THE SYNTHESIS AND PROPERTIES OF SOME HETEROCYCLIC NITROGEN COMPOUNDS

by

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P R E F A C E

Part I

The synthesis and study of strained cyclic compounds has always been a challenge to the organic chemist. Not only are such systems often difficult to prepare, but in addition in many cases the properties displayed by them are truly unusual when compared to their relatively strainless homologues. Two such compounds which have recently been synthesized are: 2,2a,3,4-tetrahydro-1H-cyclopent [cd] indene (I) and cycl [3,2,2] azine (21,22). The purpose of this investigation then was to prepare the as yet unknown heterocyclic compounds: 1,2,4,5-tetrahydropyrrolo [3,2,1-hi] indole and pyrrolo [3,2,1-hi] indole, and to compare their properties with those of the two aforementioned tricyclic systems.

Part II

Although three tautomeric forms of indazole are theorectically possible, only 1H- and 2H- indazoles have been thoroughly studied. Simple derivatives of indiazene are virtually nonexistent. The object of this part of the research was to prepare simple derivatives of this latter, neglected tautomer of indazole. Indiazenes bear a formal analogy to Δ^1-pyrazoles and it was therefore reasoned that like these compounds, substituted indiazenes might undergo photolytic or thermal loss of nitrogen giving rise to cyclopropane derivatives. However, in this case, highly strained, as yet unreported derivatives of benzcyclopropene would arise, providing the above analogy hold.

The author gratefully thanks his research supervisor, professor F.A.L. Anet for his unfailing guidance, invaluable advice, and constant encouragement, throughout the course of this research.

The technical assistance of Miss L. Bush, Mrs. E. Osgerby, Mrs. P. Kogler and other members of the technical staff of the University of Ottawa, and Mr. A. Castaigne of the National Research Council of Canada, Division of Applied Biology, Ottawa, is gratefully acknowledged. In addition, the helpful discussion and constructive criticism of fellow students is also acknowledged.

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ABSTRACT

Part I

The previously unknown 1,2,4,5-tetrahydropyrrolo [3,2,1-*hi*] indole was prepared via a three step synthesis from 1,3-dimethoxycarbonyl-methyl-2-nitrobenzene. This base was a low melting (m.p. 32-33°), stable solid possessing no very unusual properties.

1,2,4,5-Tetramethylpyrrolo [3,2,1-*hi*] indole was synthesised by catalytic dehydrogenation of *cis*-1,2-dihydro-1,2,4,5-tetramethylpyrrolo [3,2,1 *hi*] indole. The former is a very stable, rather unreactive solid, and to date is the only known derivative of pyrrolo [3,2,1-*hi*] indole. During the course of this synthesis, it was necessary to examine the stereochemistry of the metal acid reduction of 2,3-dimethylindole. As a result, the stereoisomeric *cis*- and *trans*- 2,3-dimethylindolines have been fully characterized thus clearing up inconsistencies in the literature concerning these bases. The N.M.R. spectra of the above indolines and the other stereoisomeric intermediates leading to 1,2,4,5-tetramethylpyrrolo [3,2,1-*hi*] indole have been thoroughly examined. In some cases the chemical shifts and coupling constants of these compounds deviated from that expected, and wherever possible rationalization of this behaviour has been attempted.

Part II

Direct cyclization of various diazonium salts of 2-*iso*propyl-3-methoxycarbonylaniline failed under a wide variety of conditions. However

this study has led to the following interesting observations: benzenediazonium fluoroborates, when treated at 20-25° with potassium *t*-butoxide and *t*-butanol in the presence of furan gave good to excellent yields (50-80%) of substituted 2-phenylfurans. This procedure proved to be far superior to the existing method (110) used in the preparation of such substituted furan derivatives. In addition, a new type of hydrogen-bonded dimer formation has been discovered and characterized by means of N.M.R. and infrared spectroscopic measurements. In carbon tetrachloride, phenols with *m*-substituents (eg. methoxycarbonyl, nitro, or aldehyde groups), form cyclic fourteen-membered hydrogen-bonded dimers of unprecedented stability. Using infrared spectral measurements and application of the treatment of Liddel and Becker (123) gave the equilibrium constants ($K = [\text{dimer}] / [\text{monomer}]^2$) 457 ± 15 l/mole and 551 ± 28 l/mole for 2-*iso*-propyl-5-methoxycarbonylphenol and 3-methoxycarbonylphenol respectively. These values are approximately three orders of magnitude greater than that observed for simple phenols (125).

3,3-Dimethyl-6-methoxycarbonylindiazene was synthesised from N-nitroso-N-benzoyl-2-*iso*-propyl-5-methoxy-carbonylaniline by the modified Jacobson-Huber method (118). This compound was exceptionally resistant to thermal elimination of nitrogen and could be distilled at atmospheric pressure without decomposition. Attempted conversion of this compound to 3,3-dimethylindiazene failed. Furthermore, 3,3-dimethylindiazene could not be obtained from N-nitroso-N-benzoyl-2-*iso*-propylaniline under conditions which readily gave the 6-methoxycarbonyl derivative.

P A R T I

The Synthesis and Properties of 1,2,4,5-Tetrahydropyrrolo[3,2,1-*hi*] indole and 1,2,4,5-Tetramethylpyrrolo [3,2,1-*hi*] indole.

INTRODUCTION

The synthesis and study of strained cyclic compounds has been a subject of major interest in organic chemistry since the elaboration of the structure of benzene. In the early years many such ring systems (e.g. cyclopropane) were considered to be incapable of existence because of the severe distortion from the normal bond angles (109° 28' for carbon) which would be present in such compounds. As knowledge and synthetic methods improved the majority of these predictions were shown to have been somewhat exaggerated. During the past twenty years progress in organic chemistry in general has been so phenomenal that at present almost no cyclic system is considered to be sacrosanct.

Over the past fifty years numerous attempts have been made to synthesise a tricyclic compound* containing two saturated five-membered rings fused mutually to a benzene ring and it has only been recently that two such cyclic systems have been prepared. The first (I) was synthesised by Rapoport and Pasky (1) while the second (II) is part of the subject of this thesis. Reasons for the above failures are numerous, but perhaps the greatest single cause is the strain thought to be inherent in these ring systems. This strain can be considered to arise mainly from two sources. The first and possibly greater part of the strain arises from distortion of the carbon-carbon bond angles in the benzene ring when a five-membered cyclic system is fused to it. The carbon-hydrogen bonds in benzene are

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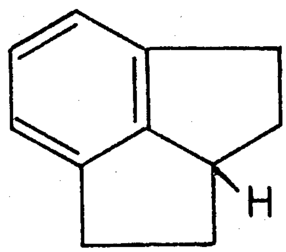
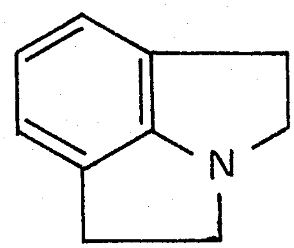
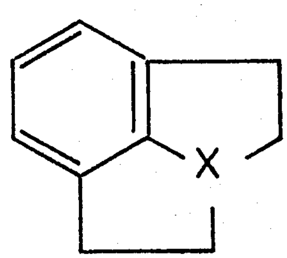
[a] Only those compounds containing no more than one hetero atom will be discussed.



I



II



II A

in the plane of the ring and form an exterior angle of 120°, while the interior carbon - carbon bond angle in cyclopentane is approximately 108°. If these two are to be fused it is obvious the latter angle must be increased along with concomitant distortion of the benzene ring.

Models of the tricyclic systems indicate they tend to be as nearly planar as possible and as a result if atom A is carbon (IIA) it must be somewhat distorted from the tetrahedral angle. The second type of strain is centered about this atom although it can be partially relieved by buckling of the five membered rings. From this standpoint alone the heterocyclic analogue (A = N, see above) might be predicted to be somewhat more stable because of the flatter nature of the nitrogen atom.

Although numerous attempts to synthesize 2,2a,3,4-tetrahydro - 1H - cyclopent [cd] indene* (I) have been made, only that one which was successful will be summarized here. As starting material Rapoport and Pasky (1) utilized the known 2a,3,4,5-tetrahydroacenaphthen-5-one(III). Oximination of this ketone with butyl nitrite in potassium t-butoxide followed by ring opening of the resulting oximino-ketone (IV) with benzenesulfonyl chloride in pyridine gave a good yield of 1-carboxy-1-indane acetonitrile (V). Basic hydrolysis gave the di-acid which was converted to its neutral lead salt (VI). This salt on pyrolysis at 350-380° in vacuo gave the tricyclic ketone (VII) in 40-50% yield.

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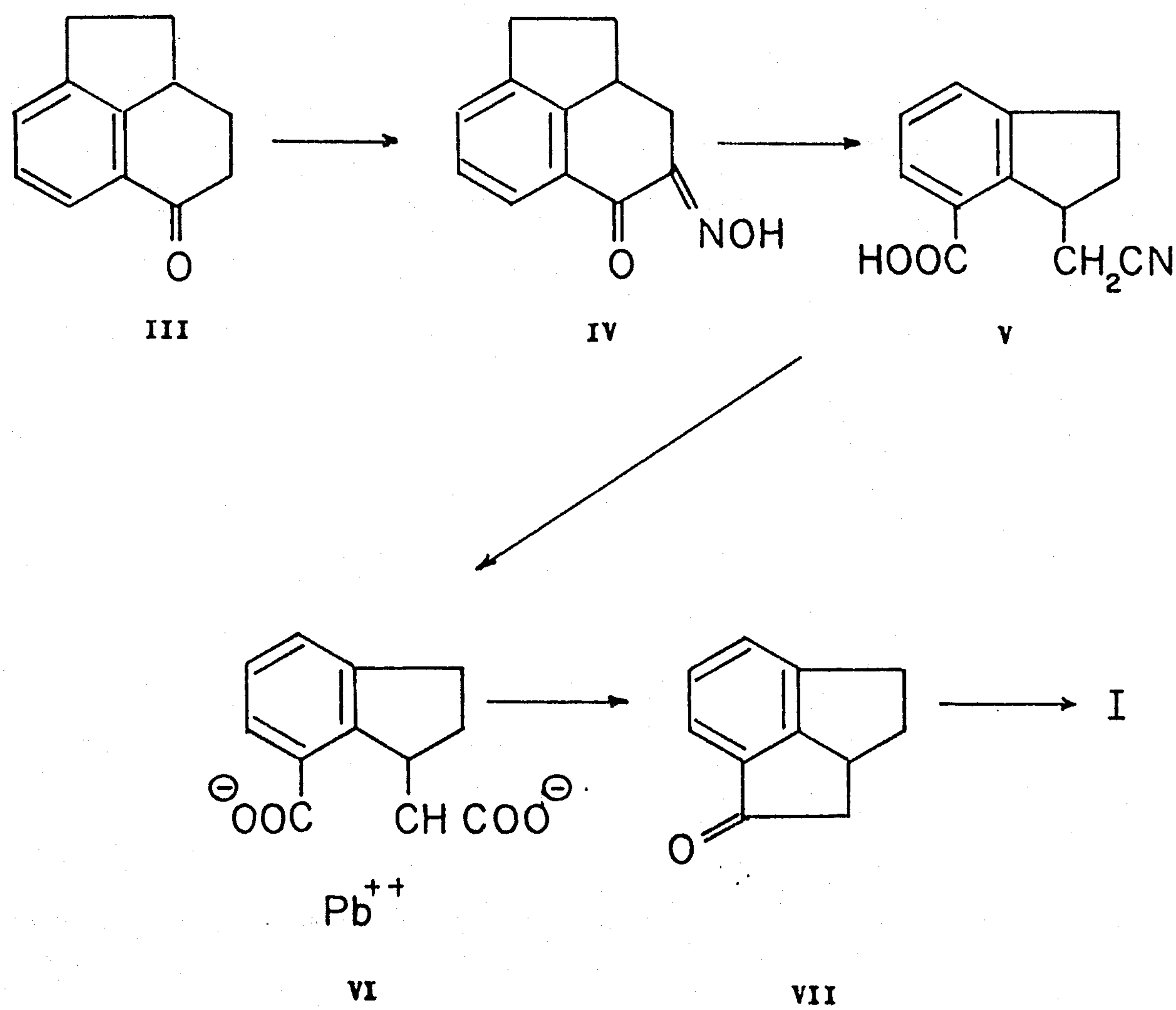
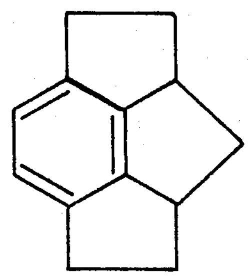
*Wherever convenient polycyclic ring systems will be named using the nomenclature followed in Chemical Abstracts.


O
III
NOH
O
IV
HOOC
CH2CN
V
⊖OOC
CH COO⊖
Pb++
VI
O
VII
I

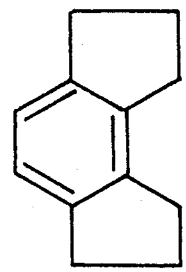
whereas pyrolytic decomposition of the lead salt gave satisfactory yields of the ketone, other salts such as those of thorium and calcium gave only small amounts (2-3%) of the required compound. The desired hydrocarbon (I) was readily obtained from the ketone by modified Wolff-Kishner reduction.

The tricyclic hydrocarbon is a stable liquid whose spectral properties are not significantly different from 2a,3,4,5-tetrahydroacenapthene, and whose chemical reactions are normal except for its unusual susceptibility to catalytic hydrogenation. The hydrocarbon absorbs three moles of hydrogen over 5% palladium-charcoal at room temperature and atmospheric pressure in two hours. The authors suggest that since hydrogenation is a surface reaction small differences in stability might be discerned in this manner. The above results seem to indicate far less strain in the tricyclic system than had been anticipated.

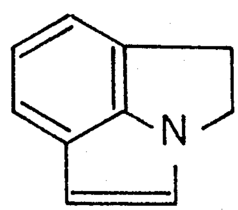
Using synthetic techniques analogous to those just mentioned Rapoport and Smolinsky (2) were able to synthesize 2,2a,3,3a,4,5-hexahydro-1H-cyclopent [jkl] as-indacene (VIII). This compound absorbed oxygen on standing in air, absorbed three moles of hydrogen over palladized carbon at room temperature and atmospheric pressure in twenty minutes, and reacted rapidly with perbenzoic acid at room temperature, whereas 1,2,3,6,7,8-hexahydro-as-indacene (IX) underwent none of these reactions. In addition the tetracyclic hydrocarbon showed a decreased extinction coefficient, a shift of the absorption maximum to longer wavelength and a loss of fine structure in the ultraviolet spectrum as compared to the tricyclic model (IX) which is identically substituted. In the opinion of the authors these observations must be attributed to severe ring strain and departure



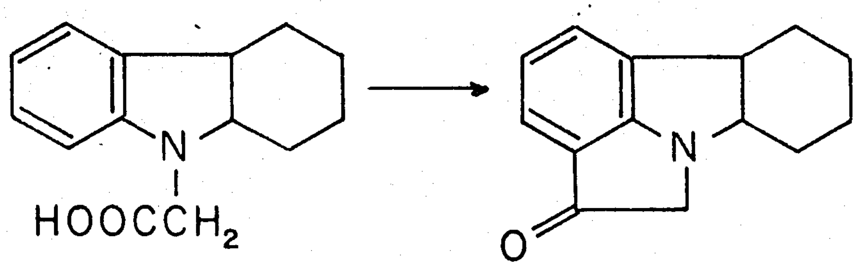
VIII



IX



X



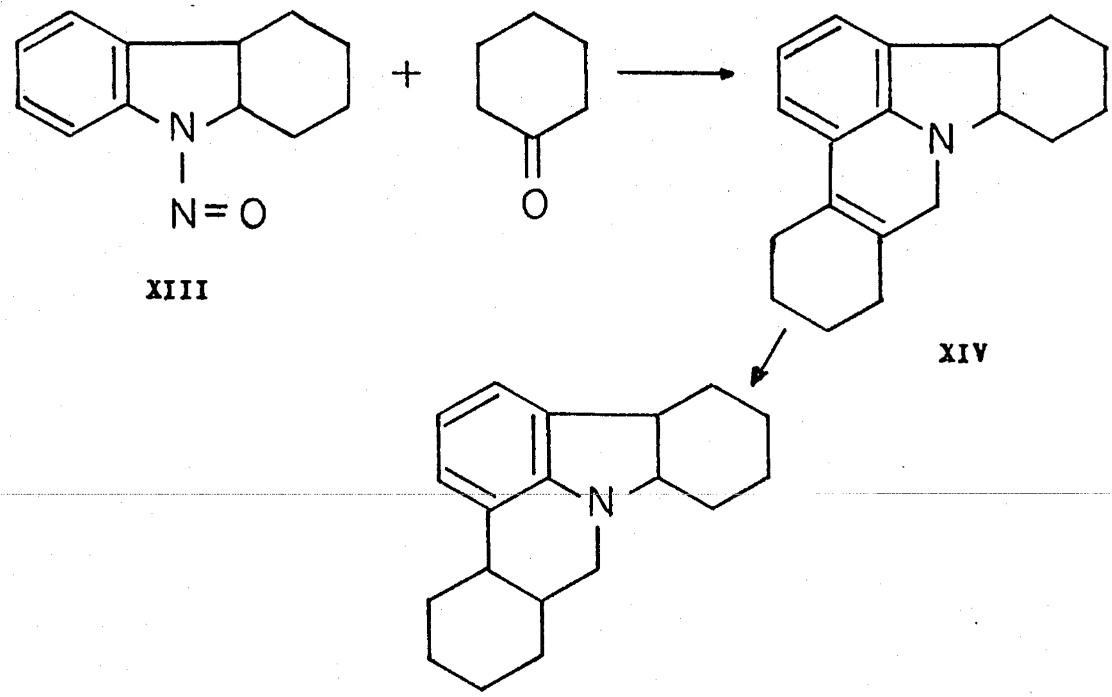
XI XII

from coplanarity. There is little doubt that sufficient strain is present to cause bending of the benzene ring with a resultant loss in resonance stabilization and increase in olefinic character.

