C15	0.8120 (3)	0.2399 (4)	0.60098(17)	3.47(18)
H3	0.9719 (18)	0.0885 (25)	0.9486 (12)	2.9 (7)
OH2	0.8410 (17)	0.0807 (24)	1.0687 (12)	2.5 (7)
H5A	1.0689 (17)	0.3159 (24)	1.0448 (12)	2.9 (7)
H5B	1.0963 (21)	0.161 (3)	1.0962 (15)	5.8 (9)
H6A	1.1243 (17)	0.3589 (24)	1.1774 (12)	2.5 (7)
H6B	1.0267 (19)	0.248 (3)	1.1872 (13)	4.8 (8)
H7A	0.9896 (19)	0.507 (3)	1.1057 (14)	4.7 (8)
H7B	0.9809 (20)	0.499 (3)	1.1855 (14)	5.8 (9)
H8A	0.8469 (19)	0.335 (3)	1.1339 (14)	4.0 (8)
H8B	0.8107 (19)	0.473 (3)	1.0838 (14)	4.7 (8)
H10	0.9226 (20)	0.047 (3)	0.8354 (14)	5.7 (9)
H11	0.8908 (18)	0.060 (3)	0.7017 (12)	3.9 (8)
H13	0.7508 (17)	0.4175 (25)	0.6931 (12)	2.7 (7)
H14	0.7928 (18)	0.434 (3)	0.8205 (13)	3.8 (7)
H15A	0.7615 (19)	0.319 (3)	0.5749 (13)	4.1 (8)
H15B	0.7680 (20)	0.162 (3)	0.5767 (14)	5.4 (9)
H15C	0.8700 (23)	0.252 (3)	0.5953 (15)	6.6 (10)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

TABLE 18 ATOMIC BONDS IN ANGSTROMS OF 172b

C4-O2-OH2	104.5(12)	C8-C7-H7B	118.0(15)
C1-N1-C4	113.73(24)	H7A-C7-H7B	95.8(22)
C1-N1-C8	124.7(3)	N1-C8-C7	109.5(3)
C4-N1-C8	119.79(24)	N1-C8-H8A	101.1(17)
O1-C1-N1	125.5(3)	N1-C8-H8B	104.2(12)
O1-C1-C2	128.2(3)	C7-C8-H8A	112.1(17)
N1-C1-C2	106.30(25)	C7-C8-H8B	119.1(13)
C1-C2-C3	107.1(3)	H8A-C8-H8B	109.1(21)
C1-C2-C9	125.1(3)	C2-C9-C10	118.9(3)
C3-C2-C9	127.6(3)	C2-C9-C14	122.7(3)
C2-C3-C4	112.1(3)	C10-C9-C14	118.4(3)
C2-C3-H3	126.0(13)	C9-C10-C11	119.9(3)
C4-C3-H3	121.9(13)	C9-C10-H10	118.6(14)
O2-C4-N1	111.57(24)	C11-C10-H10	121.6(14)
O2-C4-C3	111.9(3)	C10-C11-C12	122.4(3)
O2-C4-C5	107.39(24)	C10-C11-H11	117.3(14)
N1-C4-C3	100.50(23)	C12-C11-H11	120.3(14)
N1-C4-C5	111.5(3)	C11-C12-C13	117.6(3)
C3-C4-C5	114.0(3)	C11-C12-C15	121.4(3)
C4-C5-C6	111.0(3)	C13-C12-C15	121.0(3)
C4-C5-H5A	105.9(13)	C12-C13-C14	121.1(3)
C4-C5-H5B	110.6(15)	C12-C13-H13	118.0(13)
C6-C5-H5A	104.5(13)	C14-C13-H13	120.4(13)
C6-C5-H5B	104.7(14)	C9-C14-C13	120.7(3)
H5A-C5-H5B	120.0(20)	C9-C14-H14	125.3(14)
C5-C6-C7	110.3(3)	C13-C14-H14	113.2(14)
C5-C6-H6A	109.9(12)	C12-C15-H15A	113.4(13)
C5-C6-H6B	101.4(14)	C12-C15-H15B	112.7(15)
C7-C6-H6A	112.7(12)	C12-C15-H15C	100.4(19)
C7-C6-H6B	115.6(14)	H15A-C15-H15B	94.5(20)
H6A-C6-H6B	106.3(18)	H15A-C15-H15C	112(3)
C6-C7-C8	112.2(3)	H15B-C15-H15C	123(3)
C6-C7-H7A	115.6(16)		
C6-C7-H7B	109.5(15)		
C8-C7-H7A	104.9(15)		

TABLE 19 ATOMIC ANGLES IN DEGREES OF 172b

O1-C1	1.232(4)	C7-H7A	0.96(3)
O2-C4	1.435(4)	C7-H7B	1.05(3)
O2-OH2	1.101(23)	C8-H8A	0.89(3)
N1-C1	1.341(4)	C8-H8B	1.18(3)
N1-C4	1.449(4)	C9-C10	1.403(4)
N1-C8	1.466(4)	C9-C14	1.386(4)
C1-C2	1.519(4)	C10-C11	1.390(4)
C2-C3	1.318(4)	C10-H10	1.15(3)
C2-C9	1.474(4)	C11-C12	1.378(5)
C3-C4	1.521(4)	C11-H11	0.95(3)
C3-H3	0.972(25)	C12-C13	1.392(5)
C4-C5	1.506(5)	C12-C15	1.523(4)
C5-C6	1.554(5)	C13-C14	1.401(4)
C5-H5A	1.012(24)	C13-H13	1.031(24)
C5-H5B	1.10(3)	C14-H14	0.99(3)
C6-C7	1.514(5)	C15-H15A	1.12(3)
C6-H6A	1.157(23)	C15-H15B	1.05(3)
C6-H6B	1.07(3)	C15-H15C	0.83(3)
C7-C8	1.513(5)		

4.3.9 NON-PHOTOLYTIC OXIDATION OF 150 WITH 1 ATM OXYGEN

4.3.9.1 Without Catalyst

Oxygen gas was bubbled into a solution of 51mg (0.42mmol) of **150** in 3ml dry, freshly distilled CH_2Cl_2 for 3 days and 49.8mg brownish liquid was recovered which contained about 98% of unchanged **150** as proved by GC.

4.3.9.2 With Catalytic Amount of Oxidized $Co_2(CO)_8$

A mixture of 51mg (0.42mmol) of **150**, 6mg(0.0175mmol, calculated by the mole weight of $Co_2(CO)_8$) oxidized $Co_2(CO)_8$ (the colour had turned blue) and 3ml of dry, freshly distilled CH_2Cl_2 was placed in a glass vial and bubbled with 1atm oxygen overnight. The GC-MS analysis of this reaction mixture showed the presence of 20% of **176**.

4.3.9.3 With Catalytic Amount of $CoCl_2$

The same procedure as that described in section 4.3.9.2 was used, but 2.4mg of anhydrous Co_2Cl_2 was used instead of oxidized $Co_2(CO)_8$. Thus, the ratio of **150** to catalyst was 100 : 4.5. The reaction lead to the production of 19% of **176**.

4.3.10 SENSITIZED PHOTOOXIDATION OF 150 WITH 1 ATM OXYGEN

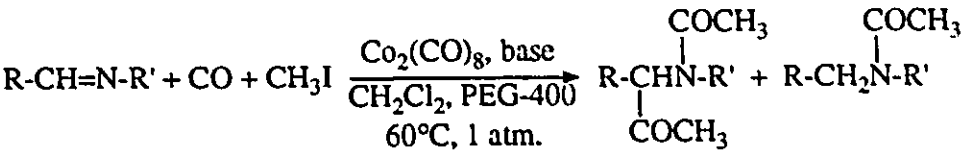
A solution of **150** (100mg, 0.826mmol), rose bengal (4.5mg) in 10ml dry methanol was placed in a quartz tube. The tube was irradiated using a 450-W high-pressure mercury immersion lamp (Hanovia 679 A36, cooled by running water) with a pyrex filter for 2h and then was left in the dark overnight. About 25% of **176** was produced (GC-MS). The attempted separation on a small column (neutral activated Al_2O_3) failed to give pure **176**.

Chapter 5

Phase Transfer Catalyzed Reductive Acylation of Nitrogen-Containing Heteroaromatics with Acetyl-cobalt Tetracarbonyl

5.1 INTRODUCTION

Phase transfer catalysis (PTC) is widely used for the in *situ* generation of anionic metal carbonyl complexes under mild conditions.[10,13,102,161] One of the more valuable phase transfer processes is the conversion of cobalt carbonyl to the mononuclear cobalt tetracarbonyl anion using aqueous alkali, benzene or toluene as the organic phase and a quaternary ammonium halide (Cl^-, Br^-) as the phase transfer agent. The subsequent reaction of cobalt tetracarbonyl anion with methyl iodide and carbon monoxide gives acetylcobalt tetracarbonyl. A variety of unsaturated substrates, e.g., dienes,[162] trienes,[163] fulvenes[164] and azadienes,[165] react with acetylcobalt tetracarbonyl under mild conditions to form the acylated products in a regioselective manner. An interesting direct diacylation of Schiff bases **179** using catalytic quantities of $Co_2(CO)_8$ under PTC conditions has also been reported.[166] Keto-amides **180** are formed as major products in fair to good yields, with the monoamides **181** as a reaction by product.



