INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

REACTIONS OF CARBANIONS STABILISED BY ADJACENT NITROGEN FUNCTIONS

by

Ion Dan Postescu

A Thesis submitted in Partial Fulfilment of the Requirements

for the degree of

Master of Science

in the

Department of Chemistry
University of Ottawa
Ottawa, Canada

May, 1972

Université d'Ottawa
BIBLIOTHÈQUES
LIBRARIES
University of Ottawa

Ion Dan Postescu
Candidate

Robert R. Fraser
Professor of Chemistry
Supervisor

© Ion Dan Postescu, Ottawa 1972

UMI Number: EC52300

INFORMATION TO USERS

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleed-through, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

UMI®

UMI Microform EC52300
Copyright 2007 by ProQuest LLC
All rights reserved. This microform edition is protected against unauthorized copying under Title 17, United States Code.

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

ACKNOWLEDGMENTS

The author wishes to express his gratitude to Professor R.R. Fraser, who promoted and expertly guided the present work.

Sincere acknowledgments are expressed also to Dr. T. Durst for his helpful suggestions and discussions.

Grateful thanks are due to all my colleagues, and to Angela Eriksen who had the task of typing this thesis.

TABLE OF CONTENTS

	Page no.
ACKNOWLEDGMENTS	i
TABLE OF CONTENTS	ii
LIST OF FIGURES, SCHEMES AND TABLES	iii
ABSTRACT	iv
INTRODUCTION	1
RESULTS AND DISCUSSION	16
EXPERIMENTAL	35
CONCLUSIONS	48
CLAIMS TO ORIGINAL RESEARCH	49
REFERENCES	50

LIST OF FIGURES, SCHEMES and TABLES

		Page no.
FIGURE 1.	The N. M. R. Spectrum of benzyl-(α-methyl)-benzylnitrosamine	26
SCHEME I.	The Alkylation of dibenzylnitrosamine	17
SCHEME II.	The Methylation of 1-nitroso-4-phenyl-piperazine	22
SCHEME III.	The Carboxylation of Nitrosamines	30
TABLE I.	The Yields of Alkylation of Dibenzyl-nitrosamine	18
TABLE II.	The Methylation of 1-nitroso-4-phenyl-piperazine in THF	23

ABSTRACT

The α-functionalisation via carbanion intermediates was effected on a series of nitrosamines. A number of alkylations were found to proceed efficiently in the case of dibenzylnitrosamine. Moderate yields were obtained in the methylation of 1-nitroso-4-phenylpiperazine. The carboxylation of this compound proved to proceed in higher yield than the alkylation. The carboxylation of 1-nitroso-pyrrolidine and 1-nitrosopiperidine was achieved in lower yield (27-28%).

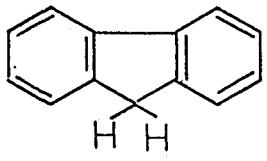
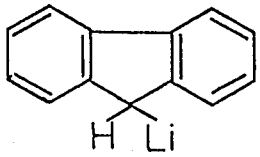
Optimum conditions for denitrosation were obtained by bubbling hydrogen chloride gas through the benzene solution of the nitrosamine. The yields of the resultant amine hydrochlorides were consistently 80-90%.

It was found that an amido group (i.e. in N,N-dibenzylbenzamide) like the nitroso group provides an activating influence for the lithiation α to nitrogen.

INTRODUCTION

Synthetic pathways involving carbanion intermediates are known to be efficient methods for the formation of carbon-carbon bonds. The versatility and ease of reactivity towards the electrophilic reagents allows the carbanions to be converted into a wide variety of derivatives.

Schlenk and Bergmann[1] first reported a lithiation reaction in 1928. They discovered that ethyllithium reacted with fluorene (1) by replacing an acidic hydrogen, to produce fluorenyllithium (2) and ethane:

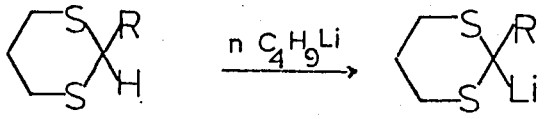
[1] C_2H_5Li +  →  + C_2H_6

1 2

The main requirement for a successful metallation is the activation of the carbon atom at which the substitution of hydrogen by metal will take place. The ease of hydrogen abstraction (acidity) depends to a large extent on the stability of the resultant anion. The following factors affecting the stabilisation are generally involved: hybridisation, conjugation (delocalisation over more centres), inductive, aromatisation and d-orbital overlap effects[2, 3].

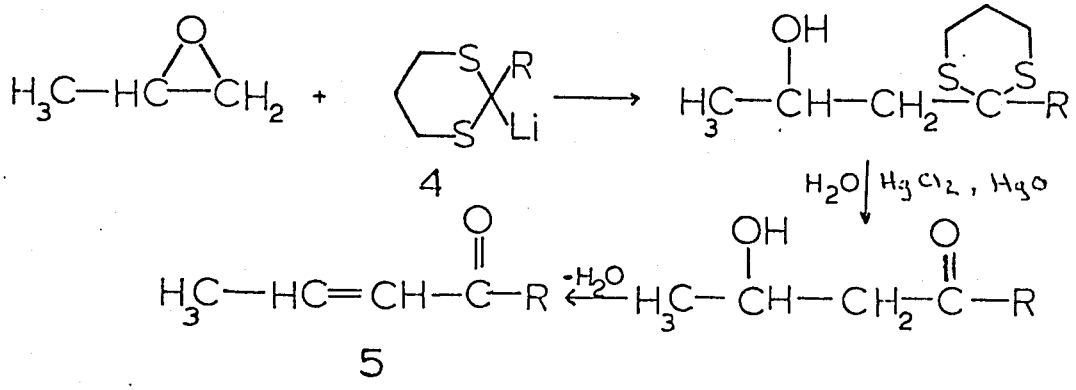
A brief review of the more recently reported applications of the lithiation, including the compounds containing nitrogen, will be surveyed in the following pages.

Corey and Seebach[4] have reported the metallation of 1, 3-dithianes (3) with n-butyllithium, in tetrahydrofuran solution (e.g. 2);

[2] 

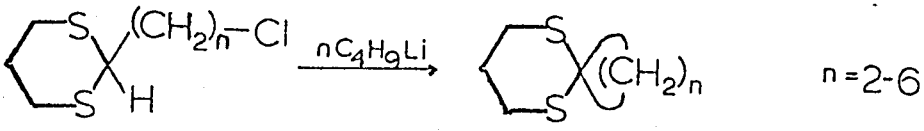
3 4 R=H, alkyl

The 1, 3-dithian-2-yl-lithium compounds (4) exhibit good nucleophilic properties, being proved as efficient reagents in many alkylation reactions[5]. Their application to the preparation of alcohols and α, β-unsaturated carbonyl compounds (5) is illustrated in eq. 3.

[3] 

5

The 2-lithio derivatives of 1, 3-dithianes react readily with alkyl halides to afford 2-alkylated dithianes in very good yields[4]. An intramolecular alkylation, the cyclisation of 2-(ω-chloroalkyl)-1, 3-dithianes (6) to the cycloalkanone trimethylenethioketals (7) has also been reported[6]:

[4] 

6 7

Rathke[7] has shown that lithium bis(trimethylsilyl) amide converted quantitatively ethyl acetate (8) to lithio ethyl acetate salt (9). This reacted almost instantly with aldehydes or ketones to give, after hydrolysis, excellent yields of the corresponding β-hydroxy esters (10);

[5] $H_3C-CO_2C_2H_5 \xrightarrow{[(CH_3)_3Si]_2NLi} LiCH_2-CO_2C_2H_5 \xrightarrow{RR'C=O} R-\underset{\displaystyle R'}{\overset{\displaystyle OH}{\underset{|}{\overset{|}{C}}}}-CH_2CO_2C_2H_5$

8 9 10

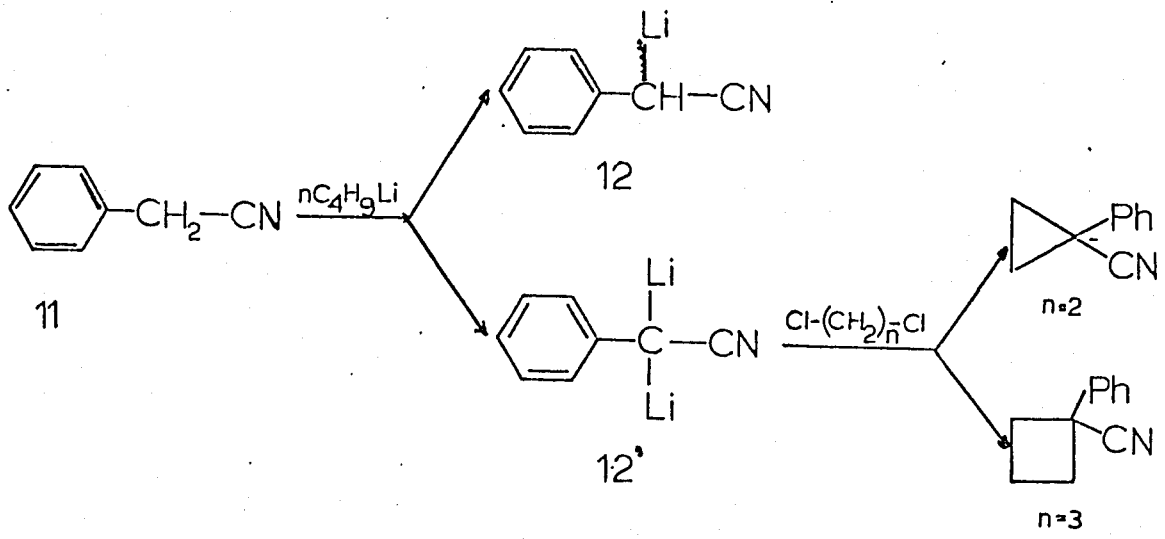
A more general procedure for the preparation of stable ester enolates has been accomplished with lithium N-isopropylcyclohexylamide as metallating reagent. The enolate solution reacts with a wide variety of organic halides to provide the corresponding alkylated esters (eq. 6). The procedure is relatively simple and potentially more versatile than the usual malonic ester synthesis[8].

[6] $$Li\underset{|}{\overset{|}{C}}CO_2R + R'X \rightarrow R'-\underset{|}{\overset{|}{C}}CO_2R + LiX$$

The ester enolates also could be dimerised in the presence of Cu^{II} salts[9], or converted with halogens to α-haloesters[10].

In the series of nitriles, acetonitrile was found to undergo mainly ionisation of an α-hydrogen, with n-butyllithium, rather than an addition involving the cyanide group[11]. Phenylacetonitrile (11) could be both mono- and dilithiated (eq. 7)[12]:

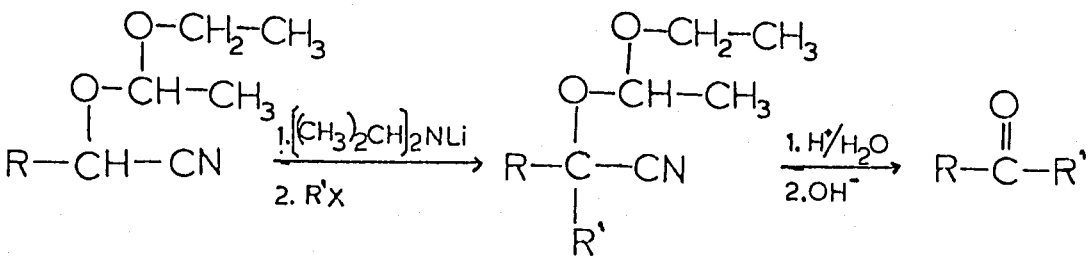
[7]



The condensation of the gem-dilithio salts (12') with dihaloalkanes provides a good method for the cycloalkane nitrile preparation[13] (eq. 7).