Prior to the submission of this thesis no tricyclic compound containing the 1,2,4,5-tetrahydropyrrolo [3,2,1-*hi*] indole system (II) was known. However, a pentacyclic compound possessing this system (see below) and several alkyl derivatives of 1,2-dihydropyrrolo [3,2,1-*hi*] indole (X) including the parent system itself had been prepared and this work will be discussed in detail below.

The earliest reported investigation along this line was published by Perkin and Riley (3) in 1923. Although no experimental details are given they state that hexahydrocarbazole-9-acetic acid (XI) showed no tendency to undergo cyclization to 2-oxo-1,2,6,7,8,9-hexahydropyrrolo [3,2,1-*jk*] carbazole (XII).

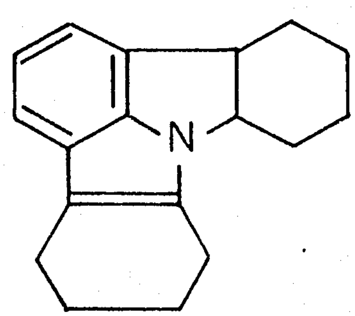
In 1927 Manjunath (4) reported that on warming a mixture of 9-nitrosohexahydrocarbazole (XIII) and cyclohexanone with zinc in acetic acid a pentacyclic compound to which he assigned the structure indicated (XIV) was obtained. This substance on electrolytic reduction gave a dihydro derivative (XV). Obviously the indicated structures are incorrect since there is no plausible manner in which the first product (XIV) could arise from the indicated reactants. Undoubtedly Manjunath actually intended structures XIV and XV to be represented by XVI and XVII since the empirical formulas stated by him are $C_{18}H_{21}N$ and $C_{18}H_{23}N$ respectively. The former (XVI) was the first known compound containing the 1,2-dihydropyrrolo [3,2,1-*hi*] indole system while the latter (XVII)



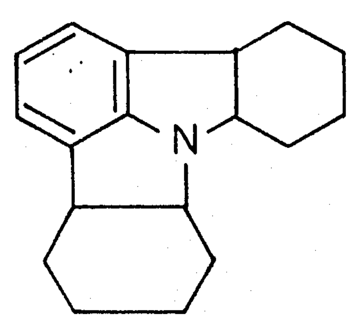
XIII

XIV

XV



XVI



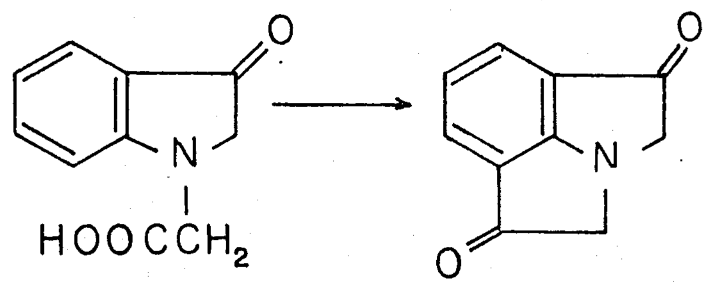
XVII

is the only one reported containing the tetrahydro system. No structural evidence (other than analyses) was given for the above compounds, but later work (5,6) coupled with the fact that 7-methyl-9-nitrosohexahydrocarbazole and cyclohexanone gave a compound similar to XVI indicate the validity of Manjunath's experiments.

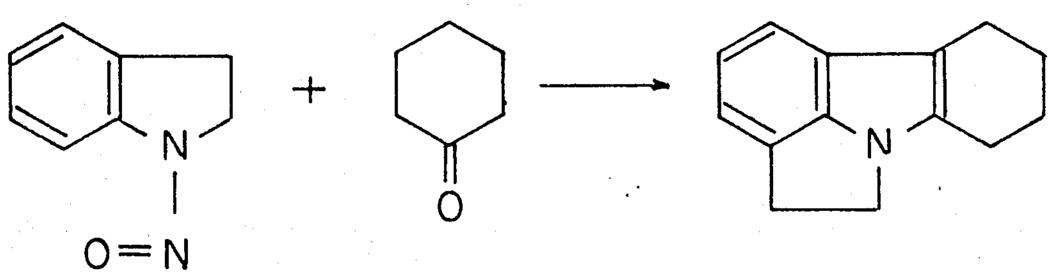
In connection with their interest in tervalent nitrogen compounds Jackson and Kenner (7) attempted to cyclise indoxyl-1-acetic acid (XVIII). Although fusion of this material with sodamide at 220° gave a small amount of a product of the expected composition, they express considerable doubt that the product actually was 2,4-dioxo-1,2,4,5-tetrahydropyrrolo[3,2,1-hi]indole (XIX).

In two papers Lions and Ritchie (5,6) report a series of experiments directed at the preparation of a compound containing the ring system in question. Despite much effort the majority of their investigations produced negative results. These authors were able to repeat Manjunath's work (4) and in support of it state that they were unsuccessful in cyclising the hydrazone obtained from 8-methyl-9-nitrosohexahydrocarbazole and cyclohexanone. Furthermore, subjecting 1-nitrosoindole and cyclohexanone to conditions identical to those outlined by Manjunath (4) gave neutral 1,2,6,7,8,9-hexahydropyrrolo[3,2,1-jk]carbazole (XX). Their structural assignment is based on the method of synthesis and an elemental analysis. Application of the same synthetic method to 1-nitrosoindole and ethylpyruvate or pyruvic acid gave no tricyclic product.

In agreement with earlier work (3) Lions and Ritchie (5,6) were unable to cyclise ethyl hexahydrocarbazole-9-acetate in the presence of



XVIII XIX



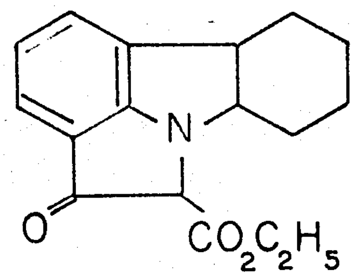
XX

concentrated sulfuric acid or by direct heating.

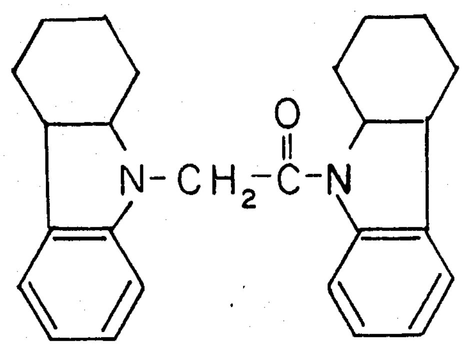
Whereas anilinomalonic esters readily gave indoxylic esters on heating (8), the above authors were unable to isolate any cyclic material corresponding to XXI from diethylhexahydrocarbazole-9-malonate. Furthermore, although mono-N-alkyl anilines were known to condense easily with glyoxalbisulfite giving oxindole sulfurous esters (9), *cis*-hexahydrocarbazole gave only a small amount of an amide (XXII) of the indicated structure. Finally, although phenacylaniline was known to yield 2-phenyl indole on cyclization with concentrated sulfuric acid or by simple distillation (10), 9-phenacylhexahydrocarbazole gave none of the expected material (XXIII) under a wide variety of conditions.

In 1950 Dunlop and Tucker (11) prepared indolo [3,2,1-*jk*] carbazole (XXV) by decomposition of the diazonium salt of 9-(2-aminophenyl) carbazole (XXIV). This substance was a stable, neutral solid, unaffected by chlorine in chloroform or boiling acetic acid. Regulated bromination gave a mono- and di-bromo derivative, while treatment with trichloroacetonitrile and anhydrous aluminum chloride in chlorobenzene, followed by acid and then basic hydrolysis (12) gave the 6-carboxy derivative of XXV.

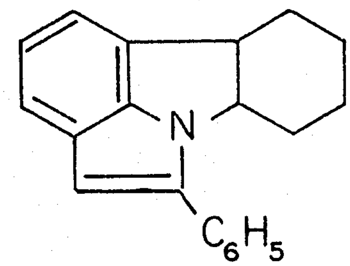
Preston and Tucker (13) confirmed the work of Dunlop and Tucker (11) and in addition prepared the same compound (XXV) by another route. Cyclization of the hydrazone (XXVI) obtained from 9-aminocarbazole and cyclohexanone, followed by dehydrogenation of the resulting pentacyclic compound (XXVII) with sulfur in boiling quinoline gave a compound (XXV) identical to that prepared by the previous workers. Preston and Tucker,



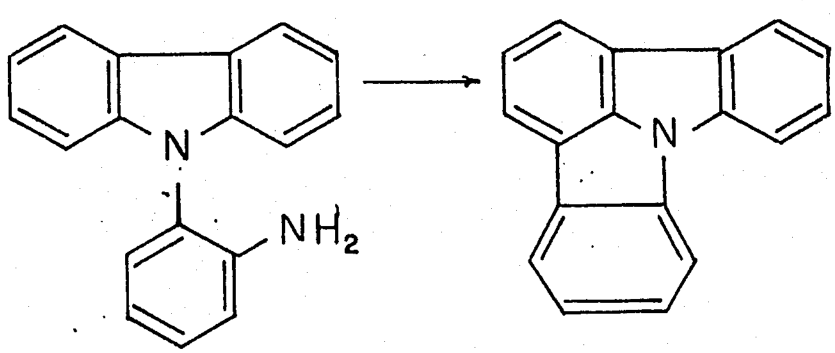
XXI



XXII

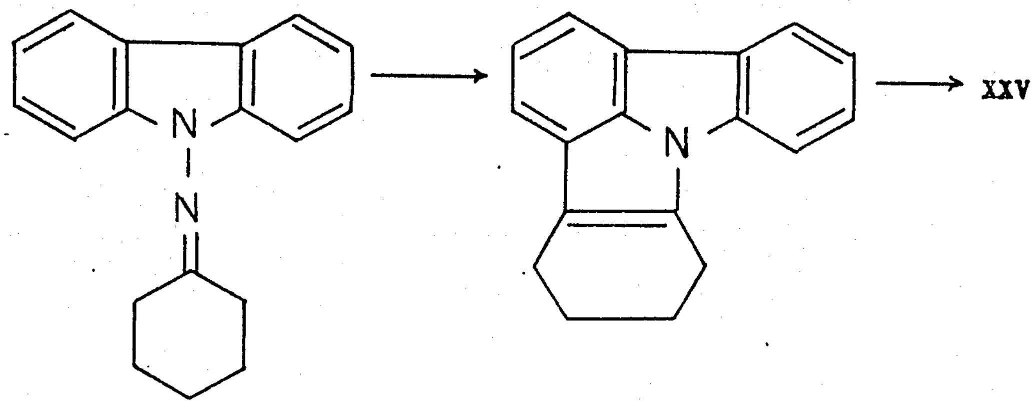


XXIII



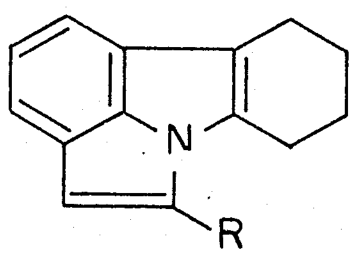
XXIV

XXV

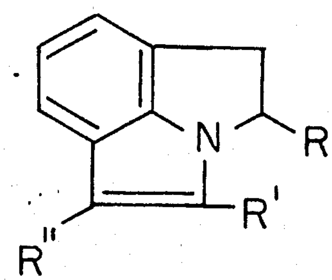


XXVI

XXVII



XXVIII

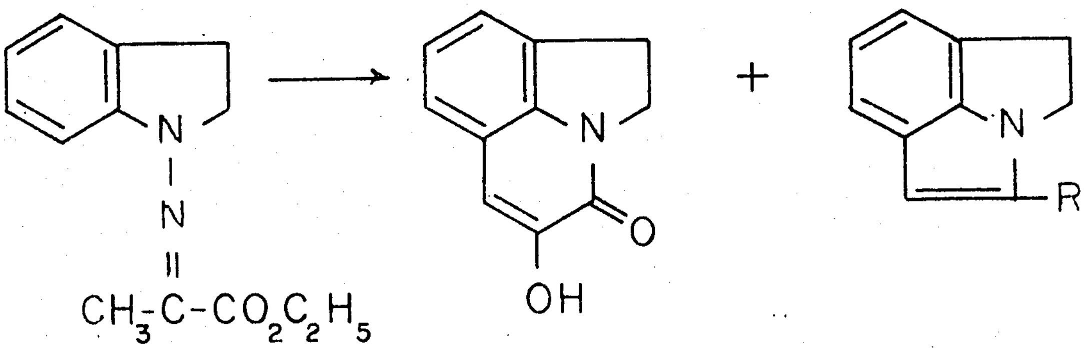


XXIX

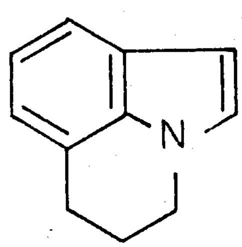
were however, unable to cyclize the carbazole-9-hydrazones of acetone, pyruvic acid, methyl pyruvate, ethyl acetoacetate, or ethyl oxaloacetate.

Recently, Yudin, Kost, and Berlin (14) and Yudin, Kost, Berlin, and Terentev (15) reported the cyclization of hydrazones obtained from 1-amino-2-alkylindolines and several ketones. The products [1-alkyl-1,2,6,7,8,9-hexahydropyrrolo[3,2,1-jk]carbazole (XXVIII) and 2,4,5-trialkyl-1,2-dihydropyrrolo[3,2,1-hi]indole (XXIX)] all contained the 1,2-dihydropyrrolo[3,2,1-hi]indole ring system (XXXII, R = H) which was simultaneously synthesized by Rapoport and Tretter (16). Whereas Lions and Ritchie (5) were unable to cyclize the indoline-1-hydrazone of ethyl pyruvate (XXX), Rapoport and Tretter obtained two products. The main product was shown to be 4-oxo-1,2-dihydropyrrolo[3,2,1-ij]quinoline-5-ol (XXXI), while the minor one was 3-carbethoxy-1,2-dihydropyrrolo[3,2,1-hi]indole (XXXII, R = $CO_2C_2H_5$). Saponification of this ester, followed by decarboxylation of the resulting acid, gave the parent ring system (XXXII, R = H). This compound was a neutral solid whose ultraviolet spectrum was similar to 5,6-dihydro-4H-pyrrolo-[3,2,1-ij]quinoline (XXXIII).

Experiments directed towards the synthesis of 1,2,4,5-tetrahydropyrrolo[3,2,1-hi]indole (II) were initiated in this laboratory by Anet and Nishizawa in 1956 (17). Although N-chloroacetylaniline was known to cyclize readily (18), N-chloroacetylindoline (XXXIV) failed to give any 4-oxo-1,2,4,5-tetrahydropyrrolo[3,2,1-hi]indole (XXXV) under various conditions in the presence of aluminum chloride, aluminum bromide, or 98% formic acid. Similar results were obtained with



XXX XXXI XXXII

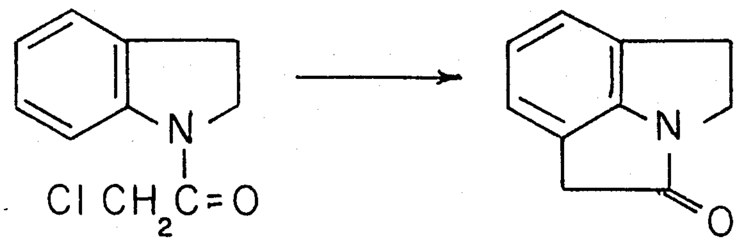


XXXIII

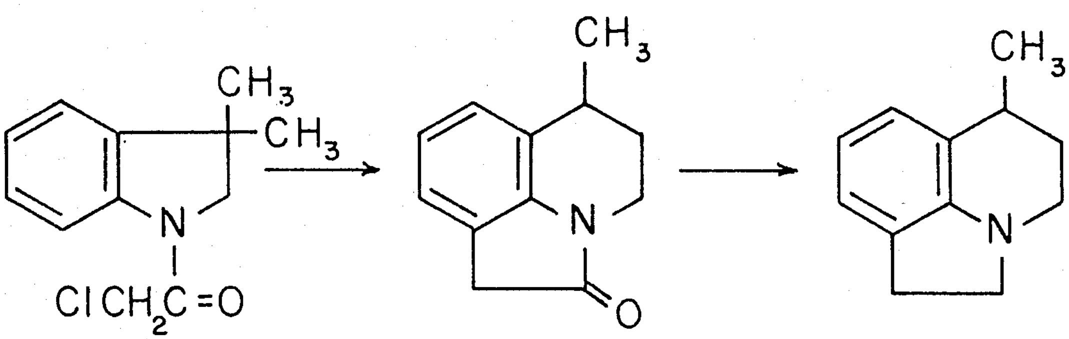
N-trichloroacetylindoline, even though N-trichloroacetylaniline easily gave 3,3-dichloro oxindole in the presence of aluminum chloride at room temperature (18,19).