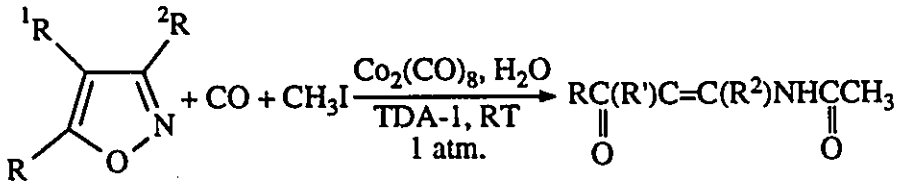
179 **180** **181**

Transition metal carbonyls such as $[Fe_2(CO)_9]$,[167] $Co_2(CO)_8$,[168] and $M(CO)_6$ [M=Mo,[169-171] Cr[170] and W[171] have been used for the reductive cleavage of heterocycles, including isoxazoles,[169c] isoxazolines,[172] isoxazolidines,[173] 1,2-oxazines[174] and azirines.[175] The highly functionalized products of these reactions such as β-amino enones and γ-amino alcohols can be used in subsequent transformations.[173]

It seemed conceivable to us that nitrogen-containing heteroaromatics would undergo reductive acylation with acetylcobalt tetracarbonyl under mild PTC conditions. We now describe the reactions of isoxazoles, isothiazoles and other five and six-membered ring nitrogen heterocycles with acetylcobalt tetracarbonyl, generated *in situ* from CO, CH_3I and dicobalt octacarbonyl. Isoxazoles or isothiazoles give N-acylated 1-amino-1-alkene-3-ones or thiones i.e. ring-cleavage acylated products while under the same conditions phthalazine, quinoline and isoquinoline give N-acylated dimers. The reactivity of several other nitrogen-containing heterocycles such as pyrazoles was also investigated.

5.2 RESULTS AND DISCUSSION

Treatment of 3,5-dimethylisoxazole **182a** with carbon monoxide, benzene, water, TDA-1 [tris(2,6-dioxaheptyl)amine] as the phase transfer catalyst, methyl iodide and cobalt carbonyl (4 : 1 ratio of **182a** : $Co_2(CO)_8$) at room temperature for 60 h gives 2-(N-acetyl)aminopenten-2-one-4 **183a** in 45% yield by gas chromatography (36% isolated yield), the remainder being recovered starting material. When the ratio of $Co_2(CO)_8$ to **182a** was increased to 1 : 1, the reaction time decreased to 48 h. In this case, the 1,2-disubstituted ethylene **183a** is formed in 79% GC yield (61% isolated yield of analytically pure material).



182a-c **183a-c**

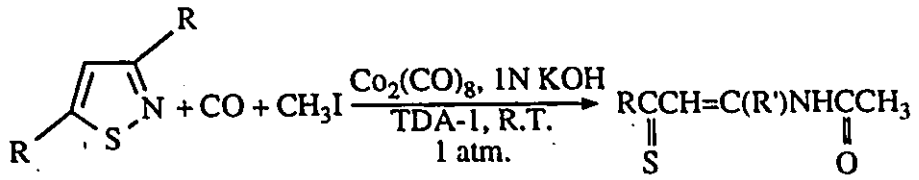
182,183 a: $R=R^2=Me, R'=H$

b: $R=Me, R'=R^2=H$

c: $R=R^2=Me, R'=CH_2OC_2H_5$

Similar treatment of 5-methylisoxazole **182b** afforded **183b** after 48 h in 42% isolated yield, the remainder being unreacted **182b**. In the case of **182c**, the yield of the corresponding acylation product **183c** was substantially lower. In all cases, a mixture of (Z) and (E) products are formed (Table 20).

Isothiazoles **184** are cleaved in the same manner as isoxazoles to give **185**, which are thia-analogues of **183**.



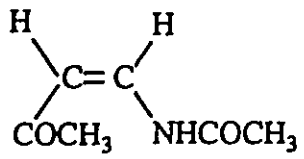
184a, b **185a,b**

184,185a: R=R'=CH_3

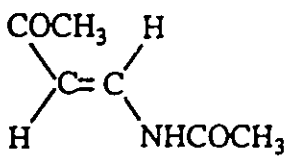
b: R=CH_3, R'=H

Isothiazoles **184a,b** are less reactive than the corresponding isoxazoles **182a,b** resulting in lower yields of (E) and (Z)-**185a,b** as compared to **183a,b**. In the case of **185a**, the stereoselectivity of the acylation (Z : E = 3 . 1 : 1) is appreciably lower when compared with that of the isostructural **183a** (Z : E = 10 : 1). The structures of **183a-c** and **185a-b** were assigned on the basis of spectral data. The Z : E ratio was determined by ^{1}H NMR spectroscopy (see experimental section). One example of these ^{1}H NMR spectra is showing as the following Fig. 20.

183b:



Z



E

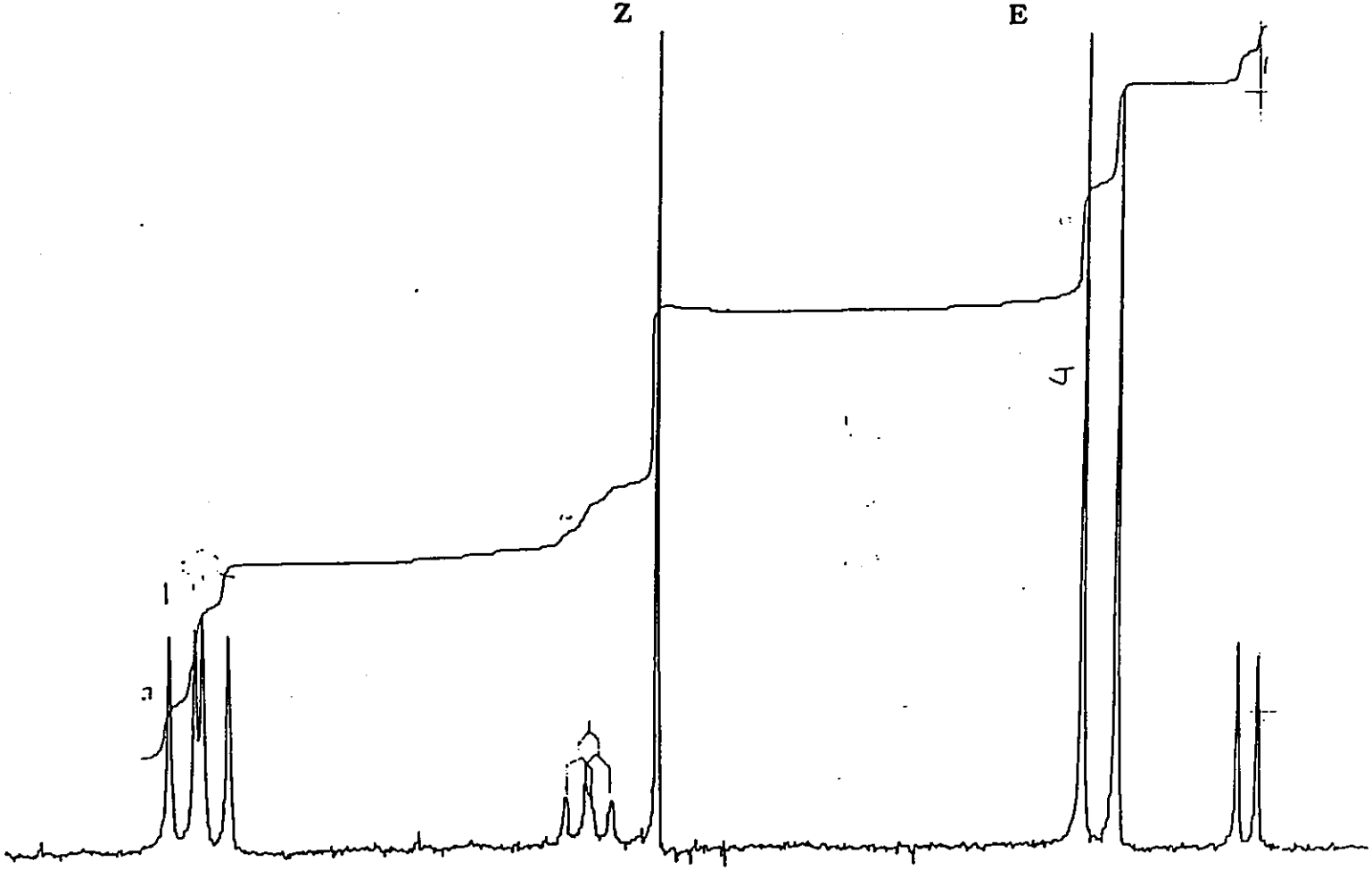
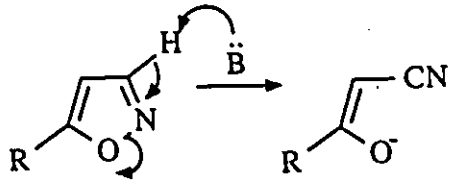


FIGURE 20 A PART OF ^{1}H NMR SPECTRUM OF 183b

A variety of reaction conditions were used in order to investigate the influence of the phase transfer catalyst, base concentration and reaction time on the yield and the E : Z ratio of the functionally substituted α-amido ethylenes (i.e., enamides - Table 20).

The experimental findings revealed that the yield of **183a** was higher when water was used as the aqueous phase rather than 3N KOH (runs 3 and 4). The substitution of PEG-400 for TDA-1 as the phase transfer catalyst did not influence the E : Z ratio of **183b** but did affect the yield (runs 3 and 5). Also, decreasing the concentration of base increases the E : Z ratio of **183b** (runs 3 and 4).