Stork and Maldonaldo[14] have reported a useful type of acyl carbanion equivalent and its use in the synthesis of ketones. The aldehyde cyanohydrins, suitably protected with ethyl vinyl ethers (13), can be transformed with lithium diisopropylamide into their anions. Addition of an alkyl halide produced the cyanohydrin derivative (14) which is easily hydrolysed to the corresponding ketone (15);

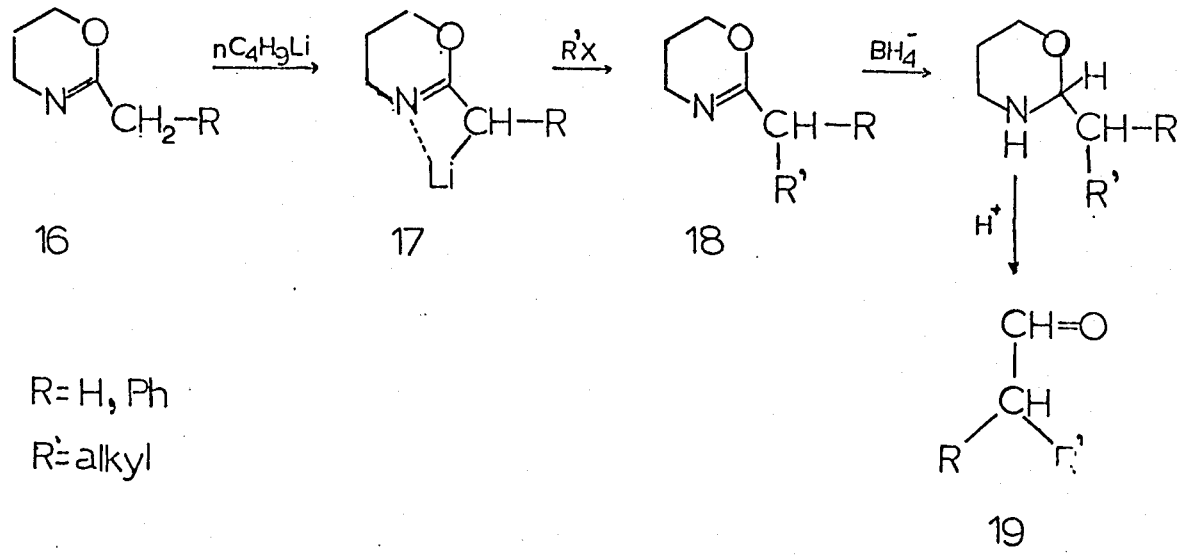
[8]



13 14 15

The lithio salts of 5, 6-dihydro-1, 3-oxazines are excellent nucleophiles and react efficiently with alkyl halides producing precursors to a variety of aliphatic aldehydes[15].

[9]



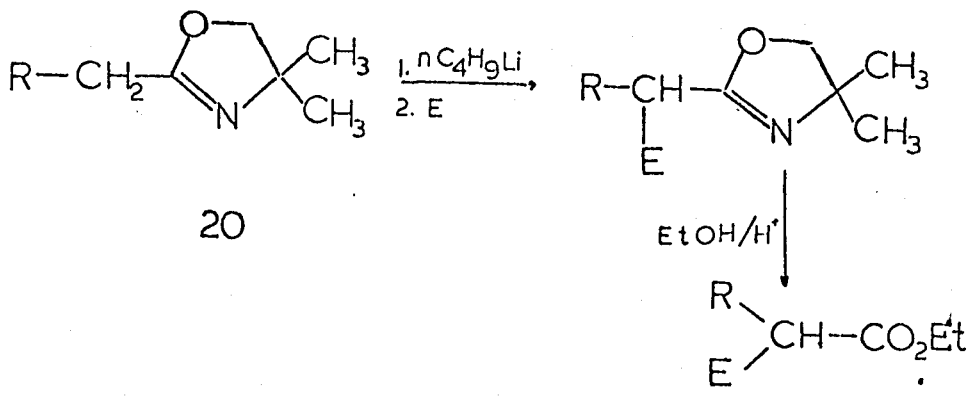
16 17 18 19

R= H, Ph
R'= alkyl

The synthesis originates from a readily available heterocyclic system (16) which was converted almost quantitatively with organolithiums into the anion (17). The anion is alkyated upon the addition of alkyl halides producing the corresponding side-chain substituted dihydro-1, 3-oxazine (18). The products were reduced with sodium borohydride and then hydrolysed to the aldehydes (19).

2-Substituted 4, 4-dimethyl-2-oxazolines (20) have shown potential utility as precursors in the synthesis of aliphatic acids and esters[16]. The 2-methylene group could be smoothly metallated with n-butyllithium. The resulting lithio derivatives have been reacted with various electrophiles E (alkyl halides, carbonyl compounds, epoxides). The subsequent ethanolysis yielded the corresponding acid esters (21), eq. (10);

[10]

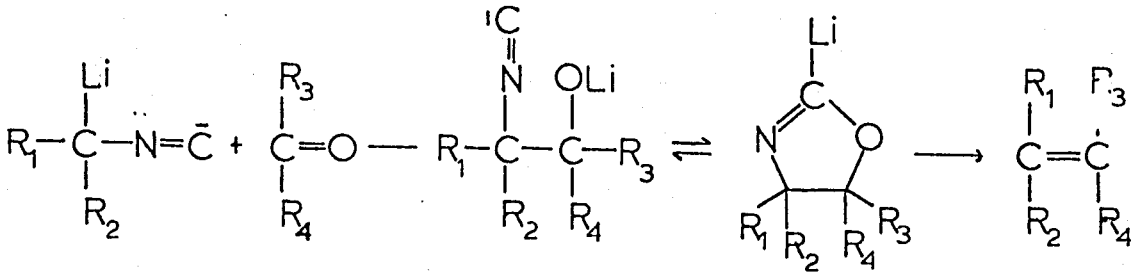


20 21

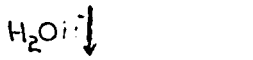
A successive alkylation via the lithium salts of the esters led to disubstituted esters.

The α-metallated alkyl isocyanides (22) have been shown to be valuable reagents in reaction with aldehydes and ketones (23) to form olefins (26)[17]:

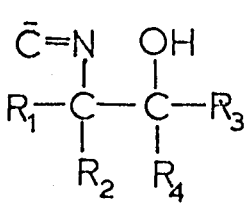
[11]

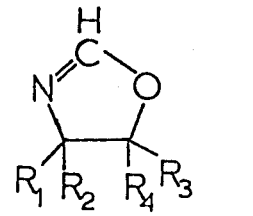


22 23 24 25 26



R_1 = H, Ph
R_2 = H, Ph,
R_3, R_4 = H, alkyl, aryl

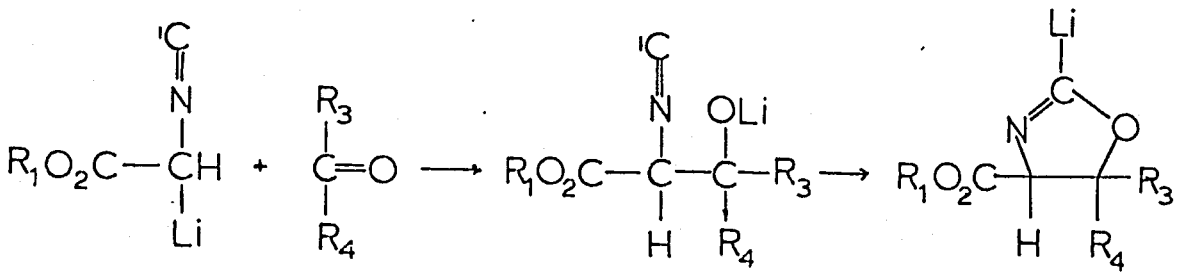




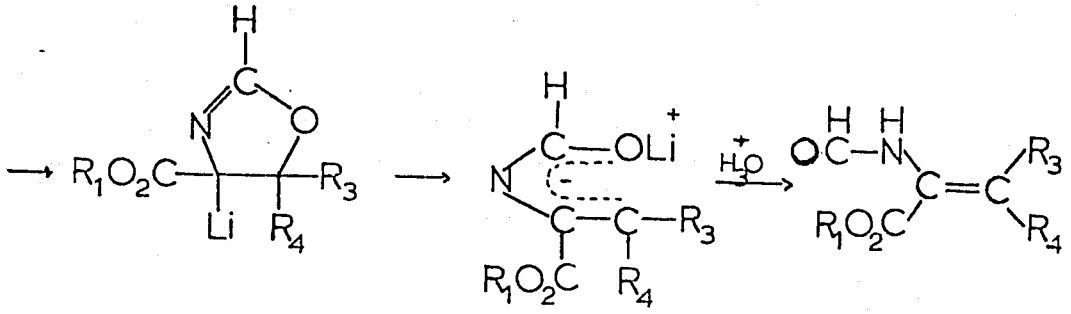
24a 25a

The reaction begins with the nucleophilic addition of (22) to the carbonyl group to form (24). This cyclises to give the metallated oxazoline (25), which fragments into olefin (26). It is possible, by suitable treatment of the reaction mixture to isolate either the adducts (24) in the form of β-hydroxy-alkyl isocyanides (24a) or the metallated oxazolines (25) as oxazolines (25a)[18].

The reaction of metallated isocyanoacetic esters (27) with aldehydes and ketones (in aprotic solvents) followed a different course[19]. It led (after acid hydrolysis) to β-substituted α-formylaminoacrylic esters (30):



[12] 27



28 29 30

An intramolecular proton shift, favoured by the acidity of the hydrogen atom on C-4, leads to the 4-anionised oxazoline (28) which opens to the salt (29). This salt, on acidification gives (30).

Metallating reagents and solvents

The most common organolithiums are n-butyl, phenyl and methyllithium. The relative basicities of these reagents have been shown by a study in which dibenzofuran was metallated with a number of different organolithiums[20]. Under comparable conditions, the yield of metallation product decreases in the order: n-butyl > ethyl > amyl > phenyl > methyllithium. The relative reactivities towards triphenylmethane showed a similar order: benzyl > allyl > n-butyl > phenyl > vinyl > methyllithium[21]. Although it is less reactive, methyllithium is preferred for the metallation of more reactive substrates due to its greater stability compared with n-butyl-and phenyllithium[22].

An alternative method of metallation involves the use of alkyl substituted lithioamides, prepared by the addition of an organolithium compound to the appropriate secondary amine. As has been shown above, lithium-bis(trimethylsilyl)amide[7] and lithium isopropylcyclohexylamide[8] were used successfully in the metallation of the aliphatic esters.

The dimetallation of the aliphatic carboxylic acids on treatment with lithium diisopropylamide was reported. This procedure has been applied by Creger[23] to metallate carboxylic acids with more extensive conjugate systems. The toluic acids (ortho, meta, para) were lithiated by the addition of 2 equiv. of lithium diisopropylamide, in THF-heptane, at 0°. Subsequent treatment of the carbanionic intermediate with 1-bromobutane gave, in good yield, the corresponding n-pentylbenzoic acids.

The role of the solvent can be rather complex. A change of solvent can change the rate of reaction, the nature of the product as well as the stereochemistry of reaction.

Ethers (diethyl ether and tetrahydrofuran), and hydrocarbons (hexane, benzene) are the most frequently used. The reaction is faster in ethereal solutions than in hydrocarbons. This effect is attributed to much greater solvating properties of the ethers for the metallating agent. It is well known that all the organolithium compounds are associated in solution. The degree of association varies with both the solvent and their structures. A more extensive complexation of ether than of hydrocarbon molecules with the metal moiety is thought to facilitate the heterolysis of the polar carbon-metal bond, lowering the energy requirement for metallation[24, 25].

Studies on various organometallics have shown that the rate of a reaction increases with the increasing donor power of the solvent, presumably because of greater dissociation of aggregations. In this view the excellent donor characteristics of tetrahydrofuran have resulted in its extensive use in organometallic chemistry. For example, Gilman and Gray[26] showed that metallation of dibenzofuran, dibenzothiophene and N-ethylcarbazole is substantially increased when tetrahydrofuran is used as solvent compared with diethylether.

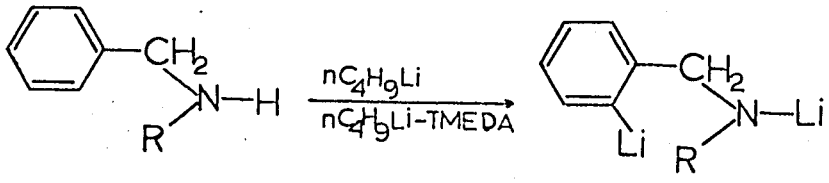
The orientation of metallation in amines and nitrosamines

In N,N-dialkyl aromatic amines the metallation occurs at the ortho position of the ring[20]. The relative acidities of the ring and of alkyl protons of dimethylaniline have been studied[27]. The methyl carbon attached to nitrogen has such low acidity then, that in general only the activating effect of nitrogen on the aromatic ring has been considered.

Surprisingly a direct α-carbon alkylation of tertiary amines was evidenced when these amines were used as solvents for the reaction of organolithium reagents with alkyl or aryl halides[28]. Trialkylamines[29] as well as N-alkylamines[30, 31] underwent this reaction. These observations seemed to be in agreement with a simple mechanism involving metallation of the amine at an α-alkyl site followed by Wurtz-type coupling with the available halide. However, the metallation experiments failed to confirm such a pathway. N-alkyl anilines[32] were mainly metallated at the ortho position of the ring, N-alkyl lithiation occurring to a very minor extent. These data lead to the conclusion that α-lithio alkyl anions could not be the intermediates in α-alkylation of tertiary amines but the mechanism of this reaction is yet undetermined.