Since part of the difficulty experienced in the above cyclizations was thought to be due to the benzylic hydrogens on the indoline ring, 1-chloroacetyl-3,3-dimethylindoline (XXXVI) was subjected to Stolle conditions (18). In contrast to the above cases a dimorphic solid possessing an empirical formula $C_{12}H_{13}ON$ was obtained. The spectral properties were in accordance with those expected for 1,1-dimethyl-4-oxo-1,2,4,5-tetrahydropyrrolo [3,2,1-*hi*] indole (XXXIX). Lithium aluminum hydride reduction of the tricyclic amide yielded a base whose infrared and ultraviolet spectral characteristics were as expected. However, the nuclear magnetic resonance spectrum of the amide demonstrated (among other things) the absence of a gem-dimethyl group and the presence of a methyl group attached to a carbon bearing one hydrogen. Since it appeared that ring expansion had occurred during the cyclization, the 3,4-and 5-methyl analogues of 1,2,4,5,6-tetrahydro-1H-pyrrolo [3,2,1-*hi*] quinol-2-one (XL) were synthesised. The 5-methyl analogue was identical to the cyclization product which therefore had structure XXXVII and not XXXIX. Needless to say, the lithium aluminum hydride reduction product of this compound then had to possess structure XXXVIII.

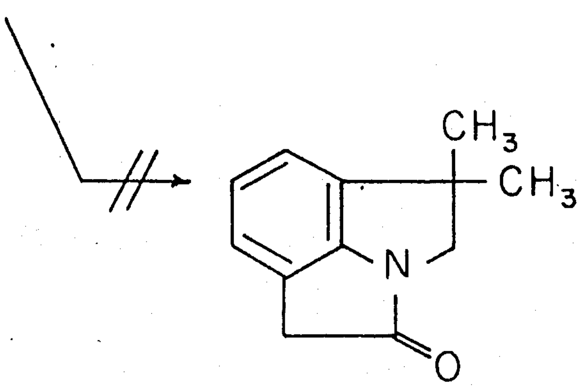
Since Friedel and Crafts type cyclization of the aforementioned N-chloroacetyl indolines did not appear promising, research along this line was abandoned in favour of another approach to the problem. Anet and Nishizawa reasoned that the geometry and reactivity of the anion of 7-(2-bromoethyl) indoline (XLVII) should favour cyclization and synthesised



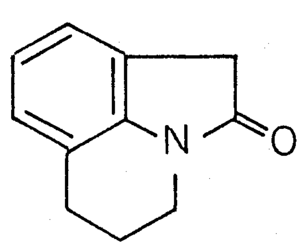
XXXIV XXXV



XXXVI XXXVII XXXVIII



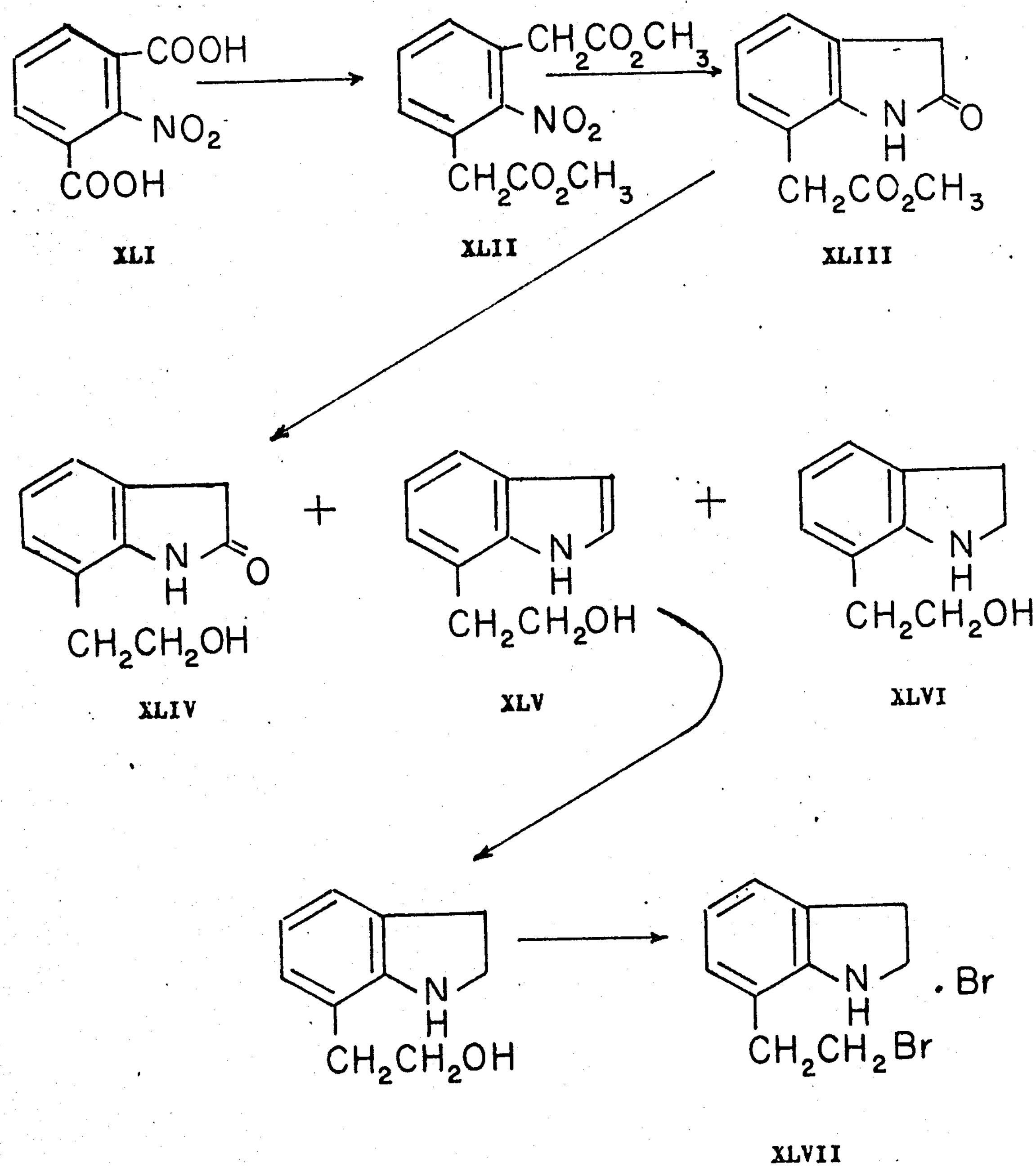
XXXIX

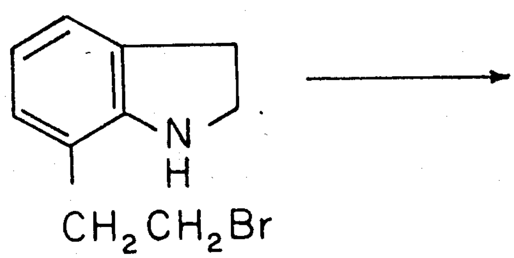


XL

the required precursor in the manner indicated below. 2-Nitro isophthalic acid (XLI) when subjected to the usual Arndt Eistert extension conditions gave 1,3-di(methoxycarbonylmethyl)-2-nitrobenzene (XLII) in respectable yield. This compound on hydrogenation over Raney nickel underwent reduction and internal cyclization giving 7-methoxycarbonylmethyl oxindole (XLIII). Lithium aluminum hydride reduction of the oxindole gave a disappointing mixture of three alcohols (XLIV, XLV and XLVI) in which the fully reduced base (XLVI) was present in vanishingly small amounts. The mixture of the three alcohols was first treated with sodium in alcohol to reduce the oxindole to the indole, then with amalgamated zinc and hydrochloric acid to reduce to indole to the indoline. The required hydroxy indoline (XLVI) was obtained in only 26% yield based on the oxindole ester (XLIII) as starting material. Treatment of the hydroxy indoline with concentrated hydrobromic acid gave 7-(2-bromoethyl) indoline (XLVII) as its hydrobromide.

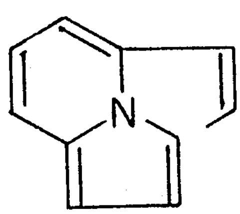
7-(2-Bromoethyl) indoline (XLVIIA) was found to be rather resistant to cyclization. This base when treated with sodium triphenylmethyl in ether gave no recognizable material. Whereas 2-(2-chloroethyl) aniline gave indoline on treatment with dilute aqueous alkali (20), 7-(2-bromoethyl) indoline gave only 7-(2-hydroxyethyl) indoline (XLVI) under the same conditions. However, addition of a solution of the bromo indoline to a suspension of sodium hydride in refluxing toluene gave a steam volatile base in low yield. This base (m.p. 22.5-23°) gave a picrate (m.p. 184-186°) and possessed the correct infrared spectral characteristics. Potentiometric titration of the


COOH
NO2
COOH
XLI
CH2CO2CH3
NO2
CH2CO2CH3
XLII
N
H
O
CH2CO2CH3
XLIII
N
H
O
CH2CH2OH
XLIV
+
N
H
CH2CH2OH
XLV
+
N
H
CH2CH2OH
XLVI
N
H
CH2CH2OH
N
H
. Br
CH2CH2Br
XLVII

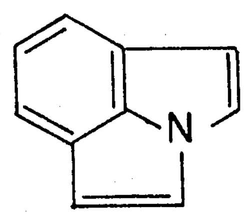


XLVIIA

II



XLVIII



XLIX

base gave an equivalent weight of 152 (calculated-145) and a pK_A of 4.9. Although the base was shown to be homogenous by vapour phase chromatography the microanalyses for both the base and its picrate were not satisfactory. This was attributed to the fact that the base rapidly decomposed in air. The ultraviolet spectrum of the base in ethanol indicated the presence of an aniline chromophore ($\lambda_{max}^{ethanol}$, 296 $m\mu$, log ε, 3.30) as was expected for 1,2-dihydropyrrolo [3,2,1-hi] indole (II). However, on standing in strongly acidic solution, the aniline chromophore disappeared and a new absorption in the visible (λ_{max} 370 $m\mu$) appeared. This behaviour was thought possibly to be due to some diprotonated species which was not described. Since only a very small amount of the base was available, it was not possible to investigate its properties and confirm its structure. Later work (presented in this thesis) indicates that the tricyclic base probably was obtained, although in rather impure condition.

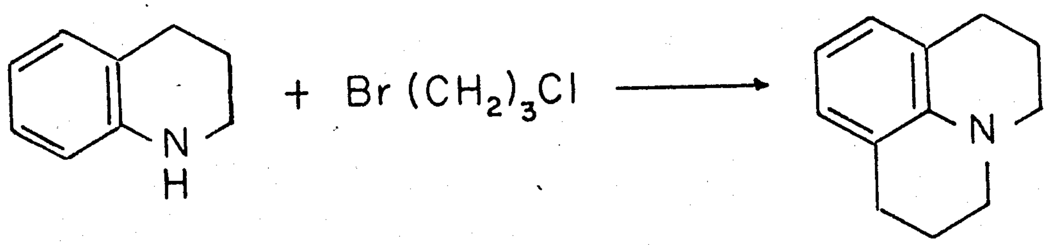
Recently Boekelheide and coworkers (21,22) have synthesised pyrrolo [2,1,5-cd] indolizine (XLVIII) a new type nitrogen heterocyclic system. It is of interest because not only does it fall in the class of 5,5,5 fused ring systems containing no more than one hetero atom, but in addition quantum mechanical calculations predict (21,22) and its chemical reactions and physical properties demonstrate its aromaticity (21,23). Furthermore it is isomeric with pyrrolo [3,2,1-hi] indole (XLIX) the synthesis of a derivative of which constitutes a portion of this thesis.

DISCUSSION

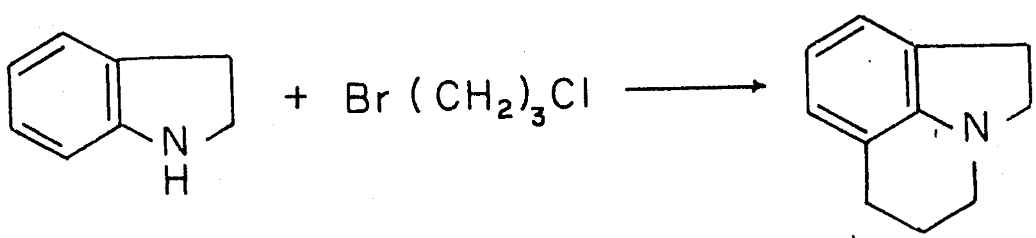
The possibility that 1,2,4,5-tetrahydropyrrolo[3,2,1-*hi*]-indole (III) had been prepared previously in this laboratory (17) required confirmation, and part of this work was repeated as described later in this section of the thesis. At this point, those synthetic approaches to the tricyclic system which were unsuccessful or abandoned for other reasons will be discussed.

Julolidene (I) the analogue of III containing three mutually fused six-membered rings is readily prepared by heating a mixture of tetrahydroquinoline and trimethylene chlorobromide (24,25,30). Substitution of trimethylene dibromide does not result in significant diminution of the yield of julolidene (27). Lilolidene (II) can be prepared in an entirely similar manner from indoline and trimethylene chlorobromide. Not unexpectedly, indoline and dimethylene dibromide under the same conditions gave only starting materials and an intractable tar.

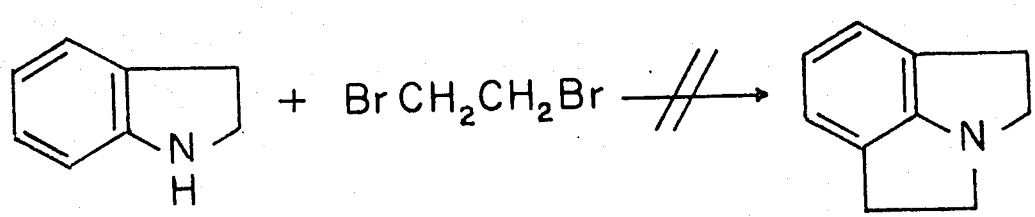
Previous work (17) indicated that 7-(2-bromoethyl)indoline and or the corresponding alcohol (formulae XLVII and XLVI of Introduction to Part I) were intermediates of paramount importance in the synthesis of III and several methods of obtaining these compounds were examined. Indoles such as IV and V would be useful precursors since saponification of the ester, followed by decarboxylation and reduction in the case of IV, and treatment with hypohalite followed by decarboxylation and reduction of V in both cases, should lead to the desired alcoholamine. 2-(2-Hydroxyethyl)aniline (VIII) which was required for the projected



I



II

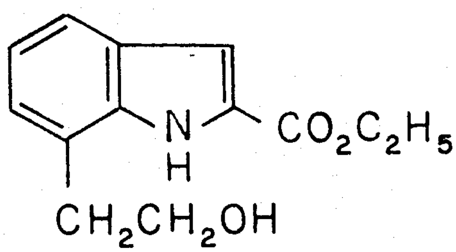


III

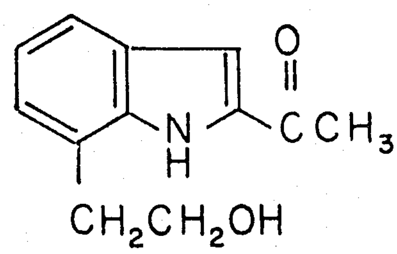
synthesis of the two indoles was prepared as described below. Following the method of Reissert (28) *o*-nitrotoluene was condensed with diethyl oxalate and the resulting ester saponified. The α-keto acid thus obtained was oxidized with alkaline hydrogen peroxide yielding *o*-nitrophenyl acetic acid which was converted to its ethylester (VI). Lithium aluminum hydride reduction of this nitro ester gave a mixture of the azo compound (VII) and 2-(2-hydroxyethyl) aniline which was not separated but treated directly with hydrazine hydrate and Raney nickel (29). The desired alcohol was thus obtained in 45% yield based on *o*-nitro toluene. This synthesis, despite its length, possesses the distinct advantages that the alcoholamine is isomerically pure and available in a yield far superior to that obtained from the nitration product of β -phenyethanol (20,30).

When diazotized 2-(2-hydroxyethyl) aniline (VIIIA) was treated at p_H 6 with a solution of the sodium salt of α-methyl acetoacetic acid a crystalline hydrazone (IX) was isolated in 57% yield. Similary, if the same diazonium salt was treated with an alkaline solution of ethyl-α -methylaceto-acetate another hydrazone (X) was obtained in somewhat poorer yield. The fact that neither of the modifications of the Japp-Klingemann (31) reaction gave a good yield of the corresponding hydrazone and since purification of these compounds was laborious (see experimental), their cyclization to indoles (IV) and (V) was not investigated.