It is well known that isoxazoles unsubstituted at the 3-position (e.g., **186**) are easily cleaved by bases giving (Z)-enolates (e.g., **187**), the reaction being stereoselective below -40°C[176].



186 **187**

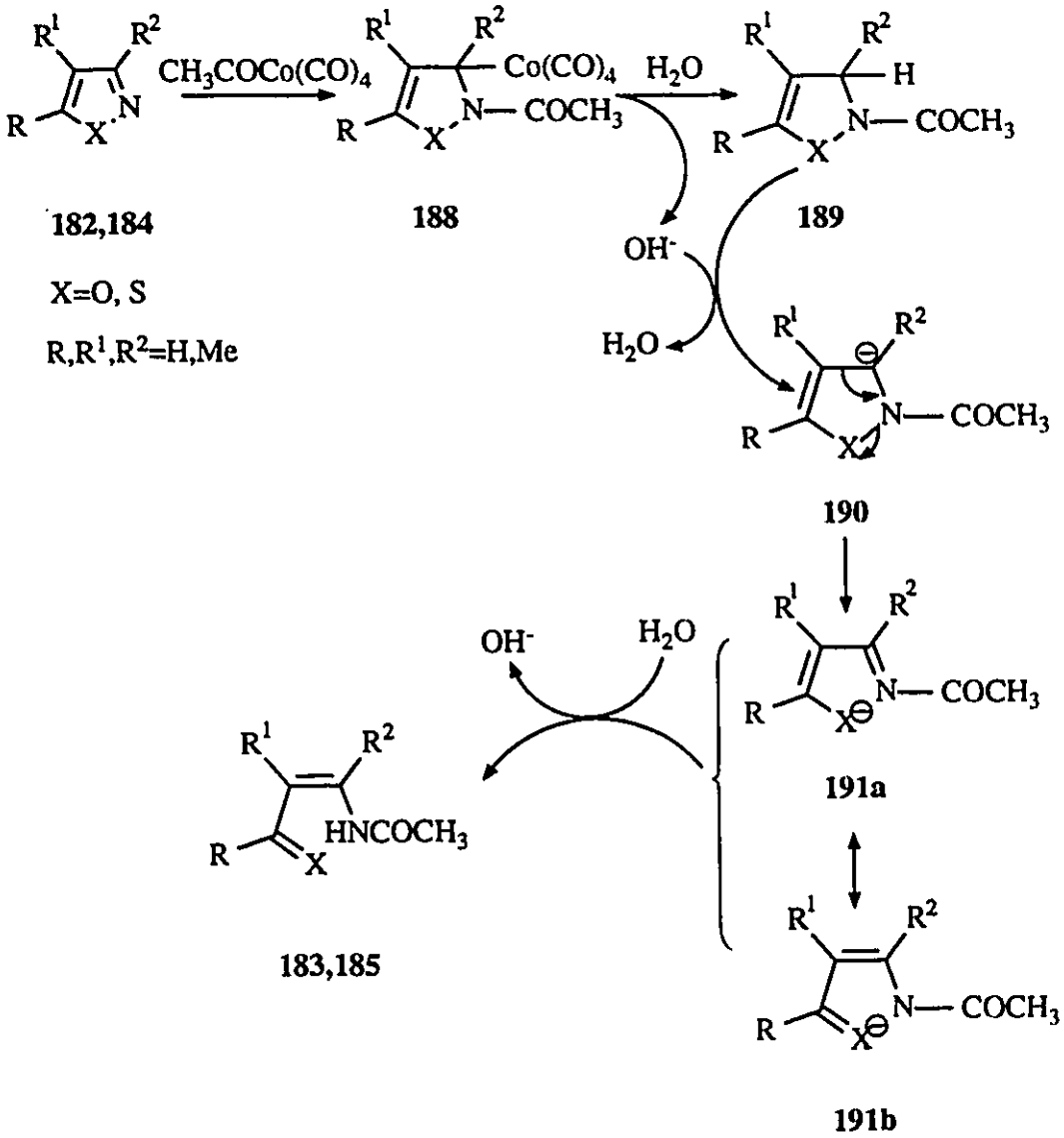
The reaction of **182a** with CO in the presence of $Co_2(CO)_8$/TDA-1 was also carried out without methyl iodide using water or 3N KOH as the aqueous phase. In both cases, the unchanged starting material was recovered quantitatively after reaction for three days. Therefore, the reaction mechanism differs significantly from the aforementioned base-induced cleavage of isoxazoles. A possible mechanism for the reductive ring-cleavage acylation reaction is outlined in Scheme 12.

TABLE 20. PTC Reactions of isoxazoles **182** and isothiazoles **184** with $Co_2(CO)_8$/CO/KOH(H_2O)/C_6H_6/CH_3I/P,T. agent/RT

Substrate	Run	Molar ratio sub./$Co_2(CO)_8$	H_2O or KOH (N)	Phase transfer agent	Reaction time (h)	Product	E : Z	Yield[a] %
182a	1	4 : 1	H_2O	TDA-1	60	**183a**	1 : 10	36 (46[b])
182a	2	1 : 1	H_2O	TDA-1	48	**183a**	1 : 10	61 (79[b])
182b	3	2 : 1	3N	TDA-1	48	**183b**	2.2 : 1	28
182b	4	2 : 1	H_2O	TDA-1	48	**183b**	3.4 : 1	42
182b	5	2 : 1	3N	PEG-400	48	**183b**	2.2 : 1	15
182c	6	2 : 1	3N	PEG-400	54[c]	**183c**	1.3 : 1	5
184a	7	2 : 1	1N	TDA-1	48	**185a**	1 : 3.1	19
184b	8	2 : 1	1N	TDA-1	48	**185b**	2.1 : 1	12

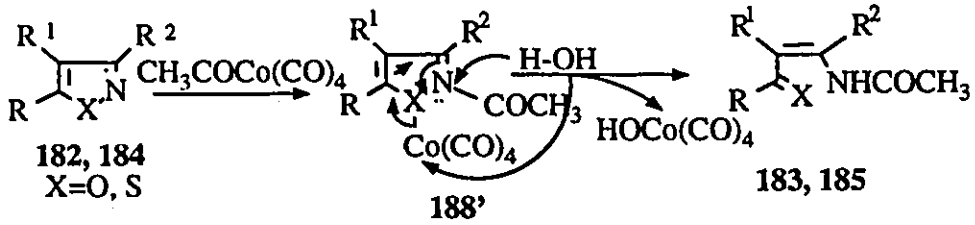
[a]Isolated yield. [b]GC yield. [c]45 - 50°C.

SCHEME 12


CH3COCo(CO)4
Co(CO)4
H2O
COCH3
182,184
X=O, S
R,R1,R2=H,Me
188
189
OH-
H2O
190
191a
191b
183,185
HNCOCH3

1,2-Addition of the organocobalt compound to **182** or **184** would generate **188**. The latter can experience C-Co bond cleavage by water to give **189**. Deprotonation of **189** can give **190** which, on N-X bond rupture, affords **191a**, which is in resonance equilibrium with **191b**. The product can then arise by protonation of **191**. The formation of the (Z)-isomer as the main product in reactions involving **182a** and **184a** is probably due to the methyl group (R^2) in the intermediate ambident open-chain anion **191**. The other possible path is shown in Scheme 12'.

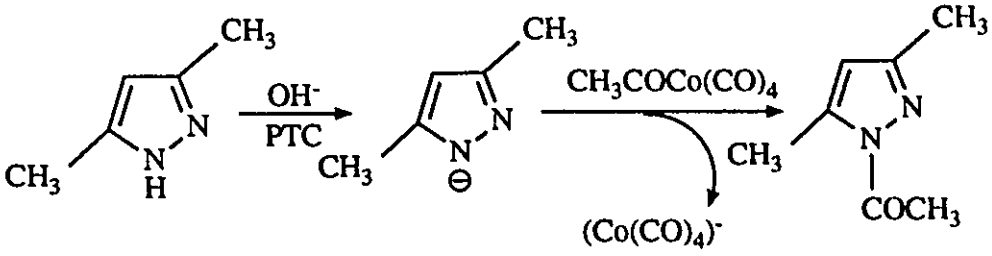
Scheme 12'



Benz[d]isoxazole, under the same phase transfer conditions, is transformed to 2-hydroxybenzonitrile in 71% isolated yield. No acylation occurred in this case, possibly due to the presence of an electron withdrawing benzene substituent which decreases the nucleophilicity of the C=N bond and, at the same time, increases the acidity of the proton in the heterocyclic ring. Thus, the addition of $CH_3COCo(CO)_4$ does not take place at the C=N bond and the base-induced ring cleavage is the only reaction.[161] As expected, this transformation does not occur under neutral (H_2O) conditions.

In the case of other five-membered ring nitrogen-containing heterocycles, e.g. pyrazoles, only 3,5-dimethylpyrazole **192** reacts with acetylcobalt tetracarbonyl

under PTC conditions to give 1-acetyl-3,5-dimethyl pyrazole **194** in 30% yield. Unlike isoxazoles and isothiazoles, pyrazole **192** reacts with $CH_3COCo(CO)_4$ only when 3N KOH is used as the aqueous phase. No reaction occurs in 1N KOH or water. Therefore, the reaction most probably proceeds by deprotonation of **192** to **193** at the interface, followed by reaction with $CH_3COCo(CO)_4$ to form **194**.