N,N-methylbenzylamine (31) and N,N-phenylbenzylamine (32) underwent dimetallation, with both n-butyllithium and n-butyllithium-tetramethylethylenediamine complex (TMEDA) at the nitrogen and the ortho positions (33)[33]:

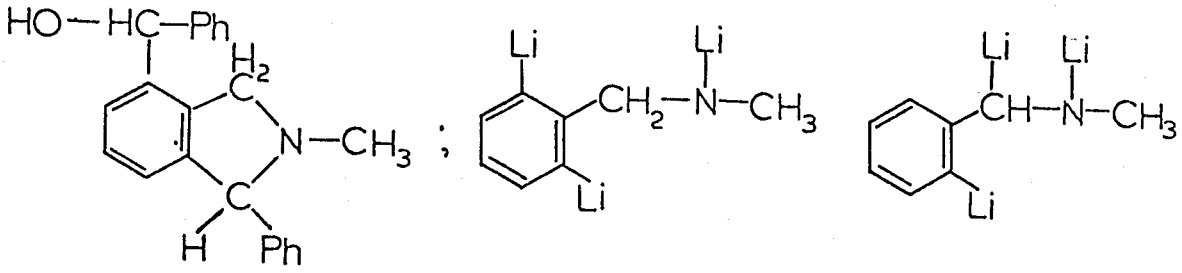
[13]



31; R=Me
32; R=Ph

33

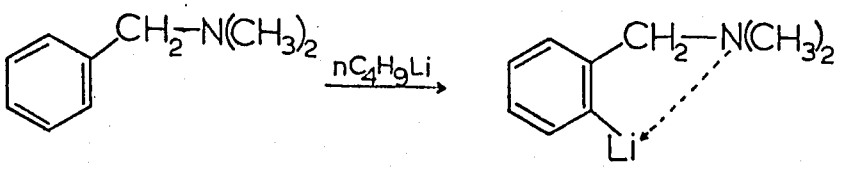
Quantitative estimations have shown that the n-butyllithium-TMEDA complex is a more efficient metallating reagent than is n-butyllithium alone. When amine (31) was reacted with a large excess of n-butyllithium-TMEDA complex (2.5 - 2.7 eq.) the 2,6-diadduct with benzaldehyde was isolated as the cyclised product (34).



34 35a 35b

This result supported the idea that a trilithioamine intermediate, conceivably either (35a) or (35b) is formed in the metallation of N,N-methylbenzylamine (31) with excess of n-butyllithium-TMEDA.

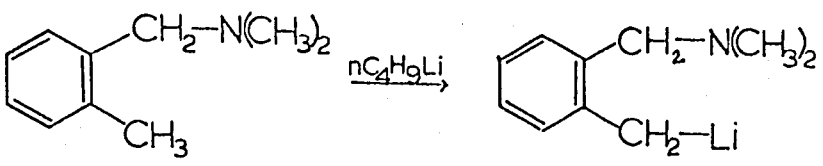
The metallation of N,N-dimethylbenzylamine (36) has been extensively studied[34]. When this compound was treated with n-butyllithium, the metal entered in the ring in the ortho position (37). Metallation

[14] 

36 37

by butylsodium revealed that the initial site of metallation is also the ortho position, but upon heating, isomerisation to the α-sodio derivative occurred. The α-sodio compound was converted to the lithium derivative with lithium bromide. When this α-lithio compound was heated (48°) it reverted to the ortho ring derivative, indicating that the ortho position is more stable than the α position for lithium. The ring ortho attack of lithium is favoured because of the greater stabilisation afforded by the formation of the five membered ring (37).

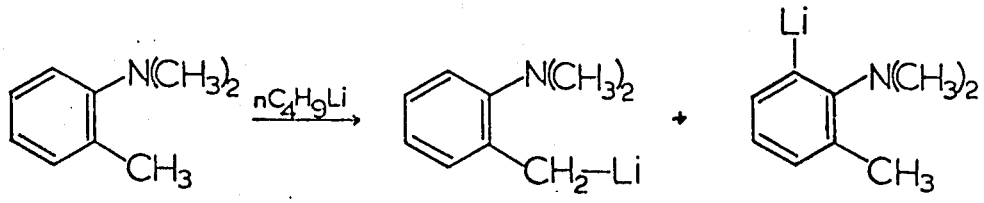
When one of the ortho positions was substituted with a methyl group, as in O-methylbenzyldimethylamine (38) the metallation occurred at the side-chain methyl[35].

[15] 

38

N,N-dimethyl-o-toluidine (39) behaved similarly[36]. Upon

[16]

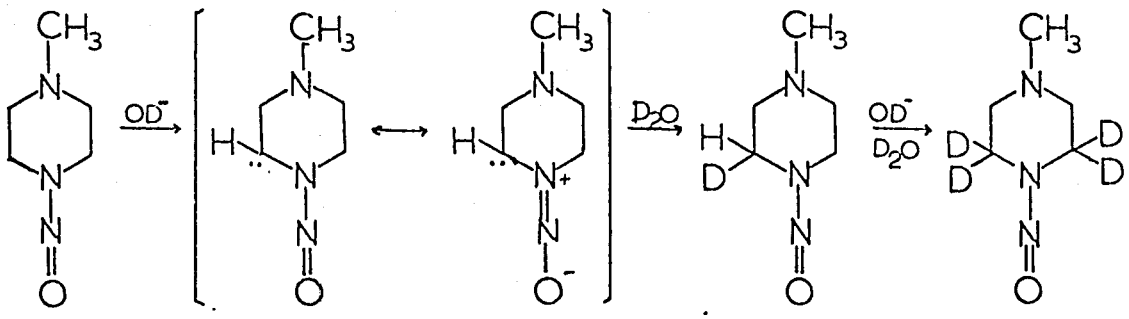


39 40 41

treatment with n-butyllithium (39) underwent metallation predominantly in the 2-methyl position to form lithioamine (40); small amounts of ring metallation product (41) were also detected. When n-butyllithium-TMEDA was used as metallating agent, a more rapid and selective metallation of (39) occurred to give a better yield of lithioamine (40).

Evidence for the formation of the nitrosamine carbanions was provided by Keefer and Fodor[37], who observed the base catalysed hydrogen-deuterium exchange in 1-nitroso-4-methyl piperazine (42). The 2- and 6- methylene protons were almost completely replaced by deuterium, after (42) was exposed to 1.3 M NaOH in D_2O at 100°, within 150 min (eq.17.)

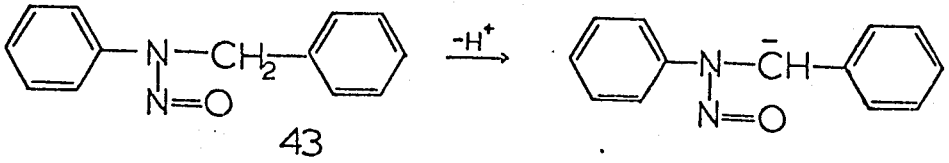
[17]



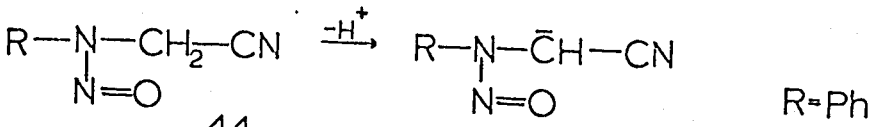
42 42a 42b

The explanation suggested by the authors for the anion formation is the labilising influence of the nitrosamine group upon the α-carbon-hydrogen bonds. The carbanion is stabilised by the formal positive charge at the heterocyclic nitrogen, as a result of the resonance ylid type structure (42b).

Previously, Daeniker [38] predicted that carbanion intermediates were involved in certain rearranagments and elimination reactions of benzylnitrosamines (43) and cyanomethylnitrosamines (44), according with the following formulation:



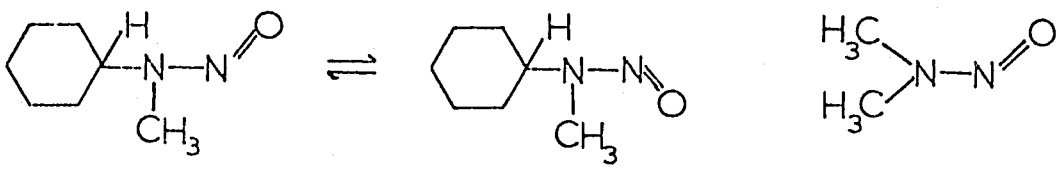
43



44

In all these α-nitrosamino carbonanions the stabilisation came mainly from the phenyl and cyano group and less from the nitrosamino function.

Nitroso-methylcyclohexylamine (45) underwent detectable incorporation of deuterium only in the methyl group[37]. The relative unreactivity of the methinyl protons of (45) is attributed to the electron-releasing alkyl substituents present at the α position which should both destabilise the anionic intermediate and sterically interfere with the approach of the attacking hydroxide ion.

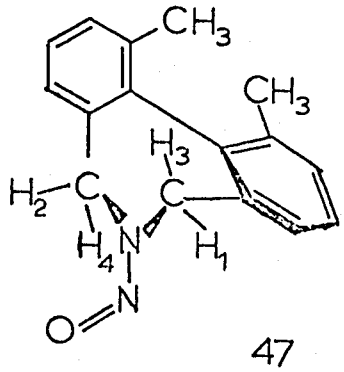


45a ⇌ 45b

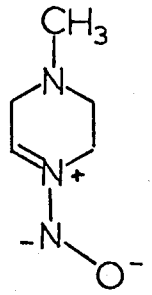
46

The occurrence of the carbanions in the nitrosamines was further indicated by α-methylation of dimethylnitrosamine (46) in 15% yield, in tetrahydrofuran solution, by refluxing with methyl iodide, and sodium hydride, for 3 hr. [37].

Fraser and Wigfield[39] investigated the influence of structure and the stereochemistry on the deuterium exchange reaction in the case of N-nitroso-6, 7-dihydro-1, 11-dimethyl-5H-dibenz[c, e]azepine (47). They assumed that the resonance stabilisation occurs more probably via contribution (42c) than (42b). The greater preference for the exchange of H_4 over H_2 and the lesser preference for H_3 over H_1 were considered to reflect the stereochemical requirement for the carbanion stabilisation by resonance of the type shown in (42c).



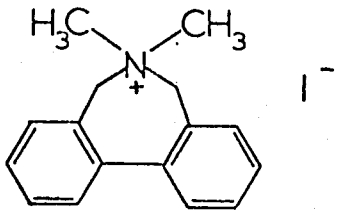
47



42c

In this case the overlap is greater for carbanions derived by abstraction of the quasi-axial protons (H_3 and H_4 were shown to be quasi-axial, whereas H_1 and H_2 are quasi-equatorial).

More direct evidence against the contribution of (42b) structure, at least in the carbanions of (47), is the failure of any deuterium exchange in the quaternary iodide (48). These authors were also able to form the carbanion of (47) by treatment of a sample in tetrahydrofuran solution at -70°, with methyllithium. Carboxylation and methylation of the anion both gave excellent yields of product[40].



48

These results provided the premises for the present work, whose subject is an investigation of the lithiation adajcent to the nitrosamino group and subsequent reactions of the intermediate carbanions. The results obtained in the case of dibenzylnitrosamine stimulated the extension of the research area to the behaviour of less acidic systems, namely the nitrosamines of 4-phenylpiperazine, pyridine and pyrrolidine in alkylation and carboxylation reactions.