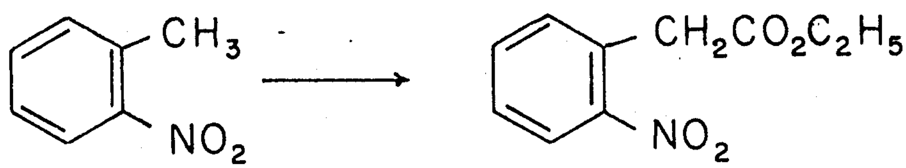
The ready availability of 2-(2-hydroxyethyl) aniline from *o*-nitrotoluene led us to attempt a similar series of reactions on 1,3-dimethyl-2-nitrobenzene with the idea that the resulting 2,6-di (2-



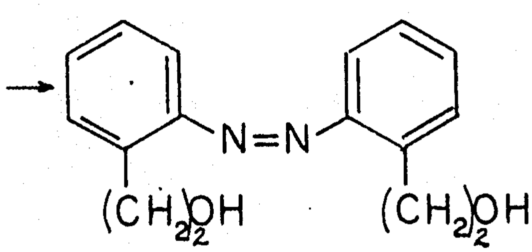
IV



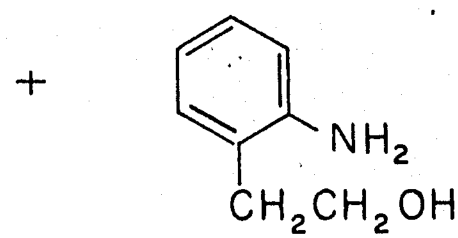
V



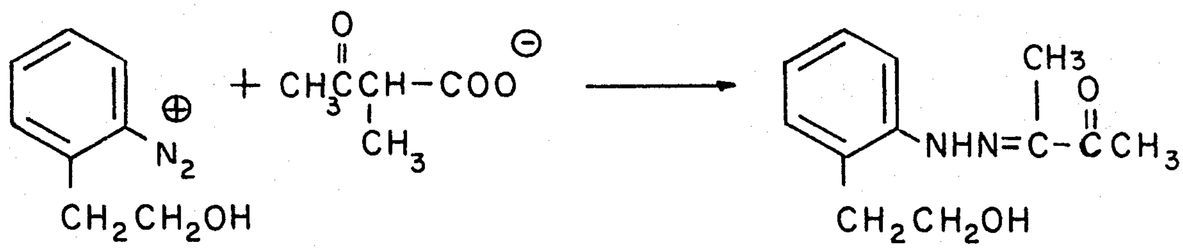
VI



VII

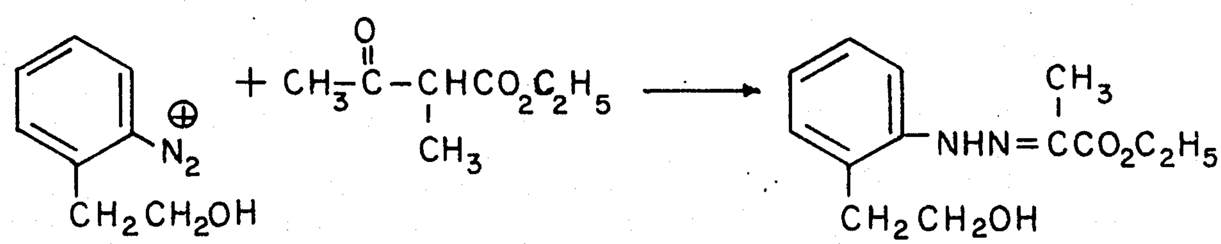


VIII


CH3
O
NHN=C-CCH3
CH2CH2OH
O
CH3CCH-COO
CH3
N2
CH2CH2OH

VIIIA

IX

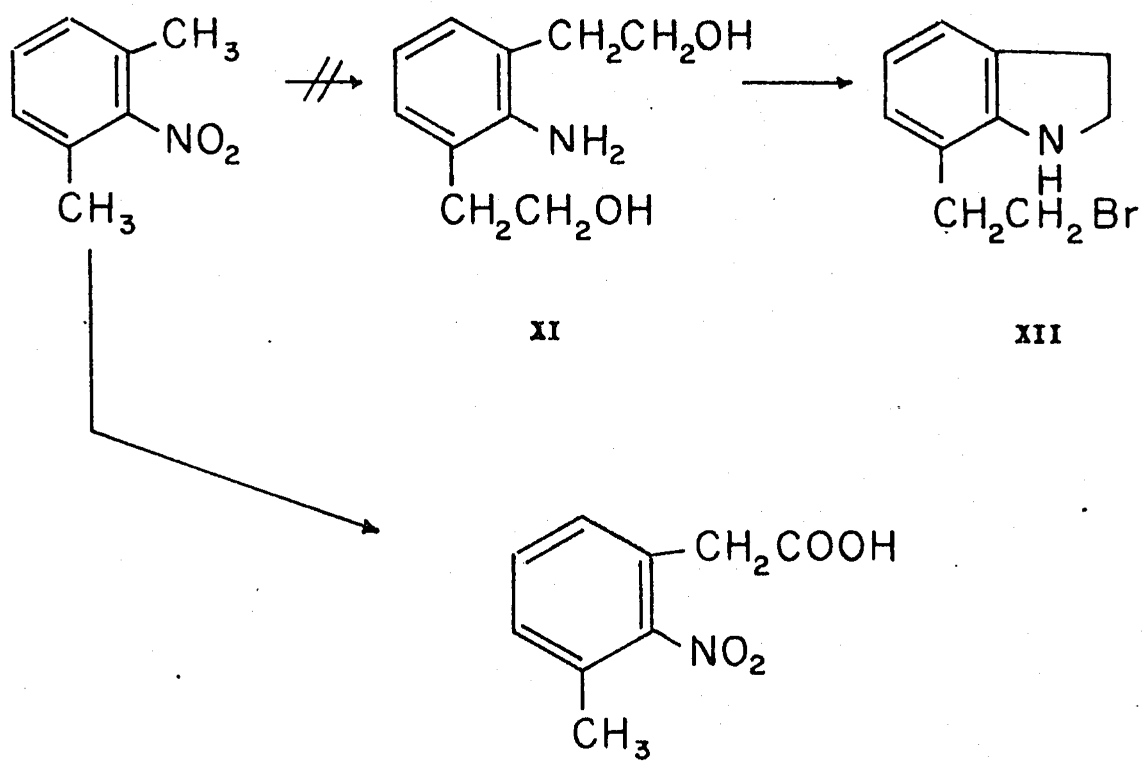

O
CH3-C-CHCO2C2H5
CH3
N2
CH2CH2OH
CH3
NHN=CCO2C2H5
CH2CH2OH

X

hydroxyethyl) aniline (XI) could be easily converted to 7-(2-bromoethyl) indoline (XII). When 1,3-dimethyl-2-nitrobenzene and diethyl oxalate were subjected to the usual Reissert conditions no condensation could be effected. When the reaction was carried out in ethereal potassium ethoxide (instead of sodium ethoxide in ethanol), a keto acid which was not characterized, was isolated in low yield. This acid on oxidation with alkaline hydrogen peroxide gave only a mono carboxylic acid whose equivalent weight and carbon-hydrogen analysis were in good agreement with that expected for 2-nitro-3-methyl phenylacetic acid (XIII). In support of these results Anet and Nishizawa (17) were unable to carry out allylic bromination of 1,3-dimethyl-2-nitrobenzene past the mono-bromo stage even under forcing conditions.

The necessity to confirm previous work carried out in this laboratory has already been mentioned. Accordingly, 7-carbomethoxymethyl oxindole was prepared following the synthetic pathway previously outlined (see formulae (XLI)-(XLVII) in Introduction to Part I of this thesis). Lithium aluminum hydride reduction gave a mixture of the same three alcohols in agreement with the aforementioned experimental results. Since reduction of the mixture of the above alcohols was considered to be lengthy, and in addition the yield of 7(2-hydroxyethyl) indoline (XLVI, Introduction, Part I) obtained in this way was poor, this approach to 7-(2-bromoethyl) indoline (XII) was abandoned.

It appeared reasonable to us that (XII) should be available via the reaction sequence pictured below. 1,3-Di(carbomethoxymethyl)-2-nitrobenzene (XIV, 17) on lithium aluminum hydride reduction was expected



XI

XII

XIII

to give the azo compound (XV) which should be reduceable by known methods to 2,6-di(2-hydroxyethyl) aniline (XI). Much to our surprise no azo compound was formed; instead the desired amino di-ol was isolated in 54% yield. This reduction was completely unexpected since it has been reported (32-36) that aromatic nitro compounds on lithium aluminum hydride reduction give rise to the corresponding azo compound exclusively. Indeed, the immediate appearance of a red "azo" color on treatment of an ether solution of lithium aluminum hydride with an aromatic nitro compound has been suggested as a sensitive test for such compounds (32, 37, 38).

To test the generality of the reaction several mono-and di-ortho substituted nitro benzenes were reduced (see Table I). Obviously, the increase in amine formation parallels increasing steric hindrance around the nitro group. The formation of azo compounds is known to take place by the condensation of the nitroso compound and the hydroxylamine or the amine (39) and these reactions would be expected to be sensitive to steric hindrance. The 1,3-disubstituted-2-nitrobenzenes investigated gave mainly the amine. On the other hand Nystrom and Brown (32) report a 71% yield of azomesitylene, but in our hands 81% mesidene and 11% azo-mesitylene were obtained on reduction of nitromesitylene, even under conditions identical with those given by these workers.

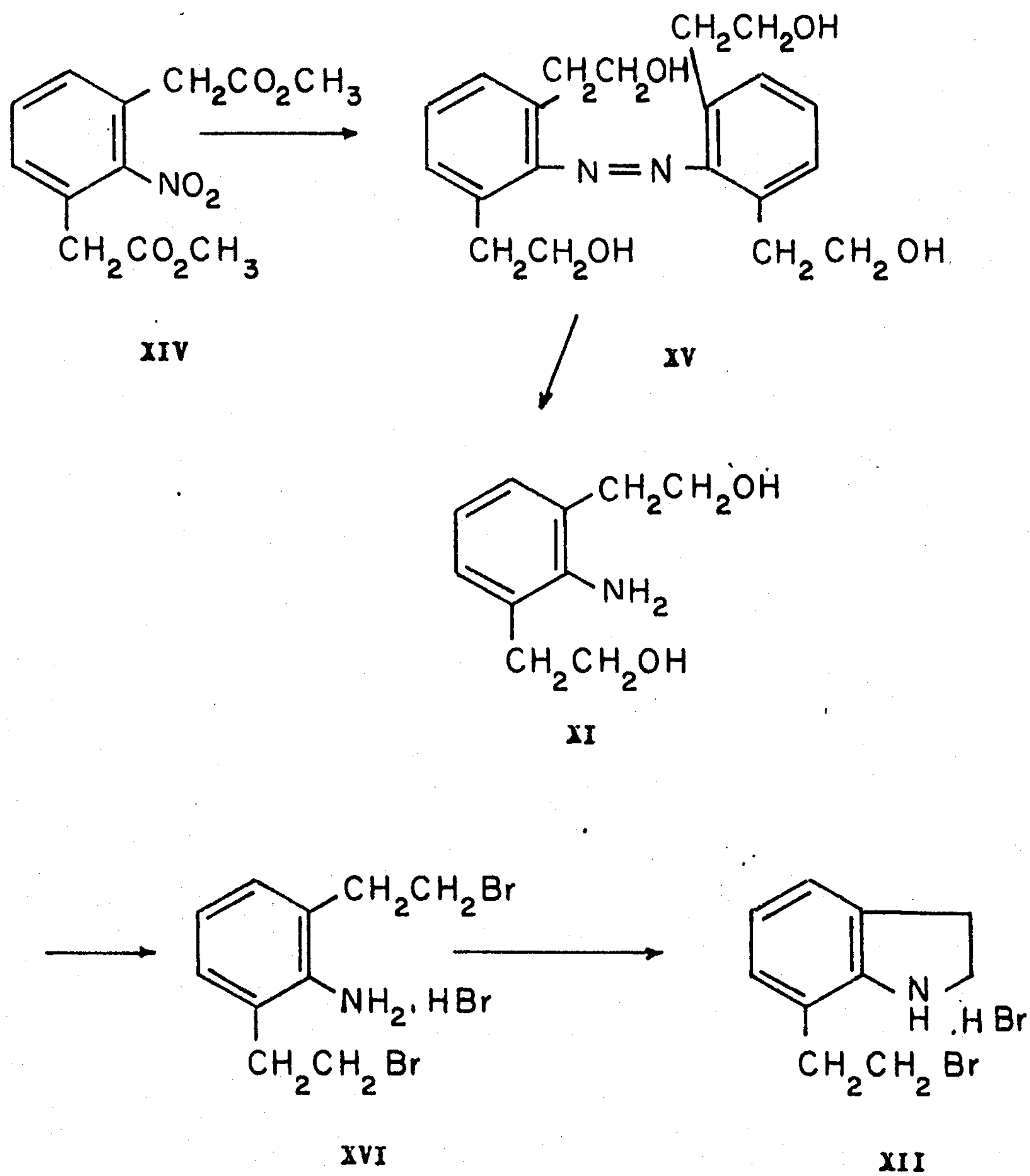

CH2CO2CH3
NO2
CH2CO2CH3
XIV
CH2CH2OH
CH2CH2OH
N=N
CH2CH2OH
CH2 CH2 OH
XV
CH2CH2OH
NH2
CH2CH2OH
XI
CH2CH2Br
NH2. HBr
CH2CH2 Br
XVI
N
H
.H Br
CH2CH2 Br
XII

TABLE I

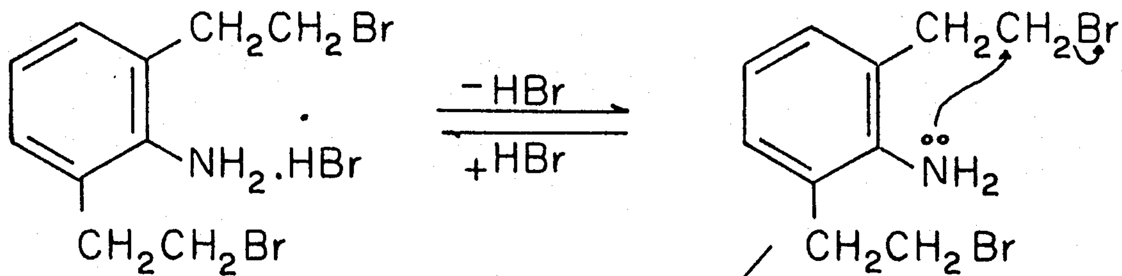
Reduction Products of some Aromatic Nitro Compounds with Lithium Aluminum Hydride.

Nitro Compound	Products (%)	
	Azo Derivative	Amine
Nitrobenzene	78.3	0.0
o-Nitrotoluene	46.0	26.5
o-Nitro-β-phenylethanol	41.0	31.0
1,3-Dimethyl-2-nitrobenzene	21.0	53.0
Nitro mesitylene	11.0	61.0
1,3-Di(methoxycarbonyl)-2-nitrobenzene	0.0	44.0
1,3-Di(methoxycarbonylmethyl)-2-nitrobenzene	0.0	54.0

It appears such anomalous reductions are not completely unknown. Ried and Müller (40) obtained 4,4'-diaminoazobenzene by lithium aluminum hydride reduction of 4,4'-dinitroazobenzene, however, in this case amine formation cannot be due to steric hindrance. Adams et al (41) were unable to reduce 3-chloro-2-nitroanisole to the azo derivative. They do not, however, mention what, if any, product was isolated. Wiberg and Jahn (42) have reported the formation of o-toluidine from o-nitrotoluene by reduction with lithium aluminum hydride, but only in the presence of aluminum chloride. In the absence of aluminum chloride o-azotoluene was the main product.

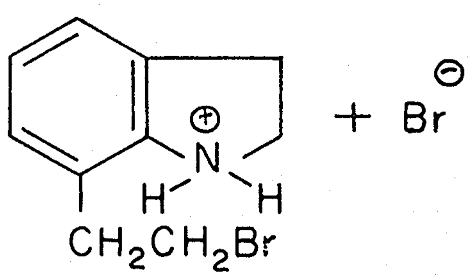
When 2,6-di(2-hydroxyethyl) aniline (XI) was treated with boiling concentrated hydrobromic acid none of the expected dibromo hydrobromide (XVI) was formed. Surprisingly enough, the required 7-(2-bromoethyl) indoline, as its hydrobromide (XII), identical in every respect to that prepared by Anet and Nishizawa was obtained. Formation of this compound can be explained if one assumes a small amount of the mono-or di-bromo base is in equilibrium with its salt, in which case the lone electron pair on the nitrogen atom would be expected to displace bromide ion by a nucleophilic attack on carbon 2 of one of the bromoethyl groups.

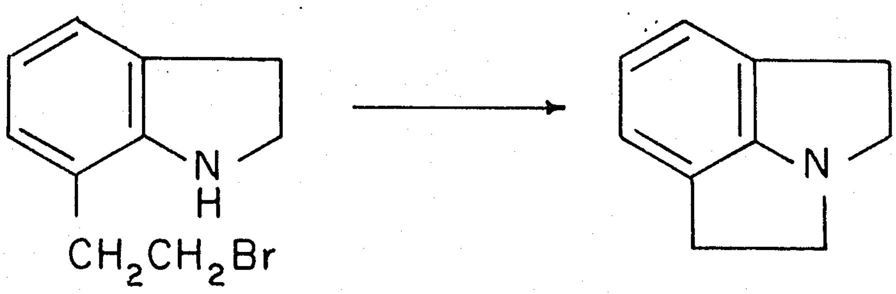
7-(2-bromoethyl) indoline (XIIA) now being readily available, the cyclization of this material was examined. Heating the bromoamine alone or in xylene caused extensive polymerization. However, when a dilute solution of the bromoamine in dry xylene was added slowly to a suspension of excess sodium hydride in boiling xylene, a steam volatile base (m.p. 32-33^{0}), purified via its sparingly soluble picrate, was obtained in 18-24% yield. The base was assigned the structure indicated (III) on the basis of its analysis, molecular weight, and spectral characteristics. Its infrared spectrum (Fig.1) proved the absence of OH or NH groups. The N.M.R. spectrum (43) showed bands for three aromatic protons (seven lines of an AB_2 system with "A" at 6.40 p.p.m., "B" at 6.08 p.p.m., and J = 7.10 c.p.s), and eight methylene protons (3.11 p.p.m). Although the chemically different methylene protons gave only a single peak in carbon tetrachloride solution, a slight chemical shift between them was observed in benzene solution (complex multiplet due to an A_2B_2 spin-spin system). The ultraviolet spectrum of the base in ethanol showed the presence of an aniline chromophore, while in acid solution,