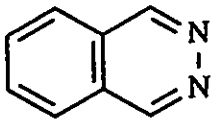
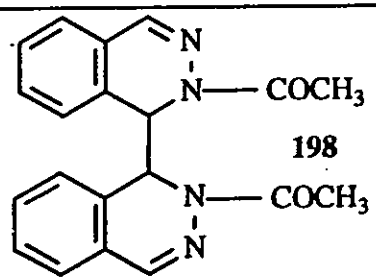
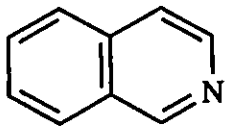
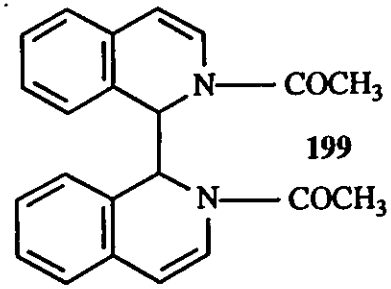
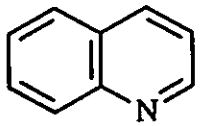
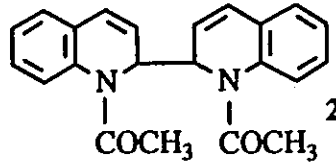


192 **193** **194**

N-Phenylpyrazole, 3-methyl-1-phenylpyrazole and 1,3,5-trimethylpyrazole, all of which are already substituted at the 1-position do not react with acetylcobalt carbonyl under the same PTC conditions even under prolonged heating.

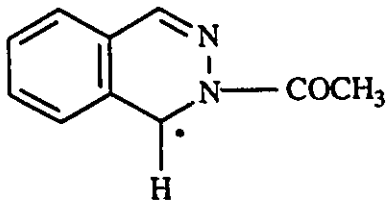
The reaction of phthalazine **195**, isoquinoline **196** and quinoline **197** with acetylcobalt tetracarbonyl under the same PTC conditions, results in the formation of acylated dimeric products **198-200** in low-moderate yields (Table 21).

TABLE 21. Reaction of Bicyclic Heterocycles with $Co_2(CO)_8$/CO/KOH(H_2O)/C_6H_6/CH_3I/TDA-1/RT

Substrate	Molar ratio sub./$Co_2(CO)_8$	KOH (N_{conc})	Reaction time	Product	Isolated Yield
 **195**	2 : 1	3N	72	 **198**	54
	2 : 1	H_2O	48		45
 **196**	2 : 1	3N	48	 **199**	27
	2 : 1	H_2O	48		27
 **197**	2 : 1	H_2O	84	 **200**	traces[a]

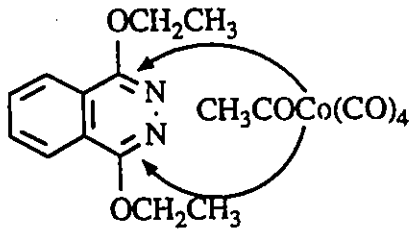
[a] Tentative structure. It is conceivable that the structure of **200** is the 4,4'-isomer, although the chemical shift of methine proton would be quite different.

The structure of these products was established by analytical and spectral data, including COSY and HETCOR NMR methods (see experimental section). These acylation and dimerization reactions may proceed via a radical pathway involving a benzyl radical and then homocoupling.



201

No acetylation-dimerization occurs in the case of 1,4-diethoxyphthalazine, due probably to steric reasons.



202

5.3 Experimental Section

5.3.1 GENERAL COMMENTS

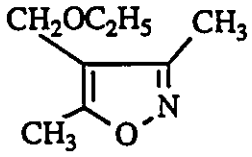
The general comments of chapter 2 are applicable here.

Cobalt carbonyl and most of the organic reactants were purchased from commercial sources and were used as received.

5.3.2 PREPARATION OF 182c AND 184b

182c was prepared in 80% yield by reacting 3.5-dimethyl-4-chloromethyl isoxazole and $NaOC_2H_5/C_2H_5OH$ at 45°C for 12 h.

182C:



^1H NMR ($CDCl_3$) δ 1.19 (t,3H,-OCH_2CH_3); 2.24 (s, 3H, CH_3 at C3); 2.35 (s, 3H, CH_3 at C5); 3.45 (q, 2H, -OCH_2CH_3); 4.23 (s, 2H, -OCH_2 at C4); MS (EI) m/e 112 $[M\text{-}CH_3CO]^+$.

184b was prepared in 35% yield from 3,5-dimethylisoxazole.[177]

1,4-Diethoxyphthalazine was prepared in 60% yield by reacting 1,4-dichlorophthalazine and $NaOC_2H_5/C_2H_5OH$ at 45°C for 12 h. ^1H NMR ($CDCl_3$) δ 1.45 (t, 6H, $2xCH_3$); 4.40 (q, 4H, $2xOCH_2$); 7.50-8.11 (m, 4H, aromatic protons);

MS (EI) m/e 218 $[M]^+$, 203 $[M-CH_3]^+$.

1,3,5-Trimethylpyrazole was prepared in 66% yield by deprotonation of 3,5-dimethylpyrazole with n-BuLi in THF, followed by methylation with CH_3I at 0°C - R.T., for 20 h, and workup by TLC.

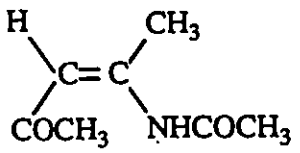
5.3.3 GENERAL PROCEDURE FOR THE REACTION OF ISOXAZOLES, ISOTHIAZOLES, BENZ[d]ISOXAZOLE, PHTHALAZINE, QUINOLINE, ISOQUINOLINE AND PYRAZOLES WITH ACETYLCOBALT TETRACARBONYL

Carbon monoxide was bubbled through a solution of 3N KOH (or 1N KOH or H_2O - 15 ml) containing 0.6 mmol (180 mg) of TDA-1. After stirring for 30 minutes, a degassed solution of $Co_2(CO)_8$ [171 mg, 0.5 mmol.] in benzene (20 ml) was added, and the mixture was heated at 35 - 40°C for 20-40 minutes (or overnight at R.T. in H_2O) to generate $[Co(CO)_4]^-$. After cooling to R.T., methyl iodide (2 ml) was added, followed 30 minutes later by the starting material (1 mmol) in benzene (5 ml). The reaction mixture was stirred under CO at R.T. and 1 atm. for 2 or 3 days (monitored by GC). After reaction was complete, the phases were separated. The

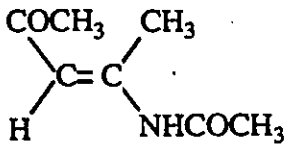
aqueous phase was neutralized (1N HCl), and extracted with ether (4 x 25 ml). The combined organic layer was dried ($MgSO_4$) and concentrated by rotary evaporation. Pure products were isolated by preparative TLC using hexane-CH_2Cl_2 (4:1) as eluant.

CHARACTERIZATION DATA FOR PRODUCTS:

183a:



Z



E

IR (neat): ν_{NH} 3500 cm^{-1}, ν_{CO} 1720 cm^{-1}, 1655 cm^{-1};

^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, $=C^1$-CH_3 (Z)); 2.10 (s, 3H, $CH_3COC^2H=$); 2.19 (s, 3H, $=C^1CH_3$ (E)); 2.31 (s, 3H, CH_3CONH); 5.27 (s, 1H, C^2H_z); 5.72 (s, 1H, C^2H_E);

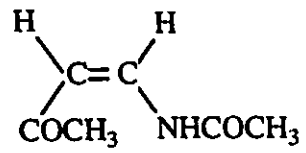
^{13}C NMR ($CDCl_3$) δ 21,80 ($\underline{C}H_3COC^2H=$), 25.39 ($\underline{C}H_3CONH$), 30.47 ($\underline{C}HC^1H=$), 105.20 ($=C^2H$), 155.09 ($=\underline{C}^1CH_3NH$), 169.48 ($\underline{C}ONH$), 199.34 ($\underline{C}OC^2H=$);

MS (m/e) 141 $[M]^+$.

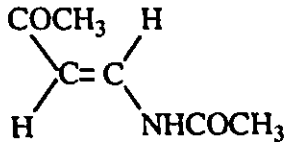
Anal. calcd. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85.

Found: C, 59.66; H, 8.61.

183b:



Z



E

IR (neat): ν_{NH} 3360 cm^{-1}, ν_{CO} 1710 cm^{-1}, 1665 cm^{-1};

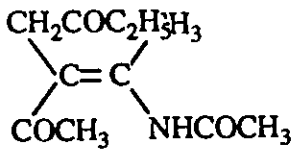
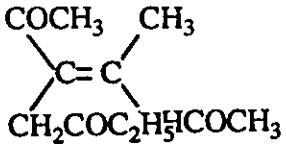
^1H NMR ($CDCl_3$) δ 2.11 (s, 3H, CH_3COC^2H=); 2.22 (s, 3H, CH_3CONH); 5.49 [d($^3J_{cis\ H^2\text{-}H^1}$= 8.7 Hz), 1H,$H^2_Z$]; 5.71 [d($^3J_{trans\ \ ^2H\text{-}^1H}$= 14.6 Hz), 1H,$H^2_E$], 7.34 [dd($^3J_{cis\ ^1H\text{-}^2H}$ = 8.7 Hz, $^3J_{H^1\text{-}NH}$= 11.0 Hz), 1H, H^1_Z]; 7.91 [dd ($^3J_{trans\ H^1\text{-}H^2}$ = 14.6 Hz, ($^3J_{H^1\text{-}NH}$ = 9.3 Hz), 1H, H^1_E]; 8.55 (S(br), 1H exchangeable with D_2O);

^{13}C NMR δ 23.29 ($\underline{C}H_3COC^2H$=), 26.15 ($\underline{C}H_3CONH$), 104.02 (=C^2HCO), 111.64 (=$\underline{C}^1HNH$), 168.94 ($\underline{C}ONH$), 198.99 ($\underline{C}OC^2H$=);

MS (EI) m/e 127 $[M]^+$;

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.14.