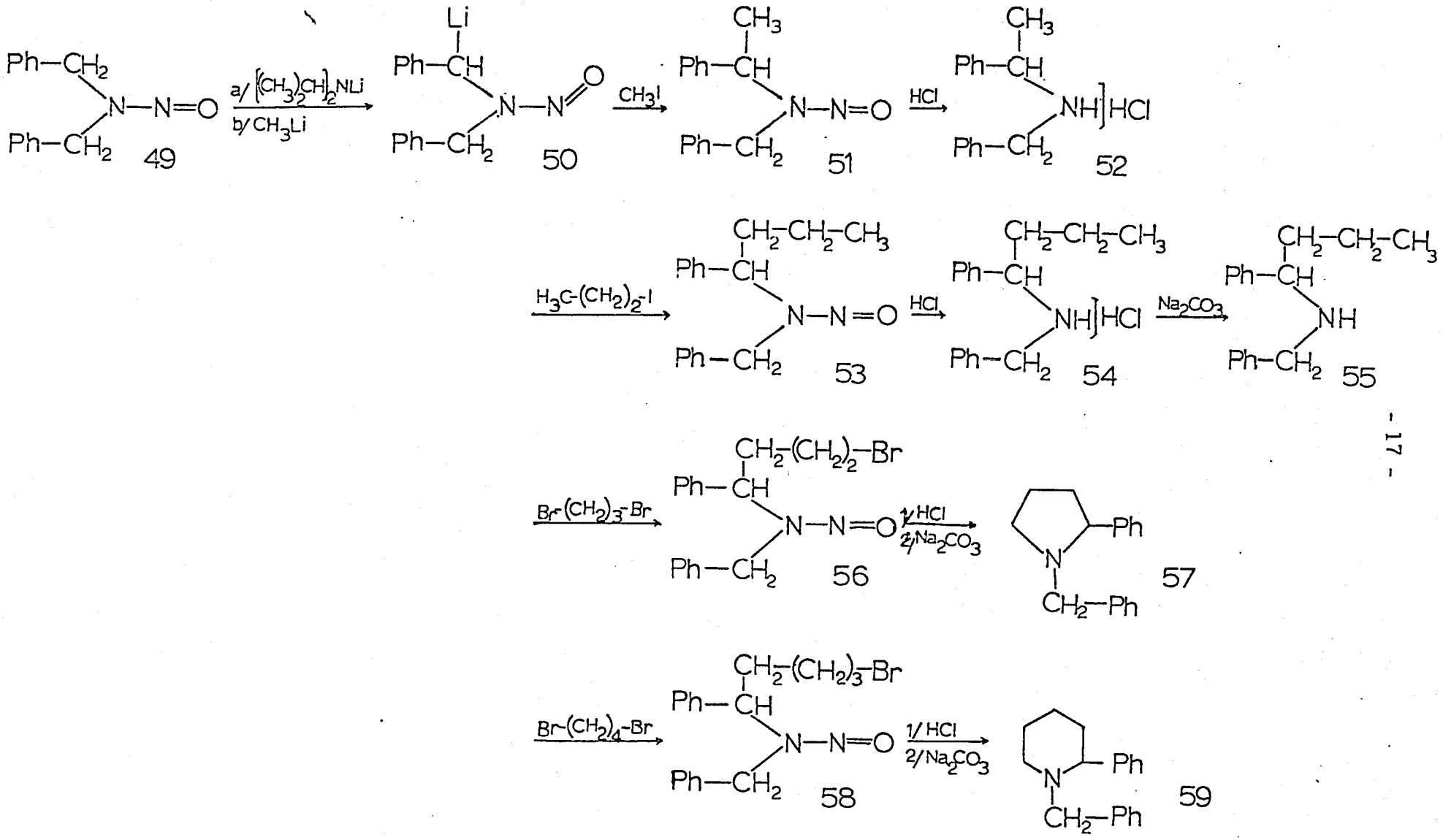
RESULTS AND DISCUSSION

I. The Alkylation of Dibenzylnitrosamine

The reactions shown in Scheme I were all conducted in the same manner. The addition of a strong base (a or b) to a solution of the nitrosamine in anhydrous tetrahydrofuran, at -75°, resulted in the formation of the carbanion, whose presence was likely responsible for the appearance of a bright red colour[20]. According to the reported data[39, 40], the proton abstraction takes place selectively at the carbon atom syn to the nitroso group. The appropriate alkyl halide was then added. Following alkylation of the lithiated nitrosamine, the crude product was examined by n.m.r. to obtain an estimate of the extent of reaction. The isolation and purification of the alkylation products was fairly difficult.Even when preparative thin layer chromatography was used, the separation of unreacted starting material from the alkylation products was particularly difficult because the differences in the R_f's were not large enough to give a good separation.

The reaction product was treated with hydrogen chloride gas in anhydrous benzene to effect the cleavage of the nitroso group[41]. The resultant amine hydrochloride was either purified by recrystallisation or, in certain cases, converted to the free base which was purified by chromatography and distillation. For all cases, the cleavage proceeded smoothly in yields of 80 - 90%. When the nitroso cleavage was carried out in ethyl ether, lower yields of amine were recovered.

The results of the various alkylations of dibenzylnitrosamine are summarised in Table 1.



Scheme I. The Alkylation of Dibenzylnitrosamine.

Table 1. The Yields of Alkylation of Dibenzylnitrosamine

Base	Alkylating agent	Crude yield %	Isolated yield %
$[(CH_3)_2CH]_2NLi$	CH_3I	91.	76.[a]
CH_3Li		90	71.[a]
$[(CH_3)_2CH]_2NLi$	$CH_3\text{-}CH_2\text{-}CH_2\text{-}I$	85	77[a]
CH_3Li		73	-
$[(CH_3)_2CH]_2NLi$	$Br\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}Br$	55-58	33[b]
$[(CH_3)_2CH]_2NLi$	$Br\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}Br$	50	33.2[b]

a Isolated as amine hydrochloride

b Isolated as cyclised product

A number of factors were varied in determining the optimum conditions for the alkylations of dibenzylnitrosamine. The anion was generated either with methyllithium alone or in the presence of an equimolecular amount of diisopropylamine (which produces lithium diisopropylamide as the reactive agent).

Essentially the same yield of crude product was obtained by either procedure in the methylation of dibenzylnitrosamine, but the use of lithium diisopropylamide gave better results in the reactions with less reactive alkyl halides.

The time allowed for the formation of anion before the addition of the alkylating agent was found to be important[42], good yields being obtained only for intervals of 4 - 5 min between the addition of

base and the addition of alkyl halide. Further, the time and the temperature for the subsequent reactions also were found to be of importance. A polymer-like by-product occurred invariably in all the reactions. This side reaction could be minimised by a proper choice of reaction temperature. The time required for the alkylation depended mainly on the reactivity of the alkylating reagent.

Preparation of benzyl-(α-methyl)-benzylnitrosamine (51)

The methylation proceeded in greater than 90% yield with both lithium diisopropylamide and methyllithium as base. Isolated yields expressed in terms of the amounts of the benzyl-(α-methyl)-benzylamine hydrochloride (52) recovered after the cleavage of the nitroso group indicated small differences between these two procedures.

Preparation of benzyl-(α-phenyl)-butylnitrosamine (53)

The extent of propylation was lower than that of methylation. Also, there was a more marked difference in the yields when the alkylation was done via the carbanion generated with lithium diisopropylamide ($\sim$ 85%) and methyllithium ($\sim$ 73%).

Creger[23] has made interesting observations which could explain these results. In the metallation of o-toluic acid with lithium diisopropylamide evidence was presented that carbanionic intermediate is associated with diisopropylamine. The n.m.r. spectrum of this lithium salt displayed integrated signals for diisopropylamine at a ratio of one molecule of diisopropylamine per molecule of o-toluic acid. In addition, the isolation of o-toluic acid after the injection of D_2O revealed no deuterium incorporation; thus the proton transfer on acidification (D_2O addition) is a more complicated process in which the diisopropylamine proton is transferred exclusively to the carbanionic site by a non-competitive process.

Probably this type of stabilisation of carbanionic intermediate is responsible for the improvement in the yield of alkylation when lithium diisopropylamide is employed as metallating agent.

Preparation of benzyl-(α-phenyl)-ω-bromobutylnitrosamine (56) and benzyl-(α-phenyl)-ω-bromopentylnitrosamine (58).

The carbanion was generated only with lithium diisopropylamide. The lower yields of alkylated product - 55-58% and 50% respectively - are obviously due to the reduced reactivity of the two dibromoalkyls.

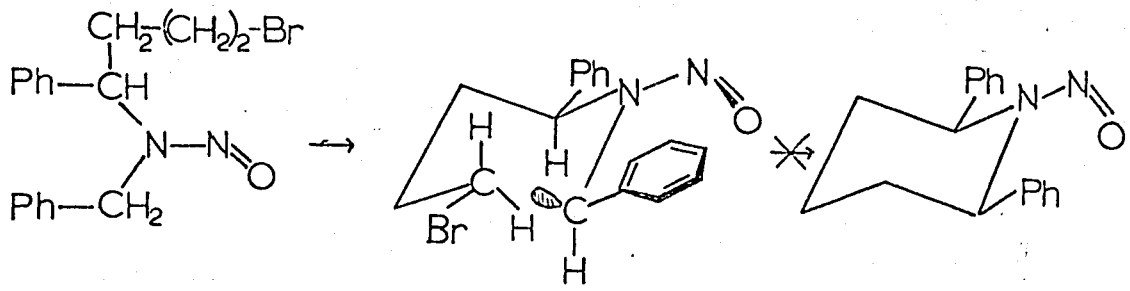
After the nitrosamine function from both (56) and (58), was removed and the hydrochlorides thus obtained were neutralised, a spontaneous loss of hydrobromic acid took place. The resultant products were shown to be 1-benzyl-2-phenylpyrrolidine (57) and 1-benzyl-2-phenylpiperidine (59), respectively.

An attractive potential use of the alkylation of nitrosamines carbanions is the construction of cyclic amines. For example, the intermediate (56) via formation of a second anion, followed by intramolecular alkylation would give 1-nitroso-2, 6-diphenylpiperidine (60). Previous examples of carbanion cyclisations had been shown to proceed readily at low temperatures. Seebach et al[6] have been reporting cyclisation products from the reaction of 2-lithio derivatives of 1, 3-dithianes with appropriate dihalides. The ring formation proceeded efficiently in the case of three, four, five and six membered rings. Accordingly, an attempt to produce a second carbanionic site on benzyl-(α-phenyl)-ω-bromobutylnitrosamine (56) and benzyl-(α-phenyl)-ω-bromopentylnitrosamine (58) was made. The anti conformation is likely predominant in both the above nitrosamines* so the proton to be abstracted

* see n.m.r. spectra discussion, page 27.

is one from the unsubstituted benzylic group, syn to the nitroso group. The intramolecular ring closure would lead to (60) (eq. 18):

[18]



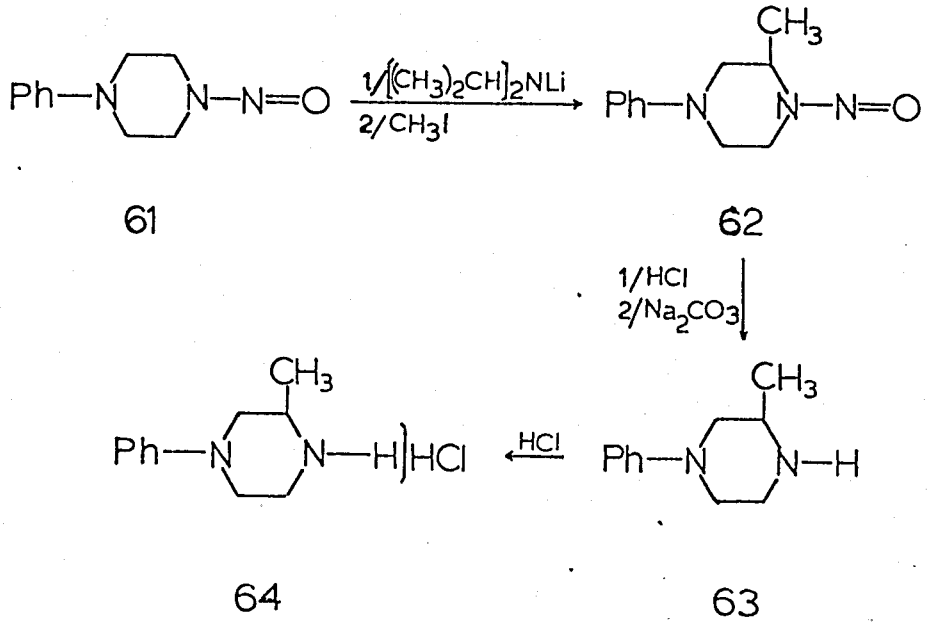
56 60

Treatment of (56) with lithium diisopropylamide gave a red colour indicating that the anion formation had occurred. However, work up of the reaction mixture revealed no evidence of the cyclic product (60).

Steric factors could be responsible for the failure of the cyclisation reaction. The displacement of bromine by the carbanionic site requires the phenyl to orient itself coplanar or nearly coplanar to the nitroso group[39] which is an unfavourable steric arrangement.

II. The Alkylation of 1-nitroso-4-phenylpiperazine

In the hope of extending this α-functionalisation to systems forming less stable carbanions, the lithiation and subsequent alkylation of 1-nitroso-4-phenylpiperazine was investigated (Scheme II).



Scheme II. The Methylation of 1-nitroso-4-phenylpiperazine

A number of reaction parameters were varied in order to determine the optimum reaction conditions.

Lithium diisopropylamide was proved to be the best reagent for carbanion formation. In contrast, complexes of alkyllithiums with tetramethylethylenediamine[44] or diazabicyclo[2.2.2]octane[45], known as more powerful metallating agents, gave poor results. Also, metallation of (61) with methyllithium was not successful (Table II).

Table II. The Methylation of 1-nitroso-4-phenylpiperazine in THF (3.3×10^{-2} M) at -75° [a]

Metallating reagent	Metallation time. min.	Yield of methylation product. %.
$[(CH_3)_2CH]_2NLi$	1	21
	3	30
	4	42
	5	38
	6	33
	7	20
	10	5
CH_3Li	4	0
	4	0
	2	0
CH_3Li + TMEDA	12	5
	20	5
	6[b]	8

a After the methyl iodide was added the reaction was gradually warmed up to room temperature.

b Reaction temperature was -45°.