XVI

XII





III

XIIA

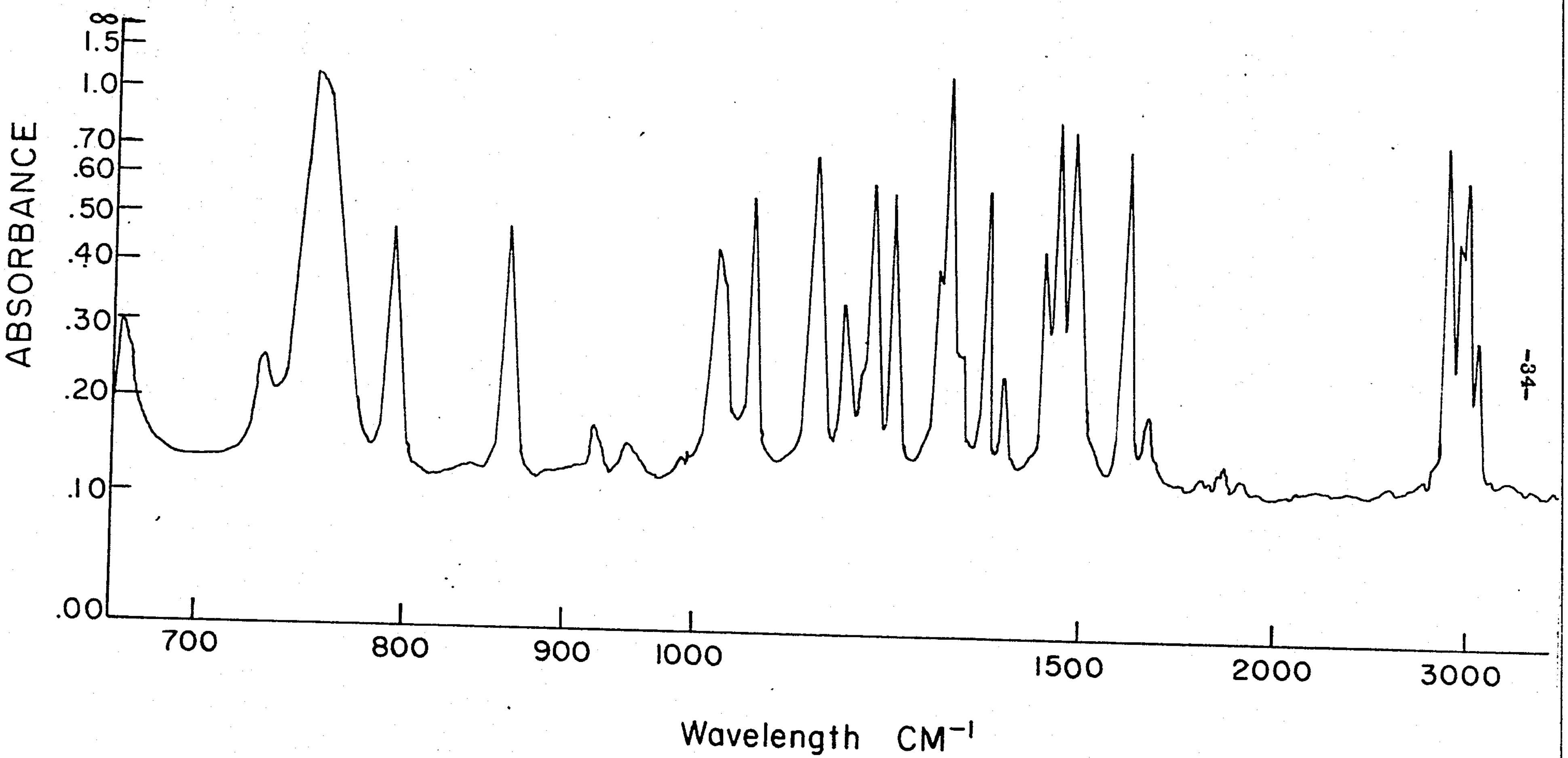


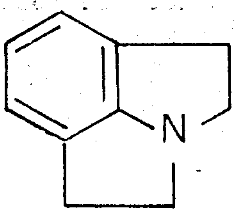
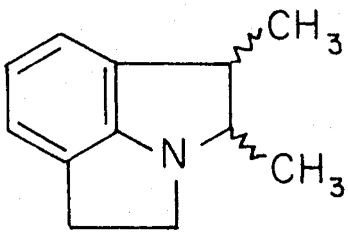
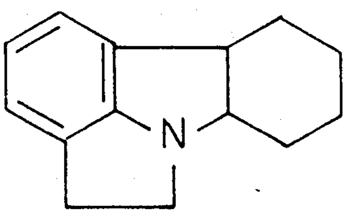
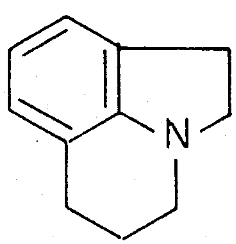
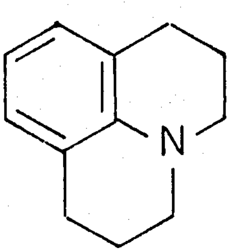
Fig.1. Infrared spectrum (liquid film) of 1,2,4,5-tetrahydropyrrolo[3,2,1-hi]indole.

only benzenoid absorption was present (Table II and Fig.2). No evidence whatsoever of an absorption band at 370 mμ was observed (17), even after long standing in concentrated hydrochloric acid.

The base had a pK_A of 4.10 (in 50% aqueous-ethanol) which was higher than that of both lilolidene (3.08) and julolidene (3.68). Although these results could not have been predicted beforehand, examination of Courtauld models of 1,2,4,5-tetrahydropyrrolo [3,2,1-hi] indole (A) and julolidene (B) brought to light several pertinent points. Whereas A was almost planar, four carbon atoms of B were out of the plane of the benzene ring; the net result of this being A possessed a significant amount of strain while B was relatively strainless. The observed pK_A values can then be rationalized as follows: with reference to base A delocalization of the lone electron pair of the nitrogen atom must necessarily result in a shortening of the benzene-nitrogen bond with a net increase in strain energy. Forcing the nitrogen atom into a tetrahedral configuration (i.e. protonation) also increases strain, but this effect must undoubtedly be more than compensated by the decrease in strain due to loss of double bond character in the benzene-nitrogen bond. Models indicate the conjugate acid of A once formed should be relatively easily solvated. Both of these effects would increase the basic strength of A over that of B, since in the latter the strain resulting from formation of a partial double bond between the aromatic ring and the nitrogen atom is easily absorbed by buckling of the two saturated six-membered rings. As a result, relative to A, no significant lowering of energy occurs on protonation of B. Indeed, the experimental results indicate that delocalization

TABLE II

Ultraviolet spectra of 1,2,4,5-tetrahydropyrrolo [3,2,1-*hi*] indole and related compounds.

Compound	Solvent	max (mμ).	log ε
	ethanol	246 296	3.80 3.36
	50% aqueous-ethanol (0.22N in HCl)	262 268	2.43 2.68
	ethanol	247 296	3.82 3.39
	ethanol	248 296	3.78 3.33
	ethanol	251 296	3.85 3.39
	ethanol	267 310	3.83 3.33

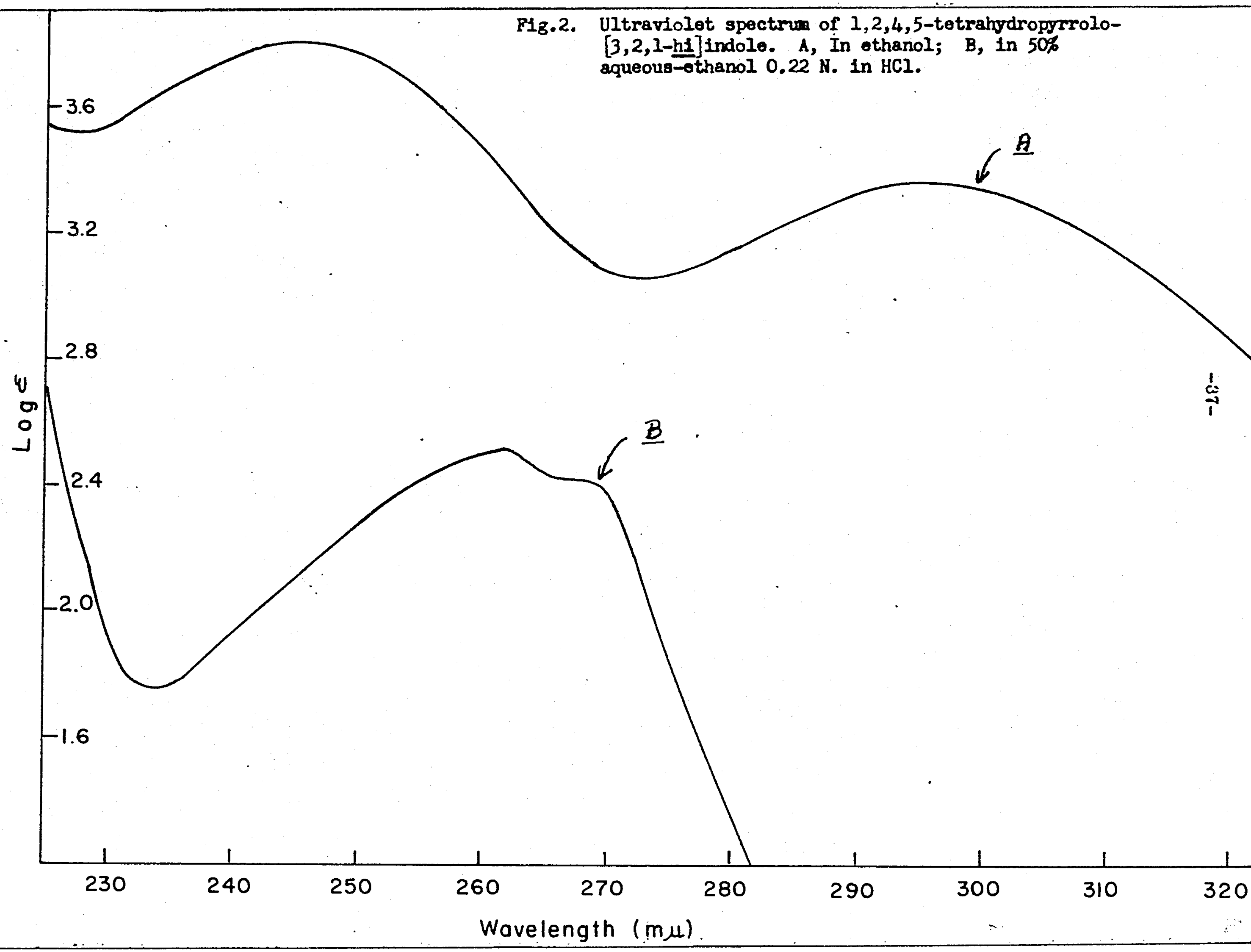
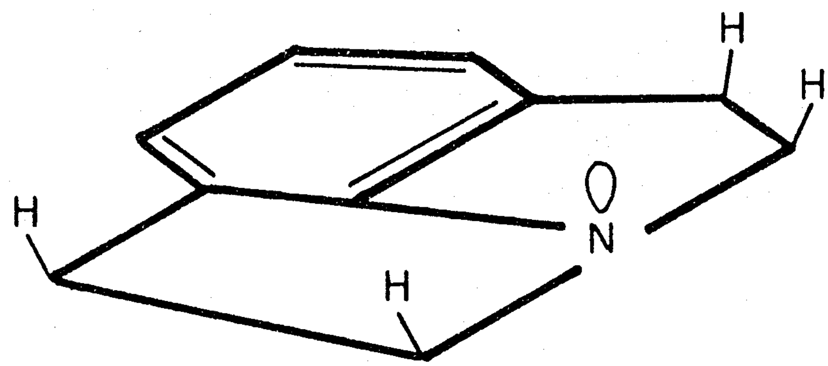
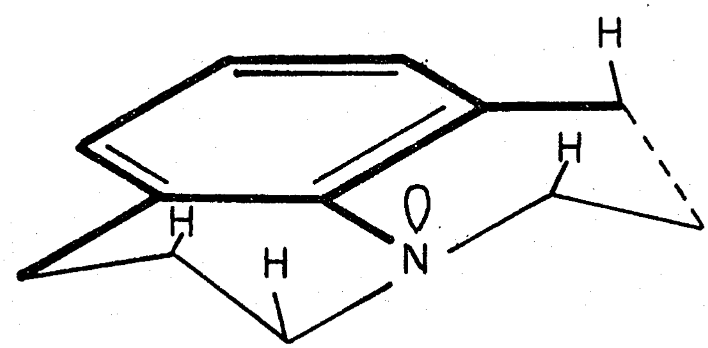


Fig.2. Ultraviolet spectrum of 1,2,4,5-tetrahydropyrrolo-[3,2,1-hi]indole. A, In ethanol; B, in 50% aqueous-ethanol 0.22 N. in HCl.



A



B

of the lone electron pair of the nitrogen atom in B as compared to A is far more important. In addition consideration of the model of the conjugate acid of B indicates solvation to be less favourable in this case. Both of these effects would decrease the basic strength of B relative to A.

If similar reasoning is applied to lilolidene, which possesses one six and one five-membered ring, a pK_A value intermediate between A and B should be observed. This was borne out by experimental fact.

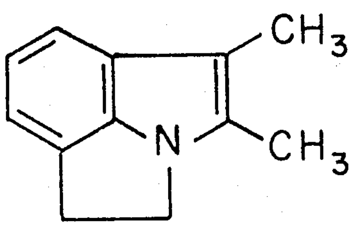
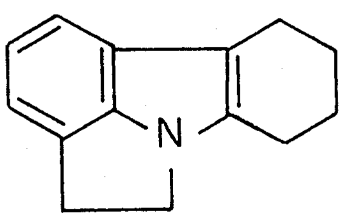
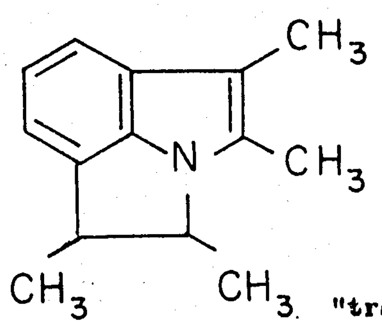
It is known that inhibition of resonance of the type described results in an hypsochromic shift of the long wavelength absorption band (ultraviolet or visible) sometimes accompanied by a decrease in absorption intensity (44). The ultra violet spectra of 1,2,4,5-tetrahydropyrrolo [3,2,1-hi] indole, lilolidene, and julolidene (see table II) are in accordance with these predictions in that the long wavelength band shifts to shorter wavelength with increasing strain.

Other than its high pK_A value, 1,2,4,5-tetrahydropyrrolo [3,2,1-hi] indole possessed no unusual properties. At room temperature it underwent slow decomposition to a brown non-distillable tar, but was indefinitely stable in the cold. In contrast to its carbocyclic analogue, the base was completely inert to catalytic hydrogenation over 5% palladized carbon at room temperature and atmospheric pressure. Furthermore, it could be recovered from concentrated hydrobromic acid even after prolonged contact at reflux temperature.

For comparison purposes two models of the above base were synthesised as described below. Utilizing conditions slightly modified

TABLE III

Ultraviolet spectra of some derivatives of 1,2-dihydropyrrolo-[3,2,1-*hi*] indole.

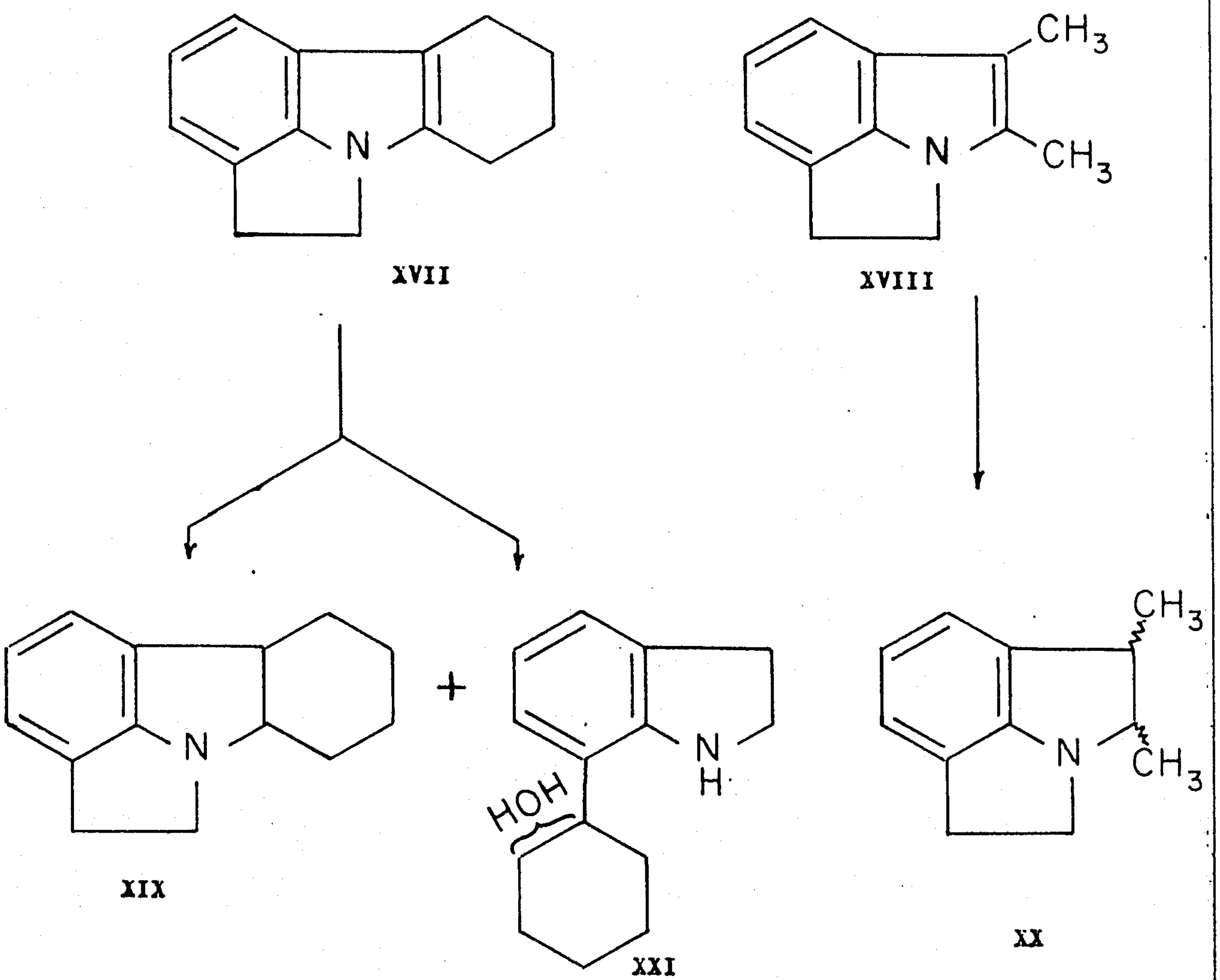
Compound	$\lambda_{max.}^{ethanol}$ (mμ)	log. ε
	234 292	4.42 3.76
	234 292	4.44 3.82
 "cis"	234 290	4.37 3.89
"trans"	234 292	4.40 3.89

from those previously reported (4,5,6,14,15), 1-aminoindoline when heated with cyclohexanone or methyl ethyl ketone provided XVII and XVIII respectively (see Table III for the ultraviolet spectra of these compounds). The properties displayed by XVII agreed with those reported by other investigators (5,6). Reduction of these compounds with tin in ethanolic hydrochloric acid (Tetrahydrocarbazole was known to suffer reduction in the presence of these reagents (45)) produced bases XIX and XX. The ultraviolet spectra (Table IV) and the chemical behaviour of these bases closely resembled that of the parent compound.