Found: C, 56.32; H, 7.22.

183c:  

Z **E**

IR (neat): ν_{NH} 3410 cm^{-1}, ν_{CO} 1718 cm^{-1}, 1680 cm^{-1};

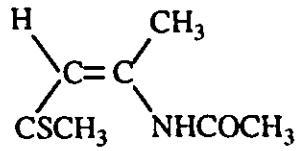
^1H NMR ($CDCl_3$) δ 1.09 (t, 3H, OCH_2CH_3 E or Z); 1.14 (t, 3H, OCH_2CH_3 Z or E); 2.03 (s, 3H, CH_3C^1H= E or Z); 2.15 (s, 3H, CH_3C^1= Z or E); 2.23 (s, 3H, CH_3COC^2= E or Z); 2.40 (s, 3H, CH_3COC^2 = Z or E); 2.52 (s, 3H, CH_3CONH E or Z); 2.66 (s, 3H, CH_3CONH Z or E); 3.355 (q, 2H, OCH_2CH_3 Z or E); 3.425 (q, 2H,OCH_2CH_3 E or Z); 4.08 (s, 2H, OCH_2C^2 = Z or E); 4.14 (s, 2H, OCH_2C^2 = E or Z);

MS (EI) m/e 156 $[M\text{-}CH_3CO]^+$, 43 $[CH_3CO]^+$ base peak.

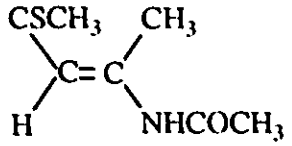
Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60.

Found: C, 59.99; H, 8.47.

185a:



Z



E

IR (neat): ν_{NH} 3415, ν_{CO} 1719, $\nu_{C=C}$ 1640, $\nu_{C=S}$ 1255cm^{-1};

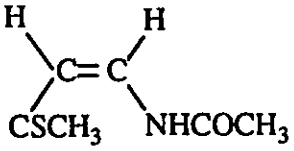
^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H, $CH_3C(S)$); 2.11 (s, 3H, CH_3C^1 = (Z)); 2.22 (s, 3H, CH_3C^1 = (E)); 2.33 (s, 3H, CH_3CONH); 5.29 (s, 1H, C^2H_Z); 5.77 (s, 1H, C^2H_E); 8.20 (s(br), 1H, NH exchangeable with D_2O);

MS (EI) m/e 142 $[M-CH_3]^+$;

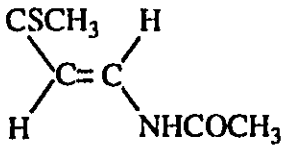
Anal. Calcd. for $C_7H_{11}NOS$: C, 53.47; H, 7.05

Found: C, 53.56; H, 7.00.

185b:



Z



E

IR (neat) ν_{NH} 3410, ν_{CO} 1720, $\nu_{C=C}$ 1645, $\nu_{C=S}$ 1255cm^{-1};

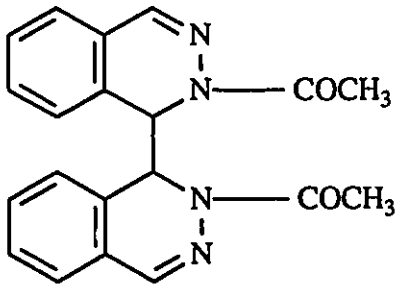
^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H, CH_3COC^2H =); 2.24 (s, 3H, CH_3CONH); 5.36 [d ($^3J_{cisH^2\text{-}H^1}$ =8.5 Hz), 1H,H^2_Z]; 5.71 [d ($^3J_{transH^2\text{-}H1}$ = 14.5 Hz), 1H, H^2_E]; 7.34 [dd ($^3J_{cis\ H^1\text{-}H^2}$ = 8.5 Hz, $^3J_{1H\text{-}NH}$ = 10.9 Hz), 1H, H^1_Z]; 7.88 [dd, ($^3J_{trans\ H^1\text{-}H^2}$ =14.5 Hz, $^3J_{1H\text{-}NH}$ =9.0 Hz, 1H,H^1_E]; 8.24 (s(br), 1H, NH exchangeable with D_2O);

MS (EI) m/e 143 $[M]^+$;

Anal. Calcd. for C_6H_9NOS: C, 50.32; H, 6.33

Found: C, 50.52; H, 6.61.

198:



M.p.: 194 - 196°C;

IR (KBr) $\nu_{CO,\ C=N}$ 1675 cm^{-1}, br;

^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3); 5.79 (s, 1H, H^1); 6.16 [d(J=7.4 Hz), 1H,H^8]; 7.11 (m, 1H, H^7); 7.35 (m, 2H, H^5,H^6); 7.79 (s, 1H, H^4);

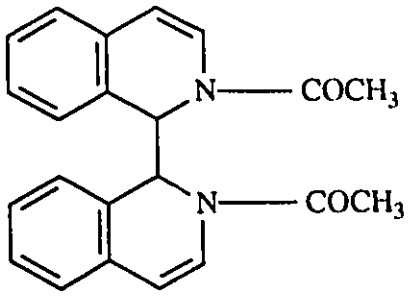
^{13}C NMR ($CDCl_3$) δ 21.29 (CH_3), 50.09 (C^1), 124.82 (C^{8a}), 128.18 ($C^{6\ or\ 5}$), 128.70 (C^8), 128.81 ($C^{5\ or\ 6}$), 130.08 (C7), 131.42 (C^{4a}), 142.00 (C^4), 171.73 (CO);

MS (EI) m/e 173 $[\frac{M}{2}]^+$, MS (CI) m/e 347 $[M + 1]^+$;

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24

Found: C, 69.47; H, 5.18.

199:



M.p. 190 - 192°C;

IR (KBr) ν_{CO} 1670 cm^{-1};

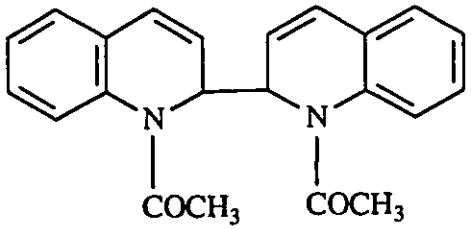
^1H NMR ($CDCl_3$) δ 2.14 (s, 3H, CH_3); 5.79 (s, 1H, H^1); 5.93 [d (J = 7.6 Hz), 1H, H^8]; 6.18 [d (J = 7.8 Hz), 1H, H^4]; 6.63 [d (J = 7.8 Hz), 1H, H^3]; 6.74 (m, 1H, H^7); 7.13 (m, 2H, H^5,H^6);

^{13}C NMR ($CDCl_3$) δ 21.62 (CH_3), 52.58 (C^1), 110.99 (C^3), 124.07 (C^4), 125.73 (C^{8a}), 127.91, 125.75 (C^5, C^6), 128.74 (C^8), 128.82 (C^7), 130.60 (C^{4a}), 168.58 (CO);

MS (EI) m/e 172 $[\frac{M}{2}]^+$, MS (CI) m/e 345 $[M + 1]^+$;

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85

Found: C, 77.00; H, 5.88.

200: 

M.p. 184 - 187°C;

IR (KBr) ν_{CO} 1650 cm^{-1};

^1H NMR ($CDCl_3$) δ 2.12 (s, 3H, CH_3); 5.70 (s, 1H, H^2); 5.91 [d (J = 7.0 Hz), 1H, $H^{4 \text{ or } 3}$]; 6.17 [d (J = 7.0 Hz), 1H, $H^{3 \text{ or } 4}$]; 6.31 [d (J = 7.7 Hz), 1H, H^5]; 6.70 [d (J = 9.4 Hz), 1H, H^8]; 7.18 (m, 2H, H^7,H^6);

MS (CI) m/e 345 $[M + 1]^+$;

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85

Found: C, 76.64; H, 5.82.

Conclusion

The process of ring expansion of heterocycles via carbonylation reactions in the presence of transition metal catalysts is one of the most simple, convenient and fascinating methods. Applying this novel carbonylation methodology and extending it in an evolutionary fashion, a series of novel, useful reactions have been discovered which appropriate to the goals of the investigation.

Cobalt carbonyl catalyzed the carbonylation of a series of 1,2-disubstituted pyrrolidines to form piperidinones in a highly regio-selective manner. When ruthenium carbonyl is present as a second catalyst, the yield of product is increased. However, in the presence of a dual metallic [$Co_2(CO)_8$/$Ru_3(CO)_{12}$] system, a new rearrangement reaction i.e., with nitrogen heterocyclic ketones [$(CH_2)_nCH_2COR$, n=4-7] occurred to lactams in good yields. During mechanistic studies a novel cobalt or ruthenium carbonyl catalyzed cyclization reaction was discovered, i.e. the reaction of 2(2,6)-(di)methylpiperidinyl ketones afforded the bicyclic 5,6,7,8-tetrahydroindolizines in good to excellent yields. The reaction of 2-aryl-5,6,7,8-tetrahydroindolizines with singlet oxygen, either generated under sensitized photoreactions or by cobalt catalyzed oxidation under very mild conditions, gave 2-aryl-8-hydroxy-6,7,8,8a-tetrahydro-3(5H)indolizinones in good yields. The PTC reactions of isoxa(thia)zoles and some other five and six-membered nitrogen-containing heteroaromatics with acetylcobalt tetracarbonyl to the corresponding acylation products were discussed.