The time required for the metallation was carefully investigated. From the data listed in Table II it follows that the maximum concentration of carbanion is present 4 min after the introduction of the metallating agent.

The optimum time for the methylation was found to be about 2 hr. When the reaction mixture was kept at -75° for this period of time the yield and purity of the alkylation product were a little better than when the reaction flask was allowed to warm up to room temperature for a short time (10 - 15 min) after the addition of methyl iodide.

The concentration of the solution has also been found to slightly influence the yield of reaction. The best yield (48%) in the methylation of (61) was obtained using the above-mentioned conditions and a nitrosamine concentration of 5×10^{-2} M.

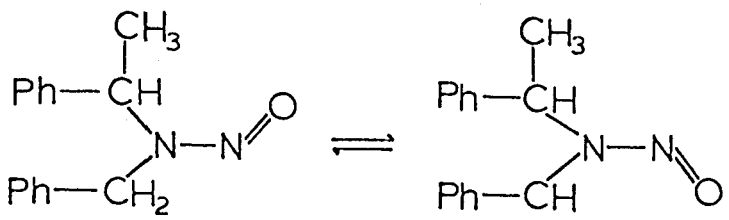
No alkylation product could be identified in the reaction of (61) with 1, 3-dibromopropane.

Finally, it should be noted that 1-nitroso-4-phenylpiperazine failed to metallate with both sodium hydride and sodium amide. The prolonged reflux of a tetrahydrofuran solution of (61) in the presence of either of the above bases together with a large excess of methyl iodide, resulted only in the recovery of the starting material. In contrast, a 15% yield had been reported[37] for the methylation of dimethylnitrosamine, in similar conditions.

III. N. M. R. Spectra of the Alkylated Nitrosamines

It has been known that unsymmetrical N-nitrosamines exhibit syn-anti isomerism due to restricted rotation about the nitrogen-nitrogen bond. The room temperature spectra of dialkylnitrosamines show separate resonances from the groups syn and anti to the nitroso oxygen. α-Methyl and α-methylene groups resonate at higher magnetic fields by about 0.3 - 0.8 p.p.m. when they are syn than when they are anti to N=O. In contrast, a syn methine proton is deshielded by about 0.2 - 0.6 l.p.m. relative to the anti[46].

The n.m.r. spectrum of (51) (Fig. 1) reveals two doublets (J = 7.5 Hz) at δ 1.13 and 1.73. The relative ratio of their integrated areas is 1:4. In accordance with the above data, it follows that 20% of the molecules of (51) adopt the syn configuration (51') and 80% the anti configuration (51'').



51' 51''

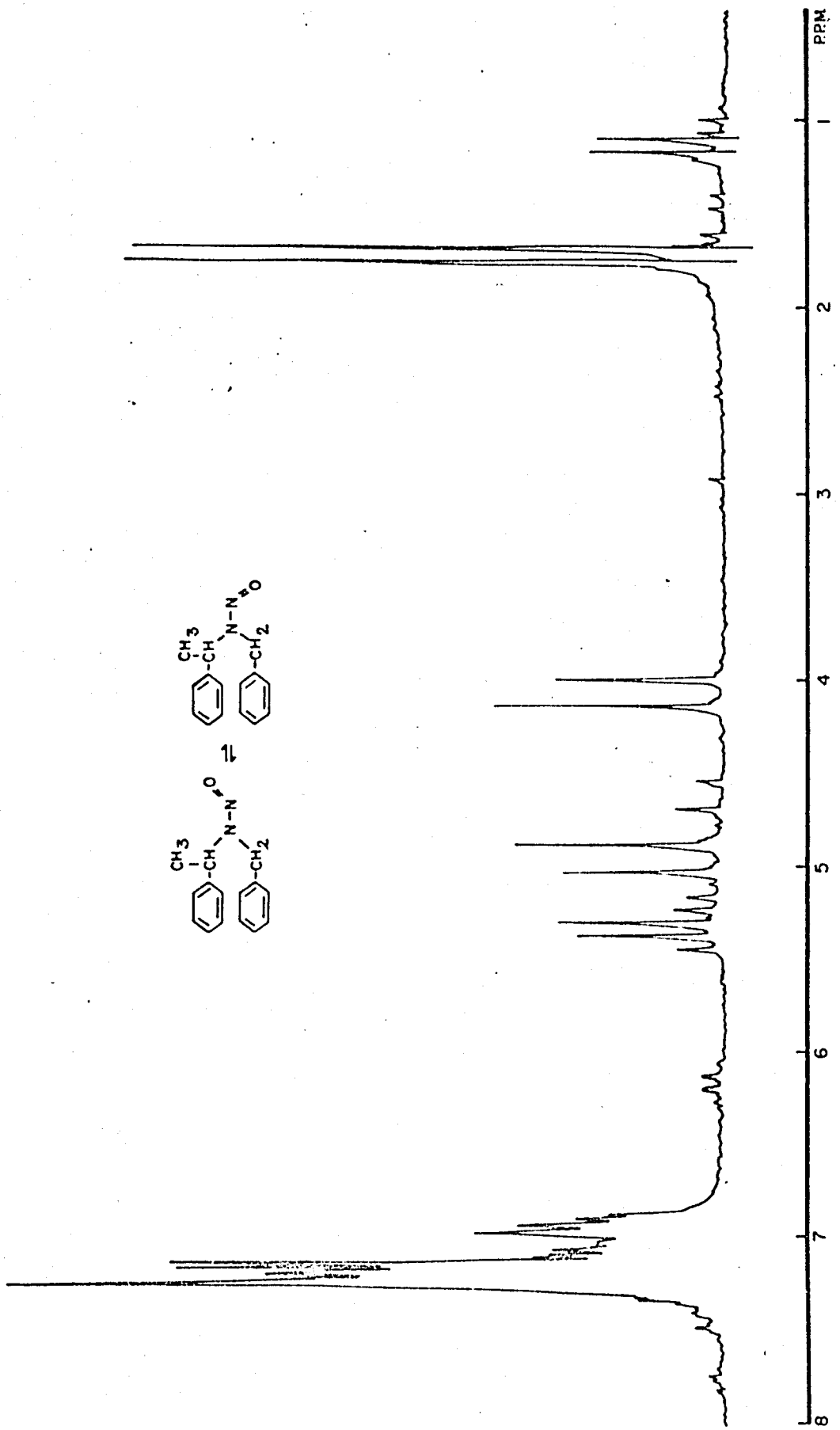


Figure 1. The NMR Spectrum of benzyl-(α-methyl)-benzylnitrosamine (100 M Hz).

Due to the presence of an asymmetric centre the benzyl methylene protons are magnetically non-equivalent. Their n.m.r. resonance shows an AB-type quartet centered at δ 4.07 and δ 4.96 (J = 14.3 Hz), which can be assigned to the predominant isomer (51''). A weaker AB pattern appeared at δ 4.62 and δ 5.25 (partially overlapped with the methine absorption) in relation to benzylic protons of (51').

The methine proton occurred as a quartet at δ 5.35 (J = 7.5 Hz), for (51'') and a similar absorption at δ 6.12 for (51'); their relative areas were approximately 4:1.

No accurate quantitative estimation could be done with regard to the ratio of the syn-anti isomerism in the 60 M Hz n.m.r. spectrum of benzyl-(α-phenyl)-butylnitrosamine (53). The high field complex multiplets found between δ 0.70 - 2.50 and assigned to the seven aliphatic chain protons do not provide any information about the geometric configuration of the molecule.

The methine triplet (anti) is overlapped by the low field part of the benzylic AB quartet. An approximate evaluation of the integrated area of the small syn methine signal (δ = 6.25) showed that the syn isomer was present to the extent of 20% at most.

Similar features characterised the n.m.r. spectra of benzyl-(α-phenyl)-bromobutylnitrosamine (56) and benzyl-(α-phenyl)-ω-bromopentylnitrosamine (58) and evidently in both nitrosamines the anti form is highly predominant.

The n.m.r. spectrum of 1-nitroso-2-methyl-4-phenylpiperazine (62) showed two doublets at δ 1.30 and δ 1.65, both assigned to the 2 methyl group. The splitting had the same value (J = 6.3 Hz) and the relative rates of the integrated areas of low field to high field

signals was 2:1. The most realistic representation for the structure of a cyclic nitrosamine is that in which the amine nitrogen has a trigonal hybridisation with a dihedral angle, between CNN and CCH_{eq}, of ca. 15° [47]. The shielding zone is extended above and below and also perpendicular to the C_{α}-N-N=O plane. This would result, again, in a greater shielding environment for the α-syn side than for the α-anti side.

On the basis of this discussion, the high field doublet belongs to the syn and the low field doublet to the anti forms of (62). The anti to syn isomer ratio is 2:1.

Harris and Sprag[48] have discussed the n.m.r. spectrum of 1-nitroso-2-methylpiperidine. They found about 27% of the isomer with methyl group syn to the nitroso group and about 73% of the anti isomer. Furthermore, the syn isomer is supposed (on the basis of chemical shifts) to have predominantly the methyl group axially oriented.

The orientation of the methyl group in our compound (62) cannot be assigned on the basis of the available chemical shift data.

IV. The Carboxylation of Nitrosamines

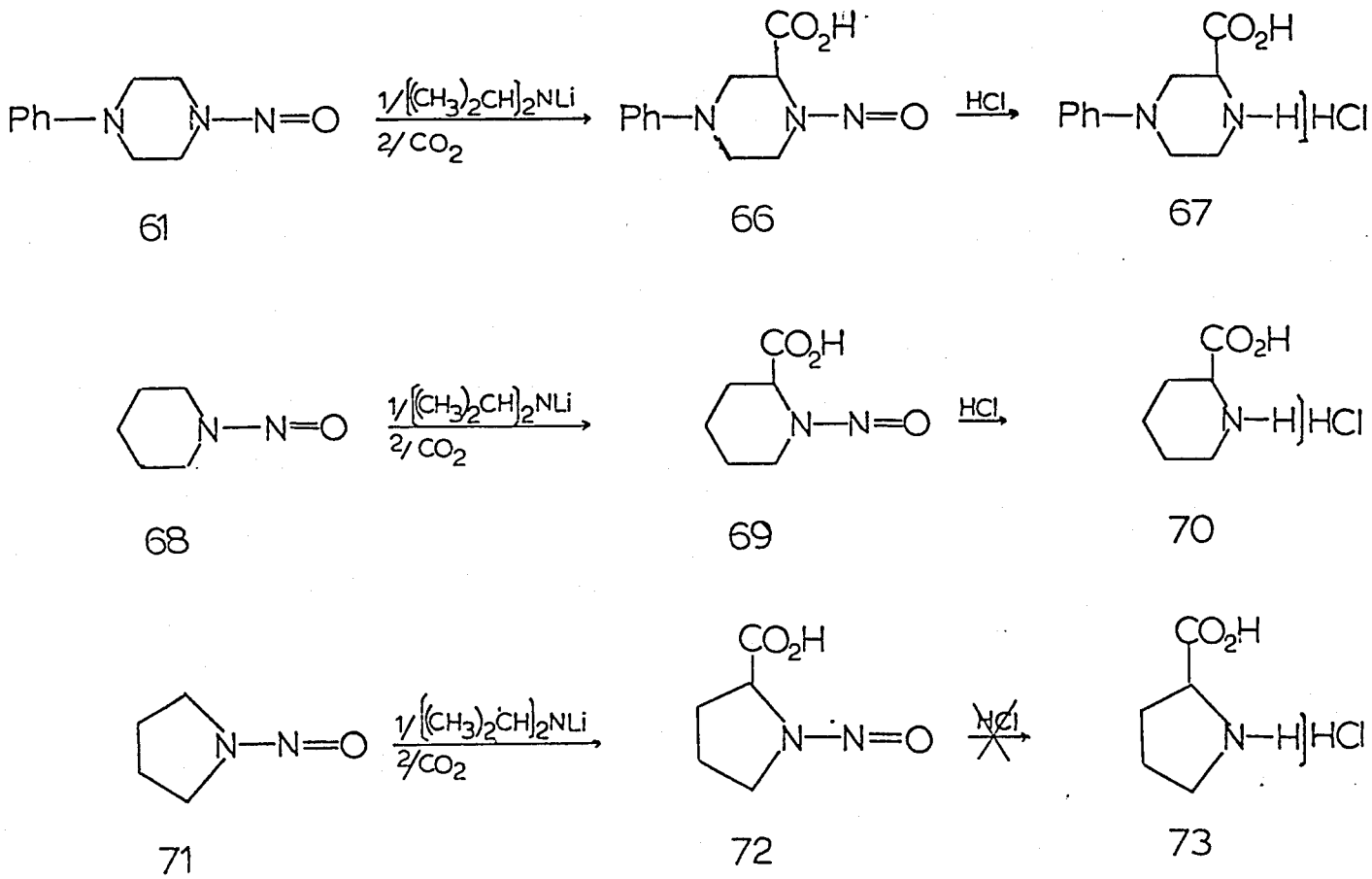
The major point of interest in these reactions was to prove the potentiality of α-carboxylation of nitrosamines, via carbanionic intermediates on less reactive systems. The results were encouraging and they showed that the carboxylation proceeded to a greater extent than the alkylation. In addition, an easier and efficient isolation of the corresponding carboxylic derivatives was possible.