In addition to XIX a compound thought to be 7(1-or-2-hydroxycyclohexyl)indoline (XXI) was obtained from XVII in low yield. This material was basic, analysed correctly for $C_{14}H_{19}ON$, and its infrared spectrum possessed OH and NH stretching absorptions at 3603 and 3408 cm^{-1} respectively. Its structure was not further investigated.

No compound analogous to XXI was isolated from the reduction product of XVIII, nor was the stereochemistry of the base (XX) determined.

Several facts lend support to the probability that Anet and Nishimura obtained the tricyclic base (III). 7(2-Bromoethyl)indoline, the immediate precursor of III, synthesized by these workers, was identical to ours prepared by a different route. The ultraviolet spectra of the reported base and III are nearly superimposable. The melting points of the reported base and its picrate are somewhat lower than those determined by us, but the analytical results stated for these compounds indicate their lack of purity. In addition the ultraviolet spectrum of the reported compound in acid solution possessed a strong absorption band at 370 mμ indicating the presence of an absorbing



XVII XVIII

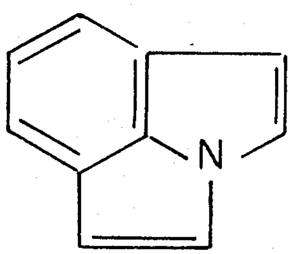
XIX + XXI XX

species other than the protonated form of III.

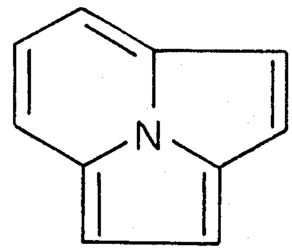
The successful synthesis of 1,2,4,5-tetrahydropyrrolo [3,2,1-*hi*] indole led us to attempt the preparation of the completely unsaturated pyrrolo [3,2,1-*hi*] indole (XXII) or a derivative thereof. Compounds containing this ring system would be of interest since models indicate even greater strain than the corresponding tetrahydro analogues. Furthermore, the parent compound is isomeric with cycl [3,2,2] azine (XXIII)(21,22) which has been shown to possess aromatic properties (21,23).

Derivatives of 1,2-dihydropyrrolo [3,2,1-*hi*] indole (XXIV) being readily available, prompted us to examine their susceptibility towards catalytic dehydrogenation. As a model 1,2,6,7,8,9-hexahydropyrrolo [3,2,1-*jk*] carbazole (XVII) was subjected to catalytic dehydrogenation. over 10% palladised charcoal in boiling *p*-cymene. Chromatography on alumina gave, besides starting material, a crystalline solid to which was assigned structure XXV on the basis of its analysis and spectral characteristics. The infrared spectrum demonstrated the absence of NH and OH functions, while its ultra violet spectrum was not unlike that of carbazole (46). That the product possessed structure XXV and not XXVI was proved conclusively by the N.M.R. spectrum which showed seven aromatic protons (complicated multiplet at 6.87-7.98 p.p.m) and four methylene protons as a pair of triplets (centered at 3.61 and 4.25 p.p.m) predicted for an A_2B_2 system approaching the A_2X_2 limit (55).

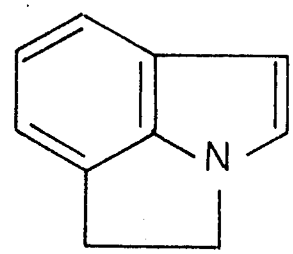
Catalytic dehydrogenation of 1,2-dihydro 4,5-dimethylpyrrolo [3,2,1-*hi*] indole (XVIII) was also unsuccessful. 5% Palladium on



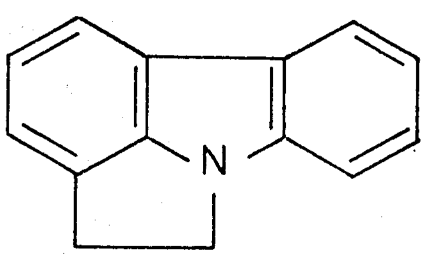
XXII



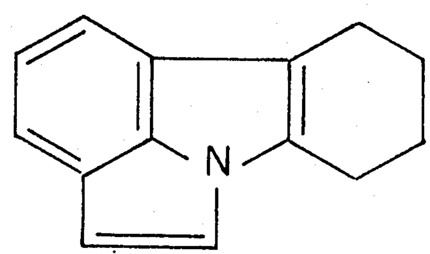
XXIII



XXIV



XXV

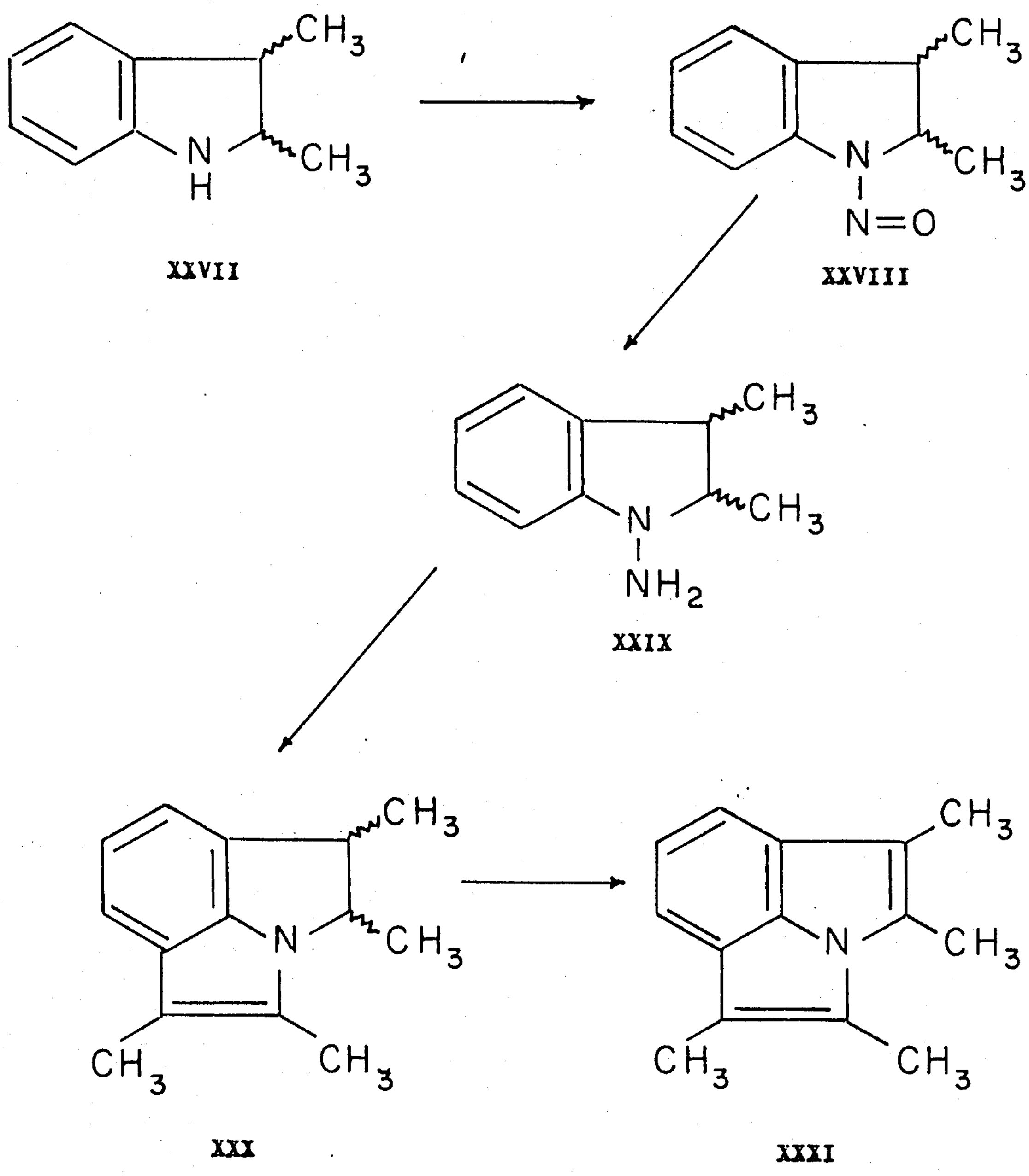


XXVI

charcoal was without effect, while 10% palladized carbon gave only an oily material possessing NH absorption in the infrared indicative of ring change.

It was hoped a 1,2,4,5-tetraalkyl derivative of XXIV would be less prone to ring opening, and since the N.M.R. spectrum of the expected product would be particularly simple we chose to attempt synthesis of the 1,2,4,5-tetramethyl analogue of XXII. Accordingly, 2,3-dimethyl indole was prepared by thermal cyclization (47) of butanone-2-phenylhydrazone. Since carbazole was known to form an isolable N-amino compound, which in turn formed cyclizable hydrazones. (13), it was thought conceivable 2,3-dimethylindole might exhibit similar behaviour. Although 2,3-dimethylindole formed a stable 1-nitroso derivative, the N-amino compound could not be prepared, nor could it be trapped as a hydrazone when the reduction was carried out in presence of methylethyl ketone. In both cases reductive deamination resulting in recovery of the indole occurred.

The series of reactions described below was then applied to the synthesis of XXXI. 2,3-Dimethyl indoline was obtained by reduction of 2,3-dimethyl indole with tin and ethanolic hydrochloric acid. The stereochemistry of the reduction was not determined at this time and consequently that of the intermediates leading to XXXI was not known. Nitrosation of the indoline followed by reduction of the product (XXVIII) with lithium aluminum hydride gave the hydrazine (XXIX). Heating the hydrazine and methylethyl ketone yielded a low melting solid whose N.M.R. spectrum indicated the presence of two isomers. Careful fractional



CH3
CH3
N
H
XXVII
CH3
CH3
N
N=O
XXVIII
CH3
CH3
N
NH2
XXIX
CH3
CH3
N
CH3
CH3
XXX
CH3
CH3
N
CH3
CH3
XXXI

crystallization of the product from aqueous-ethanol gave a single sharp melting crystalline substance which was later shown to be the cis-isomer of XXX. When this compound was heated in p-cymene in presence of 10% palladium on carbon a mixture was obtained from which 1,2,4,5-tetramethylpyrrolo [3,2,1-hi] indole (XXXI) was isolated by chromatography on alumina in about 20% yield. XXXI Was a stable, crystalline, neutral solid which gave an intense purple color with tetracyanoethylene, and was completely unaffected by hydrogen over 10% palladised carbon at room temperature and atmospheric pressure. The ultra violet spectrum (Fig.3) indicated greater conjugation than that present in a simple indole chromophore (46) and the infrared spectrum (Fig.4) proved the absence of a NH group. In addition, the N.M.R. spectrum showed the presence of three aromatic protons (seven lines of an AB_2 system with "A" at 6.69 p.p.m, "B" at 6.84 p.p.m and J= 7.12 c.p.s) and four methyl groups (2.11 and 2.13 p.p.m) directly attached to unsaturated carbon.

Besides XXXI, four other compounds all of which possessed NH stretching bands in the infrared spectrum, were obtained. These substances were not characterized, but their formation, and the low yield of XXXI indicate the tricyclic systems in question are particularly susceptible to rupture of one of the five-membered rings.

Since the configuration of the intermediates leading to 1,2,4,5-tetramethylpyrrolo [3,2,1-hi] indole was not known, it was necessary to establish the stereochemical path of reduction of 2,3-dimethyl indole. Previous investigations concerning the stereoisomeric 2,3-dimethyl indolines is at best confusing. Hayashi (48) prepared

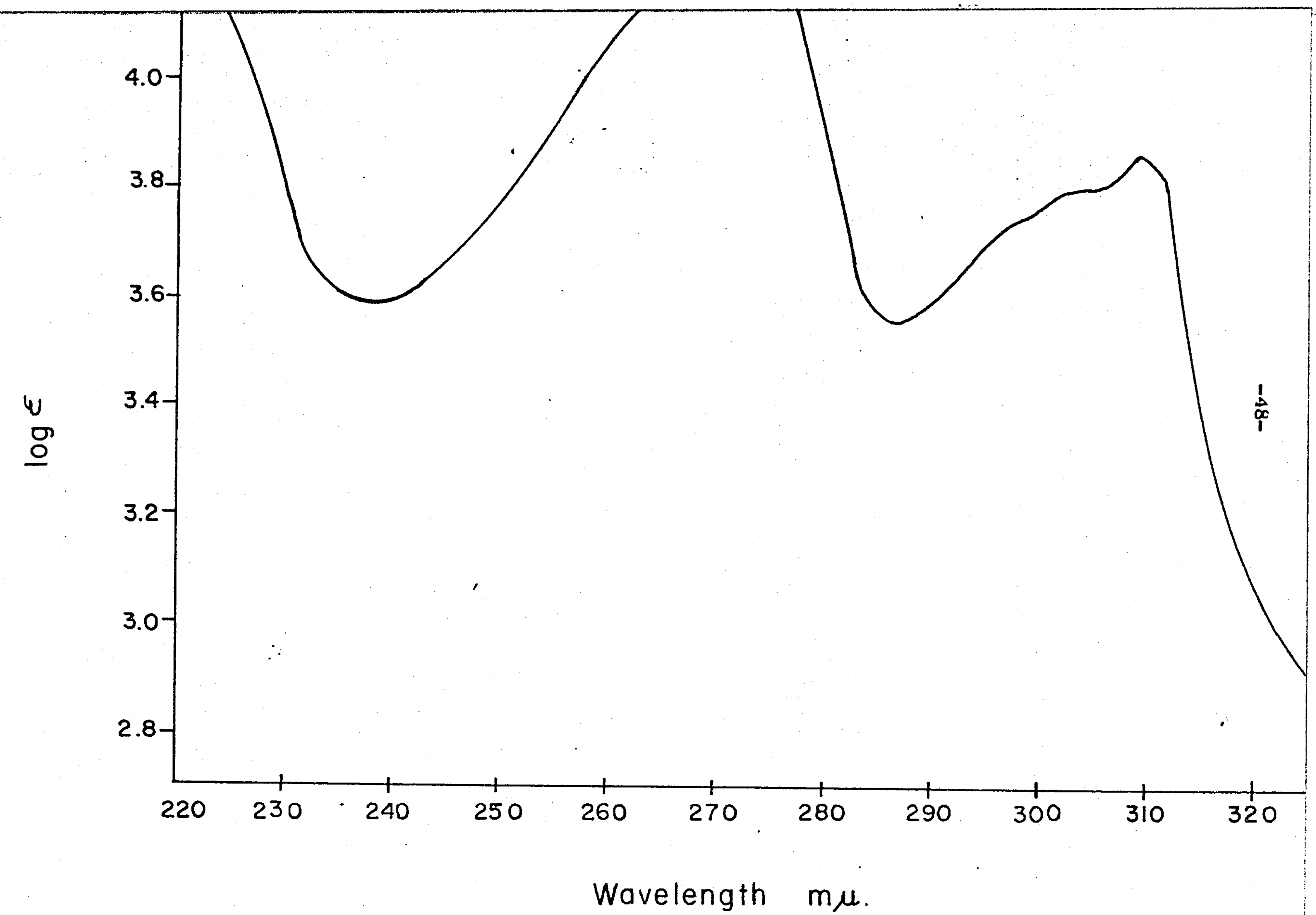


Fig.3. Ultraviolet spectrum of 1,2,4,5-tetramethylpyrrolo[3,2,1-*hi*]indole in ethanol.