In conclusion, the reactions developed in this thesis afforded biological interesting products, e.g. lactams, indolizines and multifuctionalized alkenes. One could

further extend these synthetic methods to different rings, substituted β-ethyl lactams, and bicyclic systems (e.g. 5+5, 7+5, 8+5, etc). Also, a modification of the catalytic system to other mixed metal systems, especially to large ring systems might lead to novel and interesting chemistry.

REFERENCES

[1] D.W. Goodman "Catalysis of Organic Reactions", R.L. Augustine; Marcel Dekker, Inc. New York, 1985, Part 3.

[2] J.P. Collman, L.S. Hegedus, J.R. Norton and R.G. Finke, "Principles and Applications of Organotransition Metal Chemistry", University Science Books, Millvalley, CA, 1987.

[3] W. Keim, "Fundamental Research in Homogeneous Catalysis", M. Graziani, and M. Giango, Eds., Plenum Press, New York, 1984, Vol 4.

[4] R. Ugo, "Aspects of Homogeneous Catalysis", D. Reidel Publ. Co.: Dordrecht, Neth, 1988, Vol. 6.

[5] Ch. Elschenbroich and A. Salzer, "Organometallics", 2nd edition, VCH Publ. Inc., New York, 1992, Chaper 17 and refs. therein.

[6] C.M. Starks, J. Am. Chem. Soc., 1971, 93, 195.

[7] J.E. Gordon and R.E. Kutina, J. Am. Chem. Soc., 1977, 99, 3903;

D. Landini, A. Maia and F. Montanari, J. Chem. Soc. Chem. Commun., 1977, 112;

D. Landini, A. Maia and F. Montanari, J. Am. Chem. Soc., 1978, 100, 2796;

A.Z. Trifonova, B.M. Nikolova, R.B. Kuzmanova and C. Ivanov, Z. Phys. Chem. (Leipzig), 1983, 264, 664.

[8] H. des Abbayes and H. Alper, J. Am. Chem. Soc., 1977, 99, 98.

[9] H. Alper and D. Des Roches, J. Organomet. Chem., 1976, 117, C44.

[10] Yu. Goldberg, "Phase Transfer Catalysis. Selected Problems and Applications", Gordon and Breach Sci. Publ. Ltd., London, 1992.

[11] C.M. Starks, "Phase-Transfer Catalysis", ACS Symposium Series 326, American Chemical Society, Washington, DC, 1987.

[12] H. Alper, "Fundamental Research in Homogeneous Catalysis", 1984, 4, 79.
H. des Abbayes, New J. Chem., 1987, 11, 535;
J.F. Petrignani, "The Chemistry of the Metal-Carbon Bond", F.R. Hartley, Ed.; J. Wiley and Sons. Ltd.: New York, 1989, Vol. 5.

[13] H. Alper, J. Organomet. Chem., 1986, 300, 1.

[14] H. Alper, H. Arzoumanian, J.F. Petrignani, and M. Saldana-Maldonado, J. Chem. Soc. Chem. Commun., 1985, 340.

[15] H. Alper, A. Eisenstat and N. Satyanarayana, J. Am. Chem. Soc., 1990, 112, 7060.

[16] J.P. Collman and L.S. Hegedus, "Principles and Applications of Organotransition Metal Chemistry", University Science Books, Mill Valley, Calif., 1980;
A. Yamamoto, "Organotransition Metal Chemistry", John Wiley & Sons., Inc. New York, 1986.

[17] F. Calderazzo, R. Ercoli and G. Natta, "Organic Synthesis via Metal Carbonyls", I. Wender and P. Pino, Eds., Interscience: New York, 1968, Vol. 1, 1-272.

[18] E.W. Abel and F.G.A. Stone, Quart. Rev., 1969, 23, 325; 1970, 24, 498.

[19] P.S. Braterman, "Structure and Bonding" (a) 1972, 10, 57; (b) 1976, 26, 1.

[20] F.A. Cotton, Prog. Inorg. Chem., 1976, 21, 1.

[21] C.M. Lukehart, "Fundamental Transition Metal Organometallic Chemistry", Brooks/Cole: Monterey, CA, 1985; Chapter 2.

[22] B.J. Brisdon, "Metal Carbonyls", Organomet. Chem., 1989, 17, 135-44; 1989, 18, 129-39. Nelson, J. Chem. Soc., Dalton Trans., 1980, 383.

[23] J.D. Atwood, "Inorganic and Organometallic Reaction Mechanism", Brooks/Cole: Monterey, CA, 1985.

[24] E.W. Abel and F.G.A. Stone, Chem. Soc. (London) Quart. Rev., 1969, 22, 325 and refs. therein.

[25] R.J. Angelici and F. Basolo, J. Am. Chem. Soc., 1962, 84, 2495; A. Wojcicki and F. Basolo, J. Am. Chem. Soc., 1961, 83, 525.

[26] J.D. Atwood, J. Organomet. Chem., 1990, 383, 59.

[27] [16]; H. Alper, J. Organomet. Chem. Libr. 1976, 1, 305; M. Foa and F. Francalanci, J. Mol. Cat., 1987, 41, 89-107.

[28] B.D. Dombek, Comments Inorg. Chem., 1985, 4, 241.

[29] L.S. Hegedus, "Transition Metals in Organic Synthesis", Annual Survey, Covering the year, J. Organomet. Chem., 1974, Vol. 103 - 1990, Vol. 442.

[30] M. Roper, "Studies in Surface Science and Catalysis", L. Guczi, Ed., Elsevier Sci. Publ. B.V., 1992, Vol. 64, Chapter 9.

[31] I. Ojima, "Advances in Metal-Organic Chemistry", L.S. Liebeskind, Ed., JAI Press, Inc., England, 1989, Vol. 1, 51.

[32] H. Alper and J.F. Petrignani, J. Chem. Soc., Chem. Commun., 1983, 1154.

[33] M. Hidai, A. Fukuoka and Y. Koyasu, J. Chem. Soc., Commun., 1983, 516.

[34] H. Alper, M.D. Wang and S. Calet, J. Org. Chem., 1989, 54, 20.

[35] H. Alper, and M.D. Wang, J. Am. Chem. Soc., 1992, 114, 7018.

[36] W. Reppe, Liebigs Ann. Chem., 1953, 582, 1.

[37] P. Pino, F. Piacenti and M. Bianchi, "Organic Synthesis via Metal Carbonyls", I. Wender and P. Pino, Eds., Wiley-Interscience, New York, 1977, Vol. 2, 43-231.

[38] H.M. Colquhoun, D.J. Thompson and M.V. Twigg, "Carbonylation", Plenum Press, New York, 1991, Chapter 1, 3 and 11.

[39] B. Cornils, "New Synthesis with Carbon Monoxide", J Falbe, Ed., Springer-Verlag, New York, 1980, 1-225.

[40] F.P. Pruchnik, "Organometallic Chemistry of the Transition Elements", Modern Inorg. Chem. Ser., F.P. Pruchnik, Ed., Plenum Press, New York, 1990, Chapter 13.

[41] G.J. Schulz, Rev. Mod. Phys., 1973, 45, 423.

[42] S.G. Davies, "Organotransition Metal Chemistry Application to Organic Synthesis", Pergamon Press Ltd., England, 1982, Chapter 9.

[43] J. Tsuji. "Organic Synthesis via Metal Carbonyls", I. Wender and P. Pino, Eds., Wiley-Interscience, 1977, Vol. 2, 595.

[44] D.H. Doughty, "Homogeneous Catalysis with Metal-Phosphine Complexes", L.H. Pignoler, Ed., Plenum Press, New York, 1983, 343.

[45] F. Calderazzo and K. Noack, Coord. Chem. Rev., 1966, 1, 118.

[46] J.J. Alexander, "The Chemistry of the Metal-Carbon Bond", F.R. Hartley, Ed., Wiley, New York, 1985, Vol. 2, Chapter 5.

[47] M.J. Wax and R.G. Bergman, J. Am. Chem. Soc., 1981, 103, 7028.

[48] J.P. Collman, R.G. Finke, J.N. Cawse and J.I. Brauman, J. Am. Chem. Soc., 1987, 100, 4766.

[49] F.U. Axe and D.S. Marynick, Organometallics, 1987, 6, 572.

[50] M. Bassetti, J. Chem. Soc. Dalton Trans., 1990, 1799.

[51] J.D. Cotton, G.T. Crisp and L. Latif, Inorg. Chim. Acta., 1981, 47, 171.

[52] S.L.Webb, C.M. Giandomenico and F. Halpern, J. Am. Chem. Soc., 1986, 108, 345.

[53] J.A. Connor, Topics in Curr. Chem., 1977, 71, 71.

[54] D.J. Darensbourg, B.J. Baldwin and J.A. Froelich, J. Am. Chem. Soc., 1980, 102, 4688.

[55] R.L. Kump and L.J. Todd, Inorg. Chem., 1981, 20, 3715.

[56] P.C. Ford and A. Rokicki, Adv. Organomet. Chem., 1988, 28, 139.

[57] H.A. Hoddi and D.F. Shriver, Inorg. Chem., 1979, 18, 1236.

[58] H.M. Colquhoun, D.J. Thompson and M.V. Twigg, "Carbonylation", Plenum Press, New York, 1991, Chapter 2.

[59] L. Marko and Vizi-orosz, "Studies in Surface Science and Catalysis", B.C. Gates, L. Guczi and H. Knozinger, Eds., Elsevier Sci. Publ. B.V., New York, 1986, Vol. 29, Chapter 5.