From 1-nitroso-4-phenylpiperazine (61) a 45% yield of 1-nitroso-4-phenylpiperazine-2-carboxylic acid (66) was obtained. 1-Nitroso-piperidine (68) and 1-nitroso-pyrrolidine (71), which gave no methylation products[43], afforded α-carboxyl derivatives in 28.4% and 27% yields respectively.

The practical procedure (Scheme III) follows the same sequence as was used for the alkylation reactions. The carbanions were generated in tetrahydrofuran solution using lithium diisopropylamide. A stream of carbon dioxide was bubbled through the solution at a moderate speed, for 15 - 20 min. The acids thus formed were isolated as their lithium carboxylates. A subsequent acidification gave the free acids. Among these, 1-nitrosopiperidine-2-carboxylic acid (69) and 1-nitroso-pyrrolidine-2-carboxylic acid (72) are known compounds. Recently they have been prepared by Lijinski and co-workers[50] through the reaction of the appropriate amino-acids with sodium nitrite.

The cleavage of the N-N bond was easily accomplished with hydrogen chloride in anhydrous benzene. The facile removal of the nitroso group may be illustrated by the observation that 1-nitrosopiperidine-2-carboxylic acid underwent denitrosation even on standing at room temperature in chloroform solution[50].

The resultant amino acids were isolated as hydrochlorides.

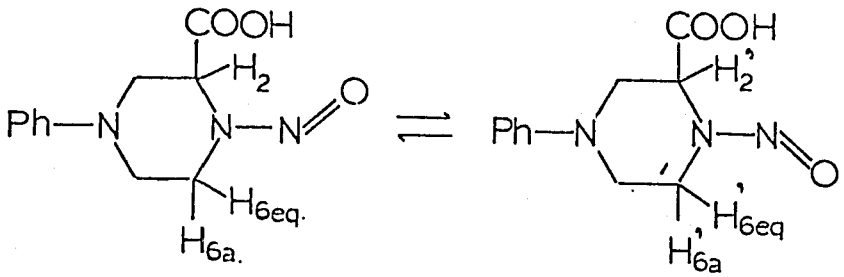


Scheme III. The Carboxylation of Nitrosamines

1-Nitroso-4-phenylpiperazine-2-carboxylic acid (66)

This was obtained as a brownish solid mass, soluble in water and most organic solvents. The i.r. spectrum showed two characteristic absorptions for carboxyl, at 3500 (ν_{OH}) and 1730 cm^{-1} ($\nu_{C=O}$), as well as a band at 1465 cm^{-1} assigned to the nitroso group.

In the n.m.r. spectrum each of the three protons α to the nitrosamino function gave rise to an isolated pattern. From the integrated area of these signals a 1:1 equilibrium between the two conformers, syn (66a) and anti (66b) (in $CDCl_3$ solution at room temperature) was determined. Because of the deshielding influence of the α-carboxyl group the methinic proton at C-2 is expected to resonate at lowest field in both (66a) and (66b). So, the two peaks at δ 5.70 and δ 5.55 can be assigned to this proton. Both patterns have the same widths at half-height (8 Hz) in agreement with an equatorial assignment of the C-2 proton[50] in both isomers.



66a 66b

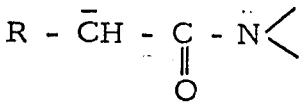
Since all the α-equatorial protons are nearly coplanar with the C_α-N-N=O plane, according to long range shielding of nitroso group depicted above (page 28) they would resonate at lower fields than the axial protons which lie perpendicular to this plane and hence in the shielding zone. Having defined this orientation one may assign the absorptions at δ 4.92 and δ 4.77, reasonably to the equatorial C-6 proton in the configurations (66b) and (66a), respectively. The multiplet centred at δ 4.20 is due to the axial proton at C-6. The above assignments also explain the fact that H_2 and H'_{6eq} resonate at lower fields than H_2' and H_{6eq}. The deshielding of these equatorial protons is stronger in <u>syn</u> than in <u>anti</u> configuration[48].

Both 1-nitrosopiperidine (69) and 1-nitrosopyrrolidine-2-carboxylic (72) acids were obtained in lower yields than the acid obtained from 1-nitroso-4-phenylpiperazine. This fact can be attributed to a supplementary stabilisation of the α-carbanion in (66) provided by the second heterocyclic nitrogen atom.

The structures of these products were supported by n.m.r. and i.r. data. The denitrosation of (69) afforded the piperidine-2-carboxylic and hydrochloride (70), whose properties were in agreement with the reported data. The cleavage of N-N=O group in (72) resulted only in an uncrystallisable material, indicating that a partial decomposition had occurred during the cleavage.

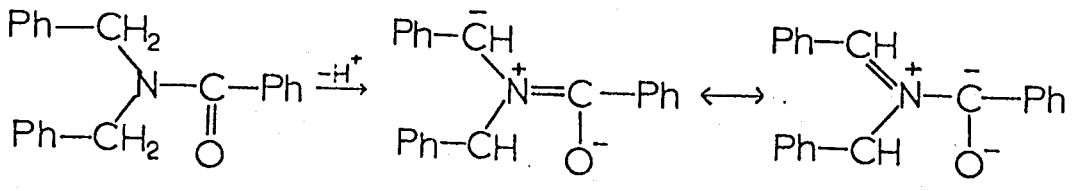
V. N,N-Dibenzylbenzamide Alkylation

The activation by an amide group of the hydrogen alpha to the carbonyl group has been widely investigated[51-53]. The anion of the type:



could be generated with sodium amide in liquid ammonia system[51]. Generally, the presence of an aryl group at the 2-position (i.e. R = aryl) has been considered a necessary condition for carbanion formation to take place. However, moderate yields in the alkylation at the α-carbon via carbanion intermediates of 2-alkyl-disubstituted amides have been obtained[52]. Martensson and Nilsson[53] have reported the alkylation of N,N-propylbenzylbenzylamide exclusively α to the carbonyl (90% yield).

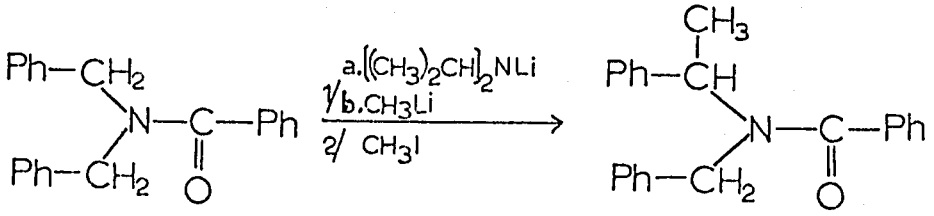
In analogy with the ability of the nitroso group to stabilise a carbanion via the above depicted resonance structures (42b ↔ 42c) we considered that an amide function might also possess this property. The N,N-dibenzylbenzamide (74) carbanion is likely stabilised as a result of resonance delocalisation (74a → 74b) :



74 74a 74b

Accordingly, the metallation and subsequent methylation of N,N-dibenzyl-

[19]



74 75

benzamide (eq.19) gave N-benzyl-(α-methyl)-N-benzylbenzamide (75).

The yields estimated from the n.m.r. spectra of crude products showed that lithium diisopropylamide employed as metallating agent furnished better results (92%) than methyllithium (58%).

The n.m.r. spectrum of (75) exhibits a quartet at lower fields (δ 5.42) for the methine proton. An AB-type pattern at δ 4.90 and δ 3.96 (J = 16 Hz) was observed for the two benzylic protons. A unique doublet appeared at higher field, δ 1.46 (J = 7.5 Hz) for the α-methyl group as a result of free rotation at room temperature around the partially double bond N-C.

The room temperature n.m.r. spectrum of the starting amide (74) also revealed only a broad singlet at δ 4.60 for all four benzylic protons.

The yield of (75) obtained via metallation with lithium diisopropylamide is comparable with those obtained in the methylation of dibenzylnitrosamine. Fewer by-products occurred in the former case and a ready isolation and purification of reaction product could be achieved.

In exchange, a careful control of the lithiation reagent is required since dialkylation could occur easily through the reaction of the monoalkylated amide with excess of reagent forming a second carbanion on the other benzylic group.

Also, the cleavage of the N-C bond was found to be difficult. The amide hydrolysis was attempted in both acidic and basic media. The prolonged refluxing of (75) with 36% hydrochloric acid or 30% ethanolic potassium hydroxide resulted in not more than 15-20% of the free amine.

EXPERIMENTAL

All the carbanion experiments were carried out under dry nitrogen atmosphere using rigorously dried glassware.

The apparatus consisted of a two-neck flask equipped with a T-shaped tube as nitrogen inlet, a rubber septum for the injection of reagents and a magnetic stirrer.

Tetrahydrofuran was dried prior to use by distillation from lithium-aluminum hydride.

Diisopropylamine was dried over calcium hydride and distilled from potassium hydroxide.

Melting points were determined using a Gallenkamp melting point apparatus and are corrected.

The n.m.r. spectra were recorded in deuterochloroform solution on a Varian HA-100 N.M.R. spectrometer or a Varian T-60 spectrometer. The chemical shifts are expressed in δ units (parts per million down-field from T.M.S. as internal standard).

The mass spectra were taken with a Hitachi Perkin-Elmer R.M.U.-6D mass spectrometer. The high resolution mass spectrum was effected with an A.E.I., MS 902-S double focussing mass spectrometer (by peak matching technique).

All the i.r. spectra were recorded on a Beckman IR-20 spectrophotometer and the absorptions are expressed in units of cm^{-1}.

The thin-layer chromatographies were done on 20 x 20 plates using Silica Gel GF-254 (Merck).

Microanalyses were performed by Scandinavian Microanalytical Laboratories, Danmark.

Dibenzylnitrosamine (49)

Dibenzylnitrosamine was prepared by a method previously described in the literature[54]. The product, after recrystallisation from ligroin, melted at 63-63.5° (lit.[54], 60-61°).

Methylation of dibenzylnitrosamine

(1) With lithium diisopropylamide

Diisopropylamine (0.24 ml, 1.65 mmole) was added to a solution of 339 mg (1.5 mmole) of dibenzylnitrosamine in 30 ml of tetrahydrofuran. The solution was cooled to -75° in an acetone-dry ice bath and 1.65 mmole of methyllithium in ether was injected, whereupon a dark red colour appeared. The reaction mixture was stirred for 4 min and treated with 0.46 ml (5 eq.) of methyl iodide. The solution was stirred at -75° for 1.5 hr, then gradually allowed to warm up to room temperature over a period of 1 hr. The solution was then quenched with 15 ml of water. The mixture was extracted three times with 15 ml of methylene chloride. The organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue, a yellow-orange oil, weighed 417 mg of crude benzyl-(α-methyl)benzylnitrosamine (51).

Two-thirds of the crude residue were chromatographed (elution system: petroleum ether/ethyl ether, 3/7) and 230 mg (91.2%) of pale yellow oil were collected. No starting material remained in this reaction mixture.

N. M. R. (100 M Hz): 1.17 and 1.73, two doublets, J = 7.5 Hz (3H); 4.07 and 4.96, respectively, 4.62 and 5.25, two AB quartets, J = 14.3 Hz (2H); 5.35 and 6.18 (1H), two quartets (1H); 6.80 - 7.40, multiplet (10H).

Cleavage of N-N bond

(a) In benzene: The crude (51) obtained from 1.5 mmole dibenzylnitrosamine was dissolved in 25 ml anhydrous benzene . Dry hydrogen chloride was bubbled through the stirred solution for 0.5 hr, at room temperature. The solution colour changed from yellow to brown soon after the bubbling was started. A strong stream of nitrogen was finally passed through the solution for 10 min, during which time it became yellow again. The benzene was evaporated to 4-5 ml and the remaining solution was diluted with ether. White crystals (220 mg) precipitated on cooling. An additional 75 mg of solid was obtained when the mother liquid was stored overnight. The total yield was 285 mg (76.4%). After recrystallisation from chloroform-ether mixture benzyl-(α-methyl)-benzylamine hydrochloride (52) melted at 180° (lit.[55], 179°).
N. M. R. (60 M Hz): 1.80, doublet, J = 6.4 Hz (3H, CH_3), 3.40 - 4.40 broad (3H, CH and CH_2); 7.50 multiplet (10H, 2 C_6H_5); 10.50 broad (2H, $\overset{+}{N}H_2$).