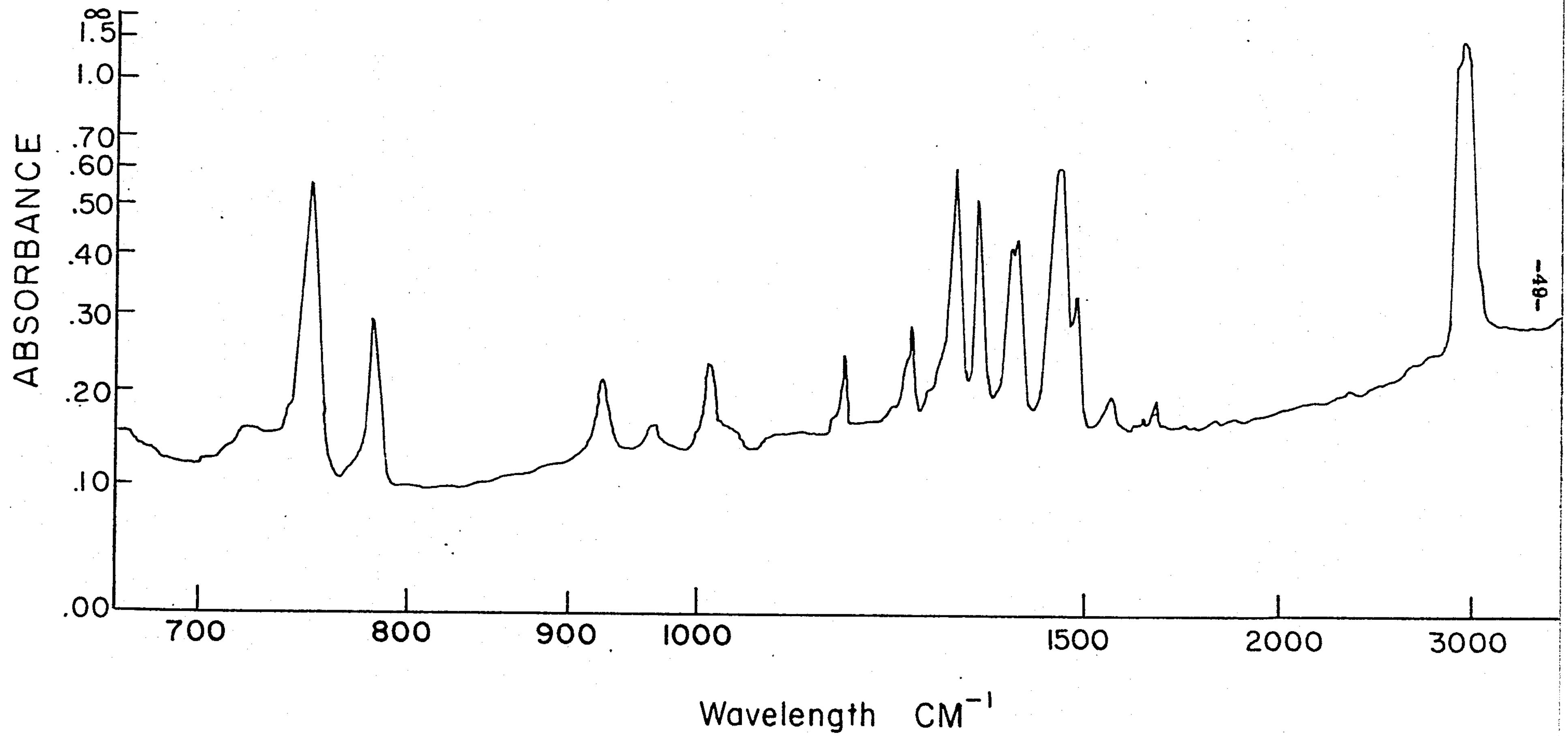


Fig.4. Infrared spectrum (nujol mull) of 1,2,4,5-tetramethylpyrrolo[3,2,1-hi]indole.

2,3-dimethyl indoline by electrolytic or zinc and hydrochloric acid reduction of the corresponding indole, but was unable to fractionally crystallize a large number of its derivatives. Hayashi therefore concluded only one isomer was formed although he hesitated to specify which one. Adkins and Burks (49) catalytically reduced 2,3-dimethyl indole over copper chromite but did not investigate the products' stereochemical composition. Hyre and Bader (50) showed 2,3-dimethylindoline was one of the products obtained from the polyphosphoric acid catalysed cyclization of N-crotylaniline. This indoline formed a benzenesulfonamide (m.p. 101-103°) different from the benzenesulfonamide (m.p. 70-71°) prepared by the action of zinc dust and hydrochloric acid (51) on 2,3-dimethylindole. For reasons that do not appear valid, they state the former was the <u>cis</u>-isomer (XXXII) while the latter possessed the <u>trans</u>-configuration (XXXIII).

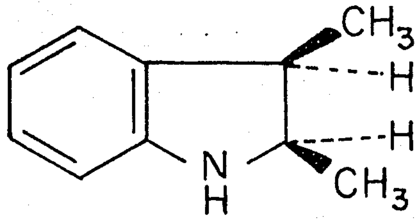
2,3-Dimethylindoline was prepared in this laboratory by reduction of the corresponding indole with tin and ethanolic hydrochloric acid. Vapor phase chromatography of the product showed the presence of two components in roughly equal amounts, and the N.M.R. spectrum was in agreement with this observation.

The picrates prepared from the above mixture could not be separated by fractional crystallization, instead a single crystalline solid (m.p. 137°) was obtained. A N.M.R. spectrum of the base isolated from this derivative was practically identical to that of the starting mixture.

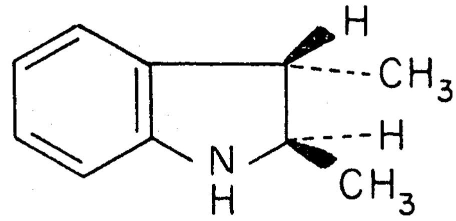
Although two sharp melting hydrobromides were obtained by fractional crystallization, these were shown to be isomerically impure by N.M.R. spectroscopy. The high melting derivative (m.p. 154-155°) consisted of two components in the ratio 4:1, while the low melting material (m.p. 138-139°) was an equimolar mixture.

When the mixture of _cis_- and _trans_- indolines was shaken with benzenesulfonylchloride and aqueous alkali a low melting solid was obtained. Careful fractional crystallization from high boiling petroleum ether resulted in isolation of two sharp melting solids. The high melting substance (m.p. 113-114°) was isomerically pure, while the low melting solid (m.p. 76-77°) was a 1:1 complex as shown by N.M.R. spectroscopy.

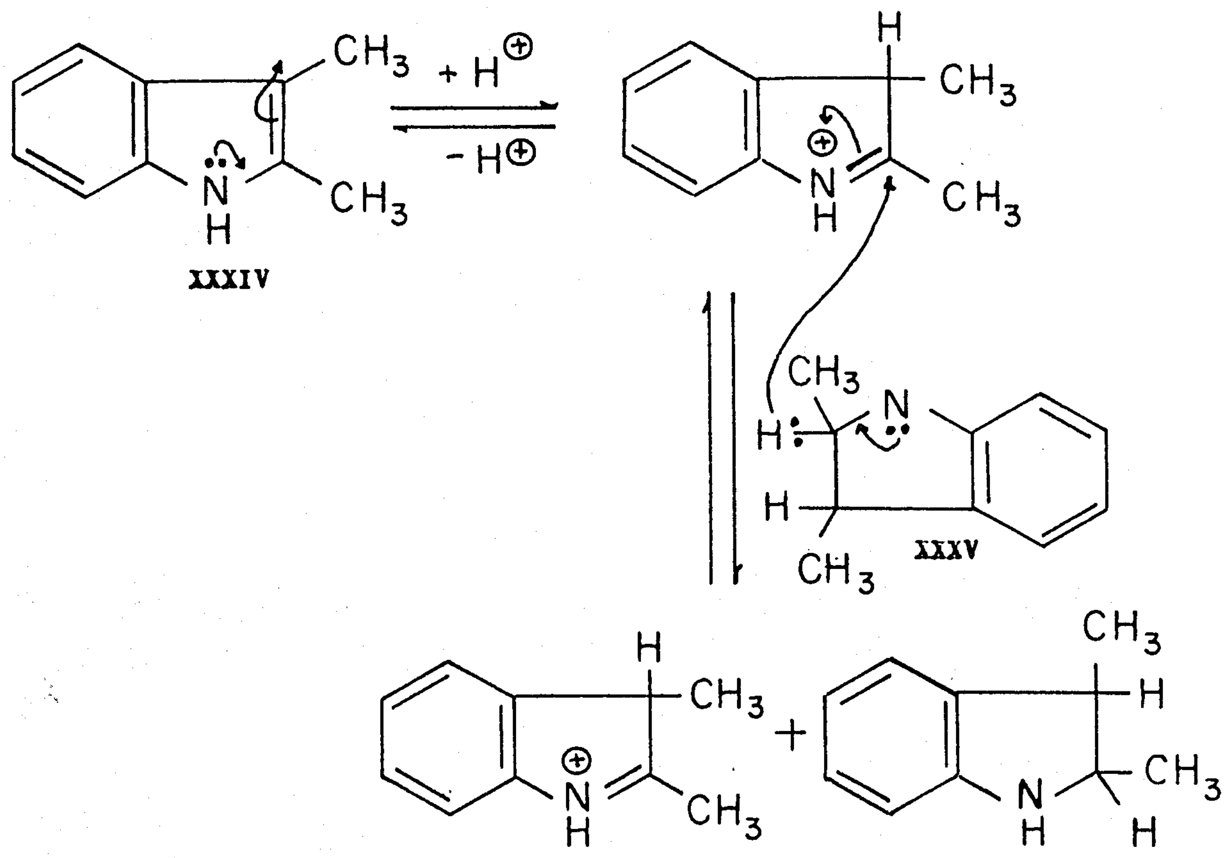
Previous work (50) suggested polyphosphoric acid might function as a dehydrogenation catalyst. From this we reasoned that in the presence of 2,3-dimethylindole, polyphosphoric acid could catalyse the bimolecular oxidation-reduction reaction illustrated below (XXXIV - XXXVI) resulting in predominant formation of the thermodynamically more stable isomer. Accordingly, the mixture of indolines was heated with polyphosphoric acid and a small amount of 2,3-dimethylindole. Fractional crystallization of the benzenesulfonamides obtained from this supposedly equilibrated mixture again gave two crystalline substances. The major product (m.p. 103°) was isomerically pure (as shown by N.M.R.) and different from the pure benzenesulfonamide (m.p. 113°) isolated from the reduction product of 2,3-dimethylindole. The crystalline material isolated in only small amounts (m.p. 76-77°) was identical to the 1:1 complex described previously.



XXXII



XXXIII



XXXIV

XXXV

XXXVI

The stereochemistry of the sulfonamides could not yet be assigned with certainty, although there was some justification for assuming the isomer (m.p. 103°) isolated as the major product from the equilibration reaction possessed the <u>trans</u>-configuration. This supposition was shown to be correct in the manner described below.

The supposed <u>cis</u>-(XXXVII) and <u>trans</u>-(XXXVIII) sulfonamides were readily decomposed by the method of Snyder and Heckert (52), and the corresponding amines prepared in this way were isomerically pure as shown by N.M.R. and vapor phase chromatography. Each of these amines was then subjected to polyphosphoric acid catalysed equilibration. That amine isolated from the sulfonamide possessing melting point 103° remained relatively unchanged, whereas the other was largely isomerized. The results given in Table IV show our previous stereochemical assignments were valid and in addition suggest the equilibrium composition of the amines lies in the neighborhood of 75% <u>trans</u>- and 25% <u>cis</u> -2,3-dimethyl-indoline. In passing, it should be

<u>TABLE IV</u>

Polyphosphoric acid catalysed equilibration of the <u>cis</u>- and <u>trans</u>- 2,3-dimethylindolines at 230°

Starting isomer	Contact time (hrs.)	Isomer distribution in product	
		% "cis"	% "trans"
"cis"	24	32.0	68.0
"	48	30.0	70.0
"trans"	24	7.0	93.0
"	48	19.0	81.0

noted that the equilibrium composition of the amines depends only on the relative stability of the corresponding salts and not on that of the bases themselves.

Isolation of pure *cis*- and pure *trans*- 2,3-dimethylindoline enabled us to examine the metal-acid reduction products of 2,3-dimethylindole. The results tabulated below (Table V) prove that neither of the metal-acid reductions proceeds in a stereospecific manner and disprove conclusions reached by other workers (46,50).

TABLE V

Vapor phase chromatographic analysis of the 2,3-dimethylindolines.

This work.

Synthetic method	Product yield (%)	Isomer distribution in product % "Cis"	% "Trans"
Zn dust and HCl on 2,3-dimethylindole.	80.0	73.5	26.5
Zn and ethanolic HCl on 2,3-dimethylindole.	75.0	66.0	34.0
Results reported by Bader *et. al.* (53)			
Cyclization of N-crotylaniline	32.0	26.0	74.0
Zn and HCl on 2,3-dimethylindole	—	60.0	40.0
Catalytic hydrogenation of 2,3-dimethylindole	73.0	0.0	100.0

Shortly after completion of the above work, Bader *et. al.* (53) published a reinvestigation of their earlier work concerning the stereochemistry of the 2,3-dimethylindolines. Their observations are tabulated in Table V and are in good agreement with our experimental results.

They were not, however, able to isolate pure <u>cis</u>-2,3-dimethylindoline since the melting point (70-71^{0}) given for its benzenesulfonamide is low. Undoubtedly this material was a mixture of the isomeric sulfonamides similar to the 1:1 complex isolated by us. It is interesting to note that polyphosphoric acid catalysed cyclization of N-crotylaniline gives rise to the expected equilibrium mixture of <u>cis</u> and <u>trans</u>- 2,3-dimethyl-indoline.

There remained only to establish the stereochemistry of the precursor (XXX) of 1,2,4,5-tetramethylpyrrolo [3,2,1-<u>hi</u>] indole. Each isomeric indoline was carried through the reaction sequence already described and <u>cis</u>, 1,2-dihydro- 1,2,4,5-tetramethylpyrrolo [3,2,1-<u>hi</u>] indole was found to be identical in all its physical properties with XXX. Rather unexpectedly, nitrosation of <u>cis</u>- or <u>trans</u>- 2,3-dimethylindoline in each case produced a product which was approximately 10% isomerized. The mode of isomerization remains unclear since the isomeric 2,3-dimethyl-indolines were isolated in 99 + % purity from the corresponding sulfonamides under conditions far more severe than those utilized in nitrosation.

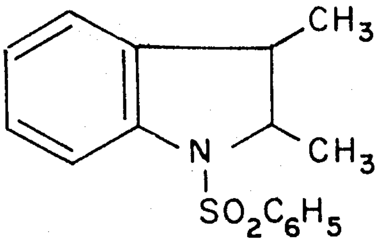
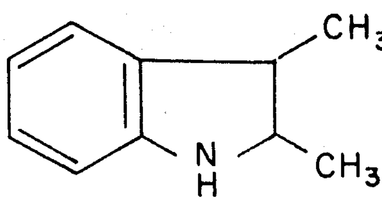
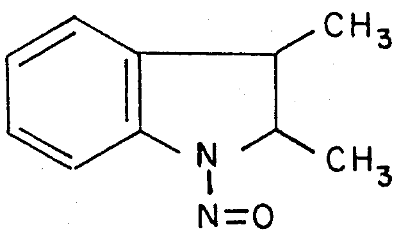
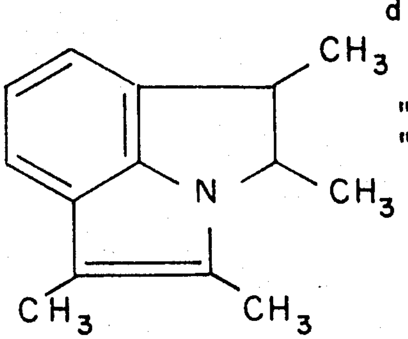
Besides providing invaluable information concerning purity of both the <u>cis</u>- and <u>trans</u>- intermediates in the reaction sequence leading to XXXI, the N.M.R. spectra of these compounds showed several interesting features. Chemical shifts and coupling constants are given in Tables VI and VII (pp. 57 and 59). Fortunately in all the compounds analysed, hydrogens which were coupled together were sufficiently well chemically shifted that analysis of the spectra could be carried out by a first order treatment.

The spectra of indoline and its derivatives possessing hydrogen(s) at positions 2(α) and 3(β) have received little attention. The available information (64) indicates the α-proton(s) appear(s) at a lower field than the β-proton(s), and spectral assignments for those two protons were made on this basis.

Normally the resonance due to the α-proton appeared as a well defined octet on the low field side of the resonance due to the β-proton. This octet obviously arises as follows: the resonance of the α-proton is split into a quartet by the methyl group at C2 (spacing equal to $JH2(CH_3)2$), each of these lines in turn being split into a doublet (spacing equal to JH2H3) by the β-proton. When JH2H3 was smaller than $JH2(CH_3)2$, as in the *trans*-sulfonamide, the spectrum of this proton had the general appearance shown in Figure 5A (p.61). When JH2H3 was less than twice $JH2(CH_3)2$, but greater than $JH2(CH_3)2$, some crossing of the lines was observed (Fig. 5B, p.61). The predicted H2 spectra for the cases when $JH2(CH_3)2 > JH2H3$, $JH2(CH_3)2 \cong JH2H3$, and $2JH2(CH_3)2 > JH2H3 > JH2(CH_3)2$ are shown in Figures 5D, 5E, and 5F (p.61) respectively. In the case of the tricyclic compound possessing *cis*-stereochemistry (XXXIX), the signals due to the α-proton appeared as a quintet. This behaviour is probably due to quadrupole broadening (65) of a spectrum such as illustrated in Figure 5B by the adjacent nitrogen atom, resulting in a broad quintet (Fig. 5C, p.61). In this case the coupling constants could not be determined accurately (see Table VII p.59). Similar, but less severe broadening was observed for the tricyclic compound possessing *trans*-stereochemistry (XL).

TABLE VI

N.M.R. Spectra of intermediates leading to 1,2,4,5-tetramethyl-pyrrolo [3,2,1-*hi*] indole

Compound		Chemical shift from tetramethylsilane (p.p.m.)[a] Aromatic protons	H2	H3	$(CH_3)2$	$(CH_3)3$
	"cis"	6.86-7.68	4.33	2.88	1.10[b]	1.23[b]
	"trans"	6.84-7.74	3.66	2.63	0.56	1.39
 [c]	"cis"	6.32-7.00	3.83	3.15	1.03	1.14
	"trans"	6.29-7.02	3.32	2.70	1.23	1.23
	"cis"	7.11-7.79	4.90	3.49	1.08	1.33
	"trans"	7.12-7.80	4.35	2.96	1.28	1.28
 [d]	"cis"	6.54-7.11	4.66	4.03	1.28[b,e]	1.35[b,e]
	"trans"	6.42-7.06	4.10	3.51	1.49[e]	1.38[e]

see page 58 for meaning of superscripts.

a.
All spectra were measured in carbon tetrachloride solution.

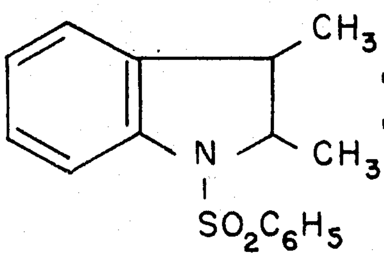
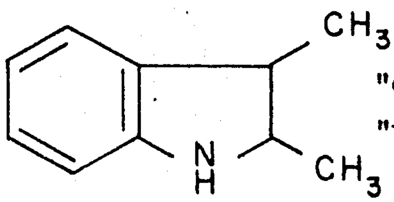
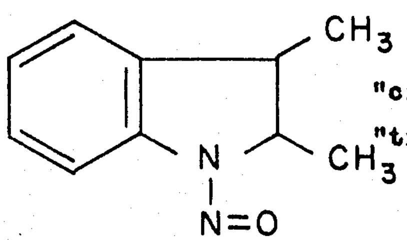
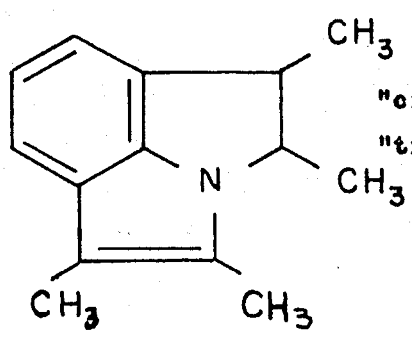
b.
The assignments for these bands are not certain.

c.
NH Exchanged with D_2O

d.
For convenience the α-and β-hydrogens and methyl groups have been numbered 2 and 3 rather than 2 and 1 as required by the systematic nomenclature used throughout the thesis.

e.
The methyls attached to unsaturated carbon appear at 2.10 and 2.28 p.p.m. for the *cis*-isomer and at 2.15 and 2.25 p.p.m. for the *trans*-isomer.

TABLE VII

Compound		Coupling constants (c.p.s.) $J_{H2\ H3}$[a]	$J_{H2\ (CH_3)2}$[a]	$J_{H3(CH_3)3}$[b]
	"cis"	8.61	6.80	7.15
	"trans"	2.71	6.30	7.02
	"cis"	8.95	6.40	6.96
	"trans"	8.85	6.16	6.83
	"cis"	8.72	6.60	6.98
	"trans"	3.02	6.53	6.70
	"cis"	7.0	6.8	7.1[c]
	"trans"	5.09	6.53	6.6[d]

a.

J_{HBHB} and $J_{HB(CH_3)2}$ were determined by averaging the results of ten or more measurements. Unless otherwise stated the standard deviation of the mean never exceeded ± 0.10 c.p.s.

b.

$J_{HB(CH_3)3}$ was determined by averaging the results of 2-4 measurements. Unless otherwise stated, the standard deviation of the mean was ± 0.10 c.p.s. or less.

c.

The values of J_{HBHB}, $J_{HB(CH_3)2}$, and $J_{HB(CH_3)3}$ for the cis-compound may be in error by ± 1.0 c.p.s.

d.

The standard deviation of the mean for $J_{HB(CH_3)3}$ in this case was ± 0.25 c.p.s.

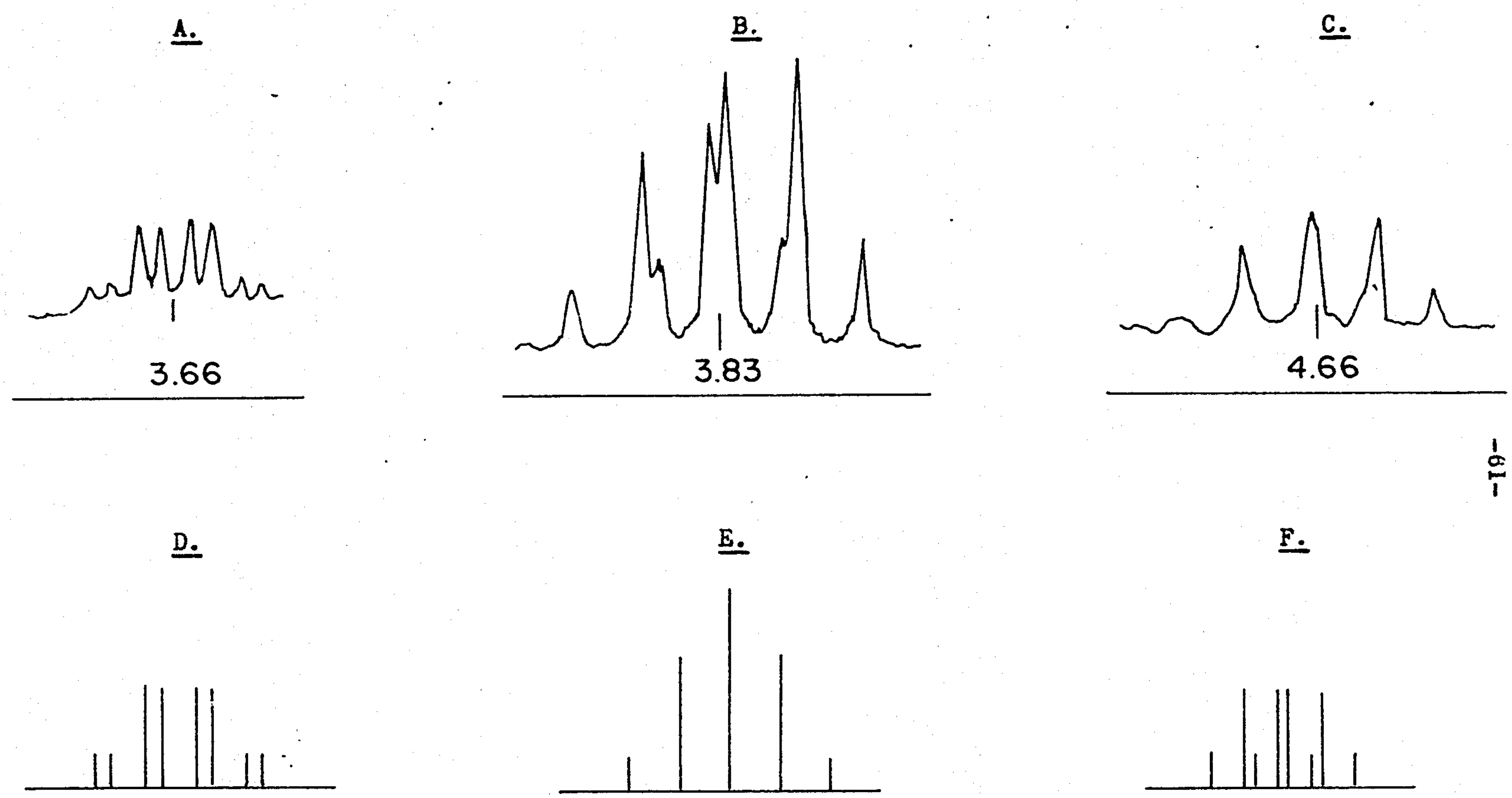
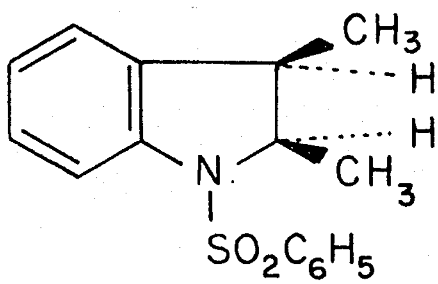
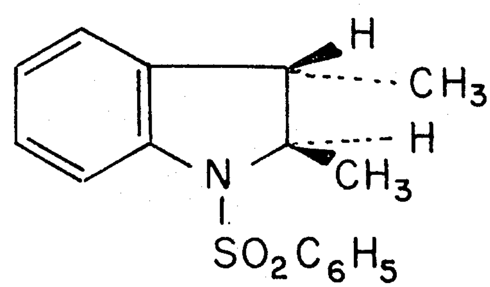


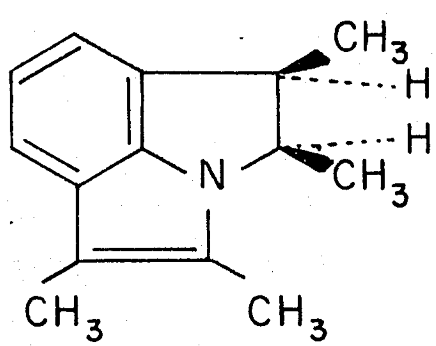
Fig.5. A, H2 spectrum of 1-benzenesulfonyl-<u>trans</u>-2,3-dimethylindoline; B, H2 spectrum of <u>cis</u>-2,3-dimethylindoline; C, H ctrum of <u>cis</u>,1,2-dihydro-1,2,4,5-tetramethylpyrrolo[3,2,1-<u>hi</u>]indole. Predicted H2 spectra when: D, H3; E, $J_{H2(CH_3)2} \cong J_{H2H3}$; F $> J_{H2H3} > J_{H2(CH_3)2}$.



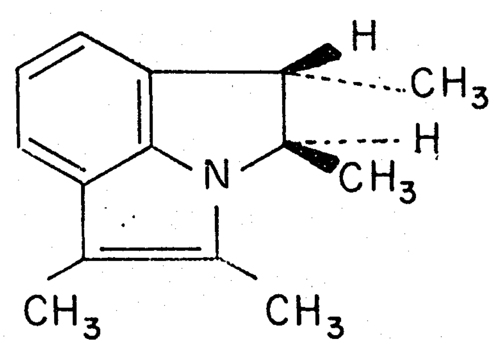
XXXVII



XXXVIII



XXXIX



XL

At first glance the β-proton should also give rise to a well defined octet. This, however, was not the case since H3 was also coupled weakly to the proton at position 4 in the aromatic ring. Such long range coupling has been recognized in several instances in the literature (55-58). When JH2H3 was small (as compared to JH3(CH_3)3), the resonance due to the β-proton appeared as an octet in which each line was broadened due to the above effect. When JH2H3 ≅ JH3(CH_3)3 or when 2JH3(CH_3)3 > JH2H3 < JH3(CH_3)3, the resonance due to β-proton showed up as a quintet, each line displaying much poorly resolved fine structure.

Depending on the chemical shift between them, the resonance due to the methyl groups appeared as two doublets sometimes partially or completely superposed. In benzene solution a greater chemical shift often existed between the methyl groups, and as a result the predicted quartet was then observed. When the doublets were not superposed the position of resonance due to the methyl groups at C2 and C3 was assigned by checking the measured coupling constants with those determined from the spectrum of the α- or β-proton. In most cases such double checking was impossible and consequently in these cases assignments given for the methyl resonances (Table VI,p. 57) were uncertain. It should be noted that the resonance due to the methyl group at C2 for 1-benzenesulfonyl-<u>trans</u>- 2,3-dimethylindoline has been assigned to that doublet which appeared at 0.60 p.p.m. We have taken this to indicate the methyl group lies above the plane of the benzene ring at position 1 and as a result its resonance is shifted upfield by the magnetic anisotropy of the aromatic ring. That the above result was not due to some type of dimer formation wherein a methyl group of one molecule is above the plane of an aromatic ring in another molecule, was excluded since the chemical shifts of the methyl groups were concentration independent. Similar observations have been reported in the spectra of the paracyclophanes (59) and ind-N-benzoyldeacetylaspidospermine (60).

In the series of compounds given in Table VI there exist appreciable differences in the chemical shifts of the methine and methyl protons. These differences, will however, not be discussed since it is difficult to correlate chemical shifts with changes in structure.

Well documented evidence exists concerning an angular dependence in the coupling constants of protons on adjacent carbon atoms (45,55,61-68). Theoretical work (66, and ref.60, p.311) has supported this dependence and suggested that large coupling constants (8-11 c.p.s) occur for dihedral angles of the CH bonds of 0^{o} and 180^{o}. The values of $J_{HH'}$ decrease gradually for other angles reaching about zero for a dihedral angle of approximately 90^{o}. Recent experimental work (60,63,67) lends support to these calculations. It is obvious from these and other results presented below, that in non-rigid five-and six-membered cyclic derivatives [the coupling constants in three- and four-membered rings do not agree well with those predicted (45, 68, 69)] the coupling constants will depend markedly on the conformation(s) which the molecules adopt in solution. If the stereochemistry and coupling constants are known, it is possible to deduce the precise conformation (in solution) of such rings, a task which is extremely difficult to carry out by other techniques. In fact, several attempts which have met with varying degrees of success have been made to do this (70-75). Conversely, if the conformation and coupling constants are known the stereochemistry about a particular CH-CH bond can be determined (76).

Of some interest is the observed variation of the coupling constants JH2H3 given in Table VII. Although the values of JH2H3 for most of the compounds examined were approximately what might be expected, those of the isomeric 2,3-dimethyl-indolines are somewhat unusual. If one accepts for the moment the value of JH2H3 for cis-2,3-dimethylindoline, one should then expect JH2H3 for the trans-isomer to be small. Even if one assumes JH2H3 to be a mean of the coupling constants for the two possible conformations of the trans-isomer, the observed value is still too high. Similar anomalous results have been observed in several instances (75-76,77) and they show that caution is needed in applying the results of Karplus to determine the conformation of five-membered rings. It is of interest to note however, that the mean of JH2H3 for cis- and trans-2,3-dimethylindoline (8.4 c.p.s) agrees exceptionally well with that reported (8.6 c.p.s) for 1-acylindolines (84).

Noteworthy also is the orderly variation of the coupling constants $JH2(CH_3)2$ and $JH3(CH_3)3$. In every case the former was smaller than the latter, an observation which is not unexpected, since the size of the coupling constant is known to be dependent on the presence of strong electron-withdrawing or donating groups (80). Furthermore, within each pair of isomers the methyl-hydrogen coupling constants for the cis-isomer were consistently larger than those observed for the corresponding trans-compound. There seems to be no immediately obvious explanation of the above behaviour, and consequently the subject will not be discussed further.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Ultraviolet spectra were measured on a Beckman DK-2 spectrophotometer and the infrared spectra on a Perkin-Elmer Infracord.

The N.M.R. spectra were measured at 60 mc/sec. with a Varian V-4302 spectrometer as 10–20% solutions in carbon tetrachloride containing tetramethylsilane as an internal standard. Spectral calibrations were carried out either by interpolation between side bands of the tetramethylsilane, or by sweeping over a band and both low and high side bands. Spectra were obtained with both increasing and decreasing magnetic fields and line positions were obtained by averaging the results of several determinations. The sideband frequencies were measured on a Hewlet-Packard frequency counter to 0.1 c.p.s. Unless otherwise stated the analysis of the spectra were carried out by a first order treatment.

All high pressure reductions were carried out in a "Magne-Dash" high pressure hydrogenator. Low pressure reductions were carried out in a "Parr" low pressure hydrogenation apparatus.

o-Nitrophenylpyruvic Acid.

The Claisen condensation was carried out according to the method of Di Carlo (78). To a cooled solution of sodium (21.0 g.) in dry ethanol (240 ml.) was added diethyl oxalate (131.4 g.) and o-nitrotoluene (123.3 g.) and the resulting solution was boiled under reflux for for 10 minutes. The deep red solution thus obtained was cooled, an equal volume of water added, and the resulting mixture boiled under reflux for 1½ hours. This material was then steam distilled until all the unreacted o-nitrotoluene was removed (30.4 g.), the non-volatile residue was cooled, and acidified with concentrated hydrochloric acid. The tan colored solid was filtered and dried (118.0 g; 83.0% based on o-nitrotoluene consumed) and used without purification in the next step.

O-Nitrophenylacetic Acid.

O-Nitrophenylpyruvic acid (132.0 g.) was dissolved in water (600 ml.) containing sodium hydroxide (27.0 g.) and cooled in an ice-bath to 10°. The stirred solution was treated dropwise with a solution of hydrogen peroxide (80 ml. of 30% hydrogen peroxide in 720 ml. of water) at such a rate that the reaction temperature did not exceed 15°. When the addition was completed the pale yellow solution was allowed to stand at room temperature overnight. This solution was carefully acidified with concentrated hydrochloric acid, the solid was removed by filtration and dried giving a pale yellow powder (97.6 g.). This material was crystallized from 20% aqueous ethanol giving pale yellow needles (91.0 g., 79.6%) m.p. 138-140°. May and Mosettig (79) report m.p. 136-139° for this acid.

O-Nitrophenylacetic Acid (Ethyl Ester).

O-Nitrophenylacetic acid (91.0 g.) in absolute ethanol (300 ml.) containing sulfuric acid (15 ml.) was boiled under reflux for 24 hours, the ethanol was removed in vacuo and the residue was poured into 500 ml. of water. This was treated with solid sodium carbonate until efforvesence ceased and then extracted with ether. The ether was removed on a flash evaporator and the residue crystallised from petroleum ether (b.p. 80-100°) giving pale yellow needles (100.3 g.) m.p. 68°. Reissert and Scherk (80) report m.p. 69° for this compound.

o-Amino-β-Phenylethanol.

A stirred solution of lithium aluminum hydride (12.0 g.) in dry ether (200 ml.) was treated dropwise with a solution of the above ester (30.0 g.) in dry ether (400 ml.) at a rate sufficiently rapid to maintain the ether at reflux temperature. When the addition was completed the solution was boiled under reflux for 1 hour, the cooled solution treated with ethylacetate and then water. The ether layer was decanted and