[60] V.A. Golodov, J. Res. Inst. Catal., 1981, 29, 49.

[61] F.P. Pruchnik, "Organometallic Chemistry of the Transition Elements", Plenum Press, New York, 1990, Chapter 3.

[62] P.C. Ford, R.G. Rinker, C. Ungermann, R.M. Laine, V. Landis and S.A. Moya, J. Am. Chem. Soc., 1978, 100, 4595.

[63] C. Ungermann, V. Landis, S.A. Moya, H. Cohen, H. Walker, R.G. Pearson, R.G. Rinker and P.C. Ford, J. Am. Chem. Soc., 1979, 101, 5922.

[64] T. Venalainen, E. Liskola, J. Pursiainen, T.A. Pakkanen and T.T. Pakkanen, J. Mol. Catal. 1986, 34, 293.

[65] J.F. Knifton, J. Chem. Soc. Chem. Commun., 1983, 729.

[66] R. Whyman, J. Chem. Soc. Chem. Commun., 1983, 1439.

[67] P. Braunstein and J. Rose, "Stereochemistry of organometallic and inorganic compounds", I. Bernal, Ed., Elsevier Sci. Publ. B.V., New York, 1989, Vol. 3, Chapter 1.

[68] M. Hidai, M. Orisako, M. Ue, Y. Yoyasu, T. Kodama and Y. Uchida, Organometallics, 1983, 2, 292.

[69] H. Alper and J.F. Petrignani, J. Chem. Soc. Chem. Commun., 1983, 1154.

[70] H. Alper, J.K. Currie and H. des Abbayes, J. Chem. Soc. Chem. Commun., 1978, 311.

[71] W.L. Gladfelter and G.L. Geoffroy, Adv. Organomet. Chem., 1980, 18, 207; D.A. Roberts and G.L. Geoffroy, "Comprehensive Organometallic Chemistry", G. Wilkinson, F.G.A. Stone and E. Abel, Eds., Pergamon, Oxford, 1982, Vol. 6, Chapter 40.; G.P. Elliot, J.A.K. Howard, T. Mise, C.M. Nunn and F.G.A. Stone,

Angew. Chem., Int. Ed. Engl., 1986, 25, 190.; R.D. Adams and W.A. Herrmann, Polyhedron 1988, 7, 2255.; L.J. Farrugia, Adv. Organomet. Chem., 1990, 31, 301.

[72] M. Ichikawa, Adv. Catal., 1992, 38, 283.

[73] T.L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., Longman Group(FE) Ltd., Hong Kong, 1992, Chapter 1.

[74] Y. Ohshiro, H. Hirao, Heterocycles 1984, 22, 859.

[75] H. Alper, Isr. J. Chem., 1981, 21, 203.

[76] R. Aumann and H. Ring, Angew. Chem. Int. Ed. Engl., 1977, 16, 50. .

[77] I. Schimizu, T. Maruyama, T. Makuta and A. Yamamoto, Tetrahedron Lett., 1993, 2135.

[78] Y. Kamiya, K. Kawato and H. Ohta, Chem. Lett., 1980, 1549.

[79] H. Alper and S. Calet, Tetrahedron Lett., 1988, 29, 1763.

[80] H. Alper, H. Arzoumanian, J.F. Petrignani and M. Saldana-Maldonado, J. Chem. Soc. Chem. Commun., 1985, 340.

[81] H. Alper, A. Eisenstat and N. Satyanarayana, J. Am. Chem. Soc., 1990, 112, 7060.

[82] S. Calet and H. Alper, Organometallics, 1987, 6, 1625.

[83] H. Alper and C. Perera, J. Am. Chem. Soc., 1981, 103, 1289.

[84] L.S. Hegedus, T. Hayashi and W.H. Darlington, J. Am, Chem. Soc., 1978, 100, 7747 and refs. therein.

[85] H. Alper and C.P. Mahatantila, J. Am. Chem. Soc., 1984, 106, 2708.

[86] J.A. Deyrup, "Small Ring Heterocycles" Part 1, ed. A. Hassner, Wiley-Interscience, New York, 1983, 1.; O.C. Dermer and G.E. Ham, "Ethyleneimine and Other Aziridines", Academic Press, New York, 1969.

[87] H. Alper and T. Sakakibara, J. Chem. Soc., Chem. Commun., 1979, 458.

[88] H. Alper, F. Urso and D.J.H. Smith, J. Am. Chem. Soc., 1983, 105, 6737.

[89] D.P. Klein, J.C. Hayes and R.G. Bergman, J. Am. Chem. Soc., 1988, 110, 3704.

[90] W. Chamchaang and A.R. Pinhas, J. Chem. Soc., Chem. Commun., 1988, 710.

[91] S. Calet, F. Urso and H. Alper, J. Am. Chem. Soc., 1989, 111, 931.

[92] D. Roberto and H. Alper, Organometallics, 1984, 3, 1767.

[93] H. Alper and N. Hamel, Tetrahedron Lett., 1987, 28, 3237.

[94] G.W. Spears, K. Nakanishi and Y. Ohfune, Synlett, 1991, 91.

[95] H. Alper, D. Delledonne, M. Kameyama and D. Roberto, Organometallics, 1990, 9, 762.

[96] I. Wender and P. Pino, "Organic Synthesis via Metal Carbonyls". J. Wiley and Sons., 1968, Vol. 1, 1977, Vol. 2 and refs. therein.

[97] D.T. Thompson and R. Whyman, "Transition Metals in Homogeneous Catalysis", G.N. Schrauzer, Ed., Dekker, New York, 1971.

[98] N.H. Cromwell and B. Phillips, Chem. Rev., 1979, 79, 331.

[99] J.A. Moore and R.S. Ayers, "Small Ring Heterocycles", A. Hassner, Ed., Wiley - Interscience, New York, 1983, Part 2.

[100] D. Roberto and H. Alper, J. Am. Chem. Soc., 1989, 111, 7539.

[101] K.S. Kochbar and H.W. Pinnik, Tetrahedron Lett., 1983, 23, 4785.

[102] H. Alper, Aldrichimica Acta, 1991, 24, 1,3.

[103] Y. Soma, N. Yamamoto, H. Sano, K. Yamauchi, K. Tamaoki, K. Tanaka and T. Yabushita JP 01.299285 (89.299.285), 1989; Chem. Abstr., 1990, 112, 216979.

[104] D. Roberto, Ph.D. Thesis, Ottawa, 1989, Chapter 5.

[105] H.M. Colquhoun, D.G. Thompson and M.V. Twigg, "Carbonylation", Plenum Press: New York, 1991; pp: 191-203.

[106] A.G.M. Barrett and M.A. Sturgess, Tetrahedron, 1988, 44, 5615.

[107] L.S. Hegedus, R. Imwinkelreid, M. Alarid-Sargent, D. Dvorak and Y. Satoh, J. Am. Chem. Soc., 1990, 112, 1109.

[108] M. Mori, K. Chiba and Y. Ban, J. Org. Chem., 1978, 43, 1684.

[109] D. Enders, P. Pieter, B. Renger and D. Seebach, Org. Synth., 1978, 58, 113.

[110] R.A. Jones, "Comprehensive Heterocyclic Chemistry", A.R. Katritzky, C.W. Rees, C.W. Bird and G.W.H. Cheeseman, Eds., Pergamon Press, Oxford, 1984, Vol. 4, Part 3.

[111] W. Keim, A. Behr and M. Roper, "Comprehensive Heterocyclic Chemistry", G. Wilkinson, F. Stone and E. Abel, Eds., Pergamon Press, Oxford, 1982, Vol. 8.

[112] J.A. Pople and A. Bothner-By, J. Chem. Phys., 1965, 42, 1339.

[113] H.E. Bryndza, W.C. Fultz and W. Tam, Organometallics, 1985, 4, 939.

[114] K.W. Blake and L. Gillies, J. Chem. Soc., Perkin Trans.I, 1981, 700.

[115] A.W. Murray, Org. React. Mech., Wiley, New York, 1989, 445.

[116] L.S. Hegedus, J. Organometal. Chem., ("Transition Metal Derivatives in Organic Synthesis" Annual Survey covering the year). 1975, 103, 421, covering

1974; 1977, 126, 151, covering 1975; 1977, 143, 309, covering 1976; 1979, 180, 301, covering 1978; 1981, 207, 185, covering 1979; 1983, 237, 231, cocering 1980; 1984, 261, 283, covering 1982; 1985, 283, 1, covering 1983; 1986, 298, 207, covering 1984; 1988, 343, 147, covering 1986; 1989, 360, 409, covering 1987; 1992, 422, 301, covering 1990.

[117] E. Charmot, A.K. Sharma and L.A. Paquette, Tetrahedron Lett., 1978, 1963.

[118] J.P. Oliver, Adv. Organomet. Chem., 1977, 16, 111.

[119] E.A. Hill, Adv. Organomet. Chem., 1977, 16, 131.

[120] E. Grovenstein, Adv. Organomet. Chem., 1977, 16, 167.

[121] J.W. Faller, Adv. Organomet. Chem., 1977, 16, 211.

[122] M. Tsutsui and A. Courtney, Adv. Organomet. Chem., 1977, 16, 241.

[123] B. Gorewit and M. Tsutsui, Adv. Organomet. Chem., 1988, 27, 227.

[124] J. Evans, Adv. Organomet. Chem., 1977, 16, 319.

[125] A.J. Deeming, Inorg. Organomet. React., 1986, 4, 377.