(b) In ethyl ether: The cleavage effected in 30 ml anhydrous ethyl-ether afforded 230 mg (62%) of (52).

(2) With methyllithium alone

A solution of 339 mg dibenzylnitrosamine in 30 ml tetrahydrofuran was cooled to -75°, 1.1 eq. of methyllithium were injected and 0.46 ml methyl iodide was added, after 4 min. The reaction was worked up as described in (1). The yield (from the N. M. R. spectrum) was ca. 90%.

The cleavage of crude product, in anhydrous benzene, gave 266 mg (71.8%) of (52).

Propylation of dibenzylnitrosamine

(1) With lithium diisopropylamide

1.5 mmole of dibenzylnitrosamine (339.5 mg) were converted with lithium diisopropylamide into the corresponding anion. After 4 min, 0.74 ml (5 eq.) of 1-iodopropane were added. The solution was stirred at -75° for 2.5 hr, then warmed up to room temperature. The total reaction time was 4 hr. The reaction mixture was worked up in the same manner as above. The yield (from n.m.r. spectrum) was about 85% of benzyl-(α-phenyl)butylnitrosamine (53).

N.M.R. (60 M Hz): 2 multiplets between 0.70 - 2.50 (7 H, CH_2-CH_2-CH_3); AB quartet at 4.10 and 5.10 (2 H, Ph-CH_2); triplets at 5.23 and 6.25 (1H, Ph-CH); multiplet between 6.80 - 2.50 (10 H, aromatic protons).

The cleavage of the nitroso group was done in anhydrous benzene (25 ml). After the evaporation of solvent the residual mass was dissolved in ethyl ether and precipitated with petroleum ether. 320 mg (77%) of solid product (54) were collected. Recrystallisation from the ethyl ether afforded white crystals which melted at 139-140.5°.

Anal. Calcd. for $C_{17}H_{22}NCl$: C, 74.03; H, 8.04; N, 5.08, Cl, 12.85.
Found: C, 73.66; H, 8.19; N, 5.47; Cl, 12.82.

NMR (60 M Hz): 0.83, broad (5H); 2.36, broad (2H); 3.90 broad (3H); 7.45, multiplet (10H); 10.50 broad (2H).

The hydrochloride (54) was dissolved in 30 ml of water and the solution made basic (to pH = 8) with 5% sodium carbonate solution. The free amine was extracted twice with 20 ml chloroform. The organic extracts were dried over sodium sulphate. The solvent removal afforded a yellow oil (56) which became colourless after vacuum distillation.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84.
Found: C, 85.31; H, 8.98.

(2) With methyllithium

The reaction was carried out in an identical manner. A yield of 73% was estimated from the n.m.r. spectrum.

Bromopropylation of dibenzylnitrosamine

A solution of 339.5 mg (49) containing 0.24 ml diisopropylamine in 60 ml of tetrahydrofuran was cooled to -75°. 1.1 eq. of methyllithium was added to the stirred mixture. After 4 min, 0.76 ml (5 eq.) of 1,3-dibromopropane were added. The mixture was stirred at -75° for 1.5 hr, then at room temperature for another 2 hr. The product was isolated as described for the previous alkylations. A yield of ca. 55-58% of benzyl-(α-phenyl)-ω-bromobutylnitrosamine (56) was estimated by n.m.r. spectrum.
N.M.R. (60 M Hz): 1.50-2.60, two multiplets (4H, CH_2-CH_2); 3.20, triplet (2H, CH_2-Br); 4.05 and 5.15, AB quartet, J = 14 Hz (2H, Ph-CH_2); 6.80 - 7.60 multiplet (10 H, $2C_6H_5$); CH absorption is overlapped by a low-field pattern of the AB quartet.

The cleavage in anhydrous benzene afforded the corresponding hydrochloride (424 mg). This was dissolved in 40 ml of warm water. The solution was made alkaline and extracted twice with 15 ml chloroform and twice with 20 ml ethyl ether. The extracts were combined, dried (over Na_2SO_4) and the solvents evaporated. The residue was thin-layer chromatographed (elution system: petroleum ether/ethyl ether, 7/3). The top band contained 117 mg (33%) of 1-benzyl-2-phenylpyrrolidine (57).

Recrystallisation from aqueous acetone: m.p. 44.5-45° (lit.[56], 43-44°).

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.02; H, 8.07; N, 5.90.

Found: C 85.57; H, 8.09; N, 6.09.

N.M.R. (60 M Hz): 1.50 - 2.50, multiplet (5H); 3.03 and 3.90, AB quartet, J = 13 Hz (2H); 3.35, multiplet (2H); 7.10 - 7.60, multiplet (10H).

Mass Spectrum: molecular ion peak m/e at 237. Calcd. 237.34.

Bromobutylation of dibenzylnitrosamine

The solution of dibenzylnitrosamine (1.5 mmole) carbanion was made up in an identical manner and then 5 eq. (0.9 ml) of 1,4-dibromobutane were added. The total reaction time was 3.5 hr (1.5 hr at -75° and 2 hr at room temperature). The crude product contained about 50% benzyl-(α-phenyl)-ω-bromopentylnitrosamine (58).

N.M.R. (60 M Hz): 1.00 - 2.60, multiplet (6H, CH_2-CH_2-CH_2); 2.33, triplet, J = 7 Hz (2H, CH_2-Br); 4.08 and 5.10, AB quartet (2H, Ph-CH_2); 6.90 - 7.70 (10H, $2C_6H_5$).

After the nitroso group cleavage, 470 mg of crude hydrochloride was obtained. This was dissolved in 40 ml of warm water, the solution neutralised, and extracted twice with both chloroform and ether. The extracts were dried and the solvents evaporated. The residue was chromatographed (elution system: petroleum ether/ethyl ether, 7/3) yielding 125 mg (33.2%) white crystals of 1-benzyl-2-phenylpiperidine (59). Recrystallisation from ethanol-water: m.p. 90-91° (lit.[57], 93-93.5°, uncorrected).

N. M. R. (60 M Hz): 1.10-2.05, multiplet (8H, CH_2-CH_2-CH_2-CH_2); 2.76 and 3.78, AB quartet, J = 14 Hz (2H, Ph-CH_2); 3.05, broad (1H, CH); 7.10 -7.60, multiplet (10H, $2C_6H_5$).
Mass spectrum: molecular ion peak, m/e at 251. Calcd. 251.37.

1-Nitroso-4-phenylpiperazine (61)

To a stirred solution of 6.5 g (0.04 mole) of 4-phenylpiperazine in 20 ml of water and 20 ml acetic acid, at room temperature, were added 2.8 g sodium nitrite dissolved in 15 ml of water, over a period of 45 min. The stirring was continued for another 45 min and the reaction mixture was then cooled (4°). The light-brown precipitate was filtered and dried. Recrystallisation, first from ether-n-heptane mixture and then from ether, afforded 5.6 g (72%) yellow needles of (61). M.p. 67-69° (lit.[58], 65-68°C).

Methylation of 1-nitroso-4-phenylpiperazine

To a solution of 288 mg (1.5 mmole) of 1-nitroso-4-phenylpiperazine (61) in 30 ml of tetrahydrofuran was added 0.24 ml (1.5 mmole) of diisopropylamine and the mixture was cooled at -75°. When methyllithium (1.1 eq.) was added the yellow solution became orange. After 4 min the mixture was treated with 0.46 ml of methyl iodide and stirred

at -75° for 2 hr. The reaction mixture worked up in the usual manner afforded 45-48% of 1-nitroso-2-methyl-4-phenylpiperazine (62) (estimated by n.m.r.).

N. M. R. (60 M Hz) of (62), after purification by thin layer chromatography (elution system: petroleum ether/ethyl ether, 1/9): 1.30 and 1.65, two doublets, J = 6.4 Hz (3H); 3.00 - 3.50 and 3.80 - 4.30, two multiplets (6H); 4.80, broad (1H); 6.90 - 8.55, multiplet (5H).

Cleavage of the nitroso group

The crude reaction product obtained in the above reaction was dissolved in 20 ml of anhydrous benzene. A brown precipitate, that subsequently turned into a violet tar, appeared a short time after hydrogen chloride bubbling was started. The hydrogen chloride stream was stopped after 30 min and nitrogen was passed through the suspension for 15 min. The solvent was evaporated and the solid mass was washed three times with ethyl ether and dissolved in 30 ml of water. This solution was made basic (pH = 8) and extracted five times with 10 ml of chloroform. The combined extracts were dried (Na_2SO_4 anh.) and the solvent was evaporated under reduced pressure. The residue (143 mg) was thin layer chromatographed (elution system: methanol/acetone, 9/1) and 70 mg (23%) of 2-methyl-4-phenylpiperazine (63) were recovered. After the vacuum distillation a colourless oil resulted.

N. M. R. (100 M Hz): 1.08, doublet, J = 6.2 Hz (3H, CH_3); 1.50, singlet (1H, NH); 2.20 - 3.60, multiplet (7H, ring protons); 8.85 and 9.24, multiplets (5H; C_6H_5).

Mass Spectrum: molecular parent peak at 176.1325 a.m.u.

$C_{11}H_{16}N_2$ = 176.1313.

2-Methyl-4-phenylpiperazine (20 mg) was dissolved in anhydrous ether and converted into the corresponding hydrochloride. 65 mg of 2-methyl-4-phenylpiperazine hydrochloride (64) were collected and recrystallised from methanol-ether mixture. M.p. 209-209.5°.

Carboxylation of 1-nitroso-4-phenylpiperazine

To a solution of 288 mg (1.5 mmole) 1-nitroso-4-phenylpiperazine (61) in 30 ml of tetrahydrofuran was added 0.24 ml (1.5 mM) of diisopropylamine. The mixture was cooled to -75° and 1.1 eq. of methyllithium were injected. After 4 min a stream of carbon dioxide was passed through the stirred solution for 15 min. The stirring was continued at -75° for 0.5 hr and then at room temperature for 1 hr. The solvent was evaporated and the solid residue, dissolved in 40 ml of water, was extracted twice with 20 ml chloroform. The aqueous layer was made acidic (pH < 4) with 10% hydrochloric acid solution and extracted four times with 20 ml chloroform. The organic extracts were dried and solvent removed. The yield of 1-nitroso-4-phenylpiperazine-2-carboxylic acid (66) weighed 162 mg (48.8%).

N.M.R. (100 M Hz): 2.50 - 3.80, multiplet (4H); 4.20, multiplet (1H); 4.77 and 4.92 multiplets (1H); 5.55 and 5.70, singlets (1H); 6.70 - 7.40, multiplet (5H); 9.40, singlet (1H).

I.R. ($CDCl_3$): 3400-3100, broad (ν_{OH}); 1730, strong ($\nu_{C=O}$); 1450 ($\nu_{N=O}$).

The crude (66) was dissolved in 60 ml of benzene (anh.) and the nitroso group cleavage was effected as described in the previous experiments. The product was filtered and 139 mg (38%) pink crystals were recovered. Recrystallisation from water-acetone mixture afforded colourless crystals (m.p. 229-230°, dec.) of 4-phenylpiperazine-2-carboxylic acid hydrochloride (67).

Anal. Calcd. for $C_{11}H_{15}N_2O_2Cl$: C, 54.43; H, 6.23; N, 11.54; Cl, 14.61.
Found: C, 54.05; H, 6.25; N, 11.05; Cl, 14.83.
I.R. (KBr pallets): 3400, broad (ν_{OH}); 3100-2500, broad (ν_{C-H} arom., ν_{CH_2}, $\nu^{+}_{NH_2}$); 1740, sharp ($\nu_{C=O}$).

1-Nitrosopiperidine (68)

The method used was adapted from that described for the nitrosation of other secondary amines[59].

Piperidine (4.3 gm., 0.05 mole) was treated with 5 ml of concentrated hydrochloric acid. The resulting mass was warmed to 70° and allowed to react with a suspension of 4.3 gm of sodium nitrite in 10 ml of water which was added over a 30 min period with strong stirring. The mixture was stirred for 3 hr at 70° and cooled, whereupon the nitrosamine separated on the surface as a yellow oil. The two layers were separated and the aqueous phase was extracted twice with ether. The oily nitrosamine and the ethereal extracts were combined, washed with water for the removal of the traces of acid and dried over calcium hydride for 6 hr. Evaporation of the solvent gave 3.4 g (60%) of 1-nitrosopiperidine (68) (b.p. 102°/18 mm).

Carboxylation of 1-nitrosopiperidine

1-Nitrosopiperidine (228 mg, 2 mmole) was converted with 1.1 eq. of lithium diisopropylamide into the corresponding carbanion. The carboxylation was conducted as described for (66).

After the acidification the free acid (69) was extracted four times with 15 ml ether. The extracts were dried and the solvent removed in vacuum at room temperature. The resultant oil crystallised on standing, yielding 90 mg (28.4%) colourless crystals of 1-nitrosopiperidine-2-carboxylic acid (69). M.p. 88-90°, dec. (lit.[50], 89-90°).