[126] K.G. Orell, Mech. Inorg. Organomet. React., 1989, 6, 337.

[127] G. Maire and F. Garin, J. Mol. Catal., 1988, 48, 99.

[128] S.I. Murahashi, T. Hirano and T. Yano, J. Am. Chem. Soc., 1978, 100, 348.

[129] M.E. Kuehne and W.H. Parsons, Tetrahedron, 1983, 39, 3763.

[130] T. Shono, Tetrahedron, 1984, 40, 811 and refs. therein.

[131] a) Org. Synth., 1965, 45, 28, 77; b) E.J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.

[132] D.J. Pasto and C.R. Johnson, "Laboratory Text for Organic Chemistry",

Prentice-Hall, Inc., New Jersey, 1979.

[133] D. Rogic, M.F. Lautie, P. Dizabo and L.C. Leitch, J. Label. Comp., 1974, 10, 655.

[134] R.G. Bergman, Science, 1984, 223, 902; J. Organomet. Chem., 1990, 400, 273.

[135] S. Kajigaeshi, T. Kakinami and T. Okamoto, S. Fujisaki, Bull. Chem. Soc. Jpn., 1987, 60, 1159.

[136] Org. React., 1942, 1, 329.

[137] S. Rajeswari, S. Chandrasekharan and T.R. Govinoachari, Heterocycles, 1987, 25, 59.

[138] For examples see: M.H. Ali, L. Hough and A.C. Richardson, J. Chem. Soc., Chem. Commun., 1984, 447; L.E. Overman, K.L. Bell and F. Ito, J. Am. Chem. Soc., 1984, 106, 4192.

[139] M.T. Pizzorno and S.M. Albonicino, J. Org. Chem., 1977, 42, 909.

[140] D.J. Robins, Adv. Heterocycl. Chem. 1976, 23, 152.

[141] S.R. Johns and J.A. Lamberton, " 'The Alkaloids' - Chemistry and Physiology", R.H.F. Manske, Ed., Academic Press, NY, 1973, Vol. XIV, 326.

[142] E. Gellert, J. Nat. Prod., 1982, 45, 50.

[143] T.R. Govindachari and N. Viswanathan, Heterocycles, 1978, 11, 587.

[144] G.R. Clemo and G.R. Ramage, J. Chem. Soc., 1931, 49; S.P. Tanis and J.W. Raggon, J. Org. Chem., 1987, 52, 819 and refs. therein.; S. Massa, A. Mai and F. Corelli, Tetrahedron Lett., 1988, 29, 6471.; A. Pawda and B.H. Norman,

Tetrahedron Lett., 1988, 29, 3041.

[145] P. Gmeiner and H. Lerche, Heterocycles, 1990, 31, 9.

[146] R.J. Abraham and P. Loftus, "Proton and Carbon-13 NMR Spectroscopy", Heyden & Son Ltd., East Kilbride, Scotland, 1981, Chapter 3.

[147] J.C. Gilbert and B.K. Blackburn, J. Org. Chem., 1986, 51, 3656.

[148] M. Hudlicky, "Oxidations in Organic Chemistry", ACS Monograph 186, Washington, DC, 1990.

[149] I. Saito, S. Matsugo and T. Matsuura, J. Am. Chem. Soc., 1979, 101, 7332.

[150] C. Kaneko, A. Sugimoto and S. Tanaka, Synthesis, 1974, 876.

[151] R.P.A. Sneeden and R.B. Turner, J. Am. Chem. Soc., 1955, 77, 190.

[152] K. Heyns and L. Blazejewicz, Tetrahedron, 1960, 9, 67.

[153] A.S. Hay, J.W. Eustance and H.S. Blanchard, J. Org. Chem., 1960, 25, 616.

[154] G. de Vries and A. Schors, Tetrahedron Lett., 1968, 5689.

[155] K.B. Sharpless and R.C. Michaelson, J. Am. Chem. Soc., 1973, 95, 6136 and refs. therein.

[156] K.B. Sharpless, K. Akashi and K. Oshima, Tetrahedron Lett., 1976, 2503.

[157] T.F. Blackburn and J. Schwartz, J. Chem. Soc. Chem. Comm., 1977, 157.

[158] R.E. Cameron and A.B. Bocarsly, J. Am. Chem. Soc., 1985, 107, 6116.

[159] H. Carpio, E. Galeazzi, R. Greenhouse, A. Guzman, E. Velarde, Y. Antonio, F. Franco, A. Leon, V. Perez, R. Salas, D. Valdez, J. Ackrell, D. Cho, P. Gallegra, O. Halpern, R. Koehler, M.L. Maddox, J.M. Muchowski, A. Prince, D. Tegg, T. Craig Thurber, A.R. Van Horn, and D. Wren, Can. J. Chem., 1982, 60, 2295.

[160] H.H. Wasserman, R. Frechette, V.M. Rotello and G. Schulte, Tetrahedron Lett., 1991, 7571.

[161] J.F. Petrignani, "The Chemistry of the Metal-Carbon Bond", F.R. Hartley, Ed., N.Y., John Wiley & Sons, 1989, 5, 63.; H. Des Abbayes, Isr. J. Chem., 1985, 26, 249.

[162] H. Alper, J.K. Currie and H. Des Abbayes, J. Chem. Soc. Chem. Commun., 1978, 311.

[163] H. Alper and J.K. Currie, Tetrahedron Lett., 1979, 2665.

[164] H. Alper and D.E. Laycock, Tetrahedron Lett., 1981, 22, 33.

[165] H. Alper and S. Amaratunga, Can. J. Chem., 1983, 61, 1309.

[166] H. Alper and G. Vasapollo, Tetrahedron Lett., 1988, 29, 5113.

[167] H. Alper and J.E. Prickett, Inorg. Chem., 1977, 16, 67.; Y. Nakamura, B. Bachmann, H.Heimgartner and H. Schmid, Helv. Chim. Acta., 1978, 61, 589.; F. Bellamy, J. Chem. Soc. Chem. Commun., 1978, 998.

[168] H. Alper and J.E. Prickett, Tetrahedron Lett., 1976, 2589.

[169] F. Bellamy, Tetrahedron Lett., 1976, 2589.; A. Inada, H. Heimgartner and H. Schmid, Tetrahedron Lett., 1979, 2983.; M. Nitta and T. Kokayashi, J. Chem. Soc. Perkin. Trans., I, 1985, 1401.

[170] H. Alper, J.E. Prickett and S. Wollowitz, J Am. Chem, Soc., 1977, 99, 4430.

[171] M. Nitta and T. Kobayashi, Chem. Lett., 1983, 1715.

[172] A. Guarna, A. Guidi, A. Goti, A. Brandi and F. Desarlo, Synthesis, 1985, 175.; P.G. Baraldi, A. Barco, S. Benetti, S. Manfredini and D. Simoni, Synthesis,

1987, 276.

[173] S. Cicchi, A. Goti, A. Brandi, A. Guarna and F. De Sarlo, Tetrahedron Lett., 1990, 31, 3351.

[174] Y. Becker, A. Eisenstadt and Y. Shvo, Tetrahedron, 1978, 34, 799.

[175] J.L. Davison and P.N. Preston, Adv. Heterocycl. Chem., 1987, 41, 49.

[176] T.L. Gilchrist, Adv. Heterocycl. Chem., 1987, 41, 89.

[177] D.N. McGregor, U. Corbin, J.E. Swigor and L.C. Cheney, Tetrahedron, 1969, 25, 389.

Claims to Original Research

1. The new methodology to synthesize piperidinones by metal catalyzed ring expansion carbonylation reactions of pyrrolidines.
2. The new metal catalyzed rearrangement reactions of heterocyclic nitrogen ketones [$(CH_2)_nNCH_2COR$,n=4-7] to alkyl(or arylethyl) lactams. The mixed-metal catalytic system, $Co_2(CO)_8/Ru_3(CO)_{12}$ is efficient for the rearangement reaction.
3. The novel metal catalyzed cyclization reactions of 2-methyl(or 2,6-dimethyl)piperidinyl ketones to 5,6,7,8-tetrahydroindolizines.
4. An examination of the roles of oxygen as the oxidant in Co-catalyzed oxidation of 5,6,7,8-tetrahydroindolizines to 8a-hydroxy-6,7,8,8a-tetrahydro-3(5H) indolizinones.
5. The new phase transfer catalysis reactions of some five and six-membered nitrogen-containing heteroaromatics with acetylcobalt tetracarbonyl.

Publications

1. M.D. Wang and H. Alper, "Regioselective Synthesis of Piperidinones by Metal Catalyzed Ring Expansion-Carbonylation. Remarkable Cobalt and/or Ruthenium Carbonyl Catalyzed Rearrangement and Cyclization Reactions", J. Am. Chem. Soc., 1992, 114, 7018-7024.
2. M.D. Wang and H. Alper, "Phase Transfer Catalyzed Reductive Acylation of Nitrogen Containing Heteroaromatics with Acetylcobalt Tetracarbonyl", J. Organomet. Chem., 1993, 451, 169-173 (special issue dedicated to Prof. Paolo Chiusoli).
3. M.D. Wang and H. Alper, "Catalytic and Photolytic Reactions of 2-Aryl-5,6,7,8-tetrahydroindolizines with Singlet Oxygen", Tetrahedron Lett., to be submitted.
4. M.D. Wang, S. Calet, H. Alper, "Regiospecific Carbonylation and Ring Expansion of Thietanes and Oxetanes Catalyzed by Cobalt and Ruthenium Carbonyls", J. Org. Chem., 1989, 54, 20-21.