N. M. R. (100 M Hz): 1.10 - 2.60, multiplet (6H); 2.78 and 3.81, two multiplets (1H); 4.78 and 4.91, two doublets, J = 14 Hz (1H); 5.52 and 5.71, two doublets, J = 5.4 Hz (1H); 10.20, singlet (1H).

I.R. ($CDCl_3$): 3400-3000, broad (ν_{OH}); 1730 sharp ($\nu_{C=O}$); 1462 ($\nu_{N=O}$).

The cleavage of the nitroso group was done in 20 ml. of benzene. The reaction mixture was filtered and 27 mg of piperidine-2-carboxylic acid hydrochloride (70) were obtained. From the mother liquid, after the solvent evaporation, an additional 12 mg of product were recovered. The recrystallisation from ethanol-chloroform mixture yielded colourless crystals which melted at 256-257° (lit.[60], 258-261°, uncorrected).

I.R. (KBr pallets): 3400, broad (ν_{OH}); 3200-2500, broad absorption with a peak at 2940 (ν_{CH_2}) and a shoulder at 2730 ($\nu_{\overset{+}{N}H_2}$); 1740, sharp ($\nu_{C=O}$)

1-Nitrosopyrrolidine (71)

This compound (b.p. 96-98°/18 mm) was prepared in 60% yield using the procedure described for (68).

Carboxylation of 1-nitrosopyrrolidine

The procedure described for the preparation of 1-nitroso-piperidine-2-carboxylic acid was followed in this experiment.

1-Nitrosopyrrolidine, 150 mg (15 mmole) yielded 50 mg (27%) of 1-nitrosopyrrolidine-2-carboxylic acid (72).
N. M. R. (100 M Hz): 1.60-2.50, multiplet (4H); 3.60 and 4.25, two multiplets (2H); 5.10 and 5.80, two multiplets (1H); 8.55, singlet (1H).
I. R. ($CDCl_3$): 3300-3000, broad (ν_{OH}); 1228 ($\nu_{C=O}$); 1440 ($\nu_{N=O}$).

N,N-Dibenzylbenzamide (74)

A well stirred mixture of 9.6 ml (0.05 mole) dibenzylamine in 20 ml, 3N NaOH was treated with 6.4 ml (1.1 eq.) of benzoyl chloride. The lumpy precipitate which formed was filtered, washed several times with water and dried. In order to remove any traces of unreacted dibenzylamine, the solid was dissolved in 100 ml chloroform and the solution washed consecutively with 10% hydrochloric acid and water. The organic layer was dried (Na_2SO_4 anh.) and the solvent evaporated. Further recrystallisation from ethanol afforded 10 gm. (70%) of white crystals. M.p. 113°C (lit.[61], 112°).

Methylation of dibenzylbenzamide

To a -75° cooled solution of 300 mg (1 mmole) dibenzylbenzamide solution containing 0.16 ml (1.1 eq.) of diisopropylamine in 25 ml of tetrahydrofuran, 1.1 eq. of methyllithium was added. The solution immediately turned dark brown and changed to bright red within a few seconds. After the mixture was stirred for 4 min., 0.3 ml (5 eq.) of methyliodide were injected. The stirring was continued for

15 min at -75° and then for a further 2.5 hr at room temperature. Finally, 15 ml of water were added and the reaction mixture was extracted twice with 20 ml of methylene chloride. The organic layers were dried (Na_2SO_4) and the solvent was evaporated. The n.m.r. spectrum of the crude product showed more than 92% yield of benzyl-(α-methyl)-benzylbenzamide (75). The residue was triturated with 10 ml of ethyl ether and 188 mg (60%) of pale yellow needles were recovered. The recrystallisation from aqueous ethanol afforded white needles, which melted at 112.5-114° (lit.[62], 109-111°).

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44.

Found: C, 83.43; H, 6.67; N, 4.52.

N. M. R. (60 M Hz): 1.46, doublet, J = 2.5 Hz (3H); 3.96 and 4.90, AB quartet, J = 16 Hz (2H); 5.47, quartet, J = 7.5 Hz (1H); 7.10 - 7.70, multiplet (15 H).

In another experiment methyllithium was employed as base. Examination of the crude reaction product indicated 58% yield of benzyl-(α-methyl)-benzylbenzamide.

CONCLUSIONS

The alkylation and carboxylation previously described provide a fairly efficient way for placing a hydrocarbon side-chain or a carboxyl group in the α-position of a nitrosamine molecule.

Taking into account the facile cleavage of the nitrosamine group, which affords the corresponding amines, the procedure can be regarded as a two-step method for the preparation of α-alkyl and α-carboxyl secondary amines, the last products being of biological interest.

Lithium diisopropylamide was proved to be a good metallating reagent in this series of reactions. This is basic enough to produce a carbanionic site and sufficiently inert with respect to the nitrosamine function. The choice of the optimum reaction conditions was of importance especially when working on nitrosamines having less stable carbanions.

A second derivative of secondary amines, dibenzylbenzamide, on preliminary examination, appears to be essentially equivalent to dibenzylnitrosamine in ease of carbanion formation.
Further work on this activating group in less reactive disubstituted amides should prove of interest.

CLAIMS TO ORIGINAL RESEARCH

1. The formation and subsequent reactions of carbanions alpha to a nitrosamino group have been studied with the aim of developing a new synthetic method for modification of secondary amines. The following specific reactions have been successfully carried out:

   a) The alkylation of dibenzylnitrosamine by 1-iodopropane, 1, 3-dibromopropane and 1, 4-dibromobutane;

   b) The methylation and carboxylation of 1-nitroso-4-phenyl-piperazine;

   c) The carboxylation of 1-nitrosopiperidine and 1-nitroso-pyrrolidine.

   The product nitrosamines have been cleaved in high yield to secondary amines. A part of these were new compounds which have been characterised by standard methods.

2. The formation and subsequent reaction of a carbanion alpha to the nitrogen of a carboxyamide group has been achieved in the case of methylation of N, N-dibenzylbenzamide.

REFERENCES

1. W. Schlenk and E. Bergmann. Ann. 463, 98 (1928).
2. J. M. Mallan and R. L. Bebb. Chem. Rev. 69, 693 (1969).
3. D. F. Cram. "Fundamentals of Carbanion Chemistry", Academic Press, 1965, p. 47.
4. E. J. Corey and D. Seebach. Angew. Chem. Intern. Ed. Engl., 4, 1075, 1077 (1965).
5. D. Seebach. Ibid., 8, 639 (1969).
6. D. Seebach., N. R. Jones and E. J. Corey. J. Org. Chem. 33, 300 (1968).
7. M. W. Rathke. J. Amer. Chem. Soc. 92, 3222 (1970).
8. M. W. Rathke and A. Lindert. Ibid. 93, 2318 (1971).
9. M. W. Rathke and A. Lindert. Ibid. 93, 4605 (1971).
10. M. W. Rathke and A. Lindert. Tetrahedron Lett. 43, 3995 (1971).
11. E. M. Kaiser and C. R. Hauser. J. Org. Chem. 33, 3402 (1968).
12. E. M. Kaiser and C. R. Hauser. J. Amer. Chem. Soc. 88, 2348 (1966).
13. E. M. Kaiser, L. E. Solter, R. A. Schwarz, R. D. Beard and C. R. Hauser. Ibid. 93, 4237 (1971).
14. G. Stork and L. Maldonaldo. J. Amer. Chem. Soc. 93, 5286 (1971).
15. A. J. Mayers, A. Nabeya, H. W. Adickes and J. R. Politzer. Ibid. 91, 763 (1969).
16. A. J. Mayers and D. J. Temple Jr. Ibid. 92, 6644 (1970).
17. U. Schöllkopf and F. Gerhart. Angew. Chem. Intern. Ed. Engl. 7, 805 (1968); U. Schollkopf. Ibid. 9, 763 (1970).
18. F. Gerhart and U. Schöllkopf. Tetrahedron Lett. 6231 (1968).

19. U.Schöllkopf, F. Gerhart and R. Schröder. Angew. Chem. Intern. Ed. Engl., 8, 672 (1969); U. Schöllkopf and D. Hoppe. Ibid. 9, 236 (1970).

20. H. Gilman. Org. Reactions. 8, 258 (1954).

21. P. West, R. Waach and J. J. Purmont. J. Amer. Chem. Soc. 92, 840 (1970).

22. H. Gilman and H. A. McNinch. J. Org. Chem. 27, 1889 (1962).

23. P. L. Creger. J. Amer. Chem. Soc. 92, 1397 (1970).

24. J. F. Eastman and G. W. Gibson. Ibid. 85, 2171 (1963).

25. R. Waach and M. A. Doran. Chem. Ind. (London), 1290 (1962).

26. H. Gilman and S. Gray. J. Org. Chem. 23, 1476 (1958).

27. A. J. Shatenshtein and Yu. J. Ranneva. Zhur. Obshchei. Khim. 31, 1423 (1961); Chem. Abstr. 55, 22192 (1961).

28. A. R. Lepley and A. G. Giumanini. Chem. Ind. (London), 1035 (1965).

29. A. R. Lepley and W. A. Khan. J. Org. Chem. 31, 2061 (1966).

30. A. R. Lepley and W. A. Khan. Ibid. 31, 2064 (1966).

31. A. R. Lepley and A. G. Giumanini. Ibid. 31, 2055 (1966).

32. A. R. Lepley, W. A. Khan, A. B. Giumanini and A. G. Giumanini. Ibid. 31, 2047 (1966).

33. R. E. Ludt and C. R. Hauser. Ibid. 36, 1607 (1971).

34. W. H. Peterbaugh and C. R. Hauser. J. Amer. Chem. Soc. 85, 2467 (1963).

35. R. L. Vaulx, I. N. Jones and C. R. Hauser. J. Org. Chem. 29, 1387 (1964).

36. R. E. Ludt, G. P. Crowter and C. R. Hauser. Ibid. 35, 1288 (1970).

37. L. K. Keefer and C. H. Fodor. J. Amer. Chem. Soc. 92, 5747 (1970).

38. H. U. Daeniker. Helv. Chim. Acta, 47, 33 (1964).

39. R. R. Fraser and Y. Y. Wigfield. Tetrahedron Lett. 27, 2511 (1971).

40. R.R.Fraser and Y.Y.Wigfield. Private communication.

41. P.Quit, R.O.Studer and K.Vogler. Helv.Chim.Acta, 47, 166 (1964).

42. R.R.Fraser and G. Boussard. Unpublished works.

43. F.H.Rash, S.Boatman and C.R.Hauser. J.Org.Chem. 32, 372 (1967).

44. R.West and P.Jones. J.Amer.Chem.Soc. 90, 2656 (1968).

45. G.G.Eberhardt and W.A.Buthe. J.Org.Chem. 29, 2928 (1964).

46. G.J.Karabatsos and R.A.Taller. J.Amer.Chem.Soc. 86, 4373 (1964).

47. Y.L.Chow and C.J.Colon. Can.J.Chem. 46, 2827 (1968).

48. R.K.Harris and R.A.Spragg. J.Molec.Spect. 23, 158 (1967).

49. R.R.Fraser and Y.Y.Wigfield. Unpublished works.

50. W.Lijinski, L.K.Keefer and J.Loo. Tetrahedron, 26, 5137 (1970).

51. P.G.Gassman and B.L.Fox. J.Org.Chem. 31, 982 (1966).

52. H.L.Needles and R.E.Whitfield. Ibid. 31, 989 (1966).

53. O.Martensson and E.Nilsson. Acta Chem.Scand. 14, 1129 (1960).

54. C.G.Overberger, L.C.Palmer et al. J.Amer.Chem.Soc. 77, 4100 (1955).

55. A.P.Terent'ev, E.G.Rukhadze, V.V.Dunina and E.V.Drobyshevskaya. Zhur.Obshchei.Khim. 38, 715 (1968); Chem.Abstr. 69, 51, 756 (1968).

56. A.V.Eltsov, A.G.Cuiganev and I.T.Starykh. Ibid. 34, 3344 (1964); Chem.Abstr. 62, 3995 (1965).

57. R.A.Abramovitch, K.S.Ahmed and Choo-Seng Siam. Can.J.Chem. 41, 1752 (1963).

58. C.H.Lovell. U.S.Patent No. 3,287,454; Chem.Abstr. 66, 65,512 (1967).

59. H.Zimmer, L.F.Andrietti, M. Zimmer and R.V.Rowe. J.Amer. Chem.Soc. 77, 790 (1955).

60. C. M. Stevens and P. B. Ellman. J. Biol. Chem. 182, 75 (1950).

61. H. Frausen. Ber. 42, 2465 (1909).

62. L. Amoros-Marin and R. B. Carlin. J. Amer. Chem. Soc. 81, 733 (1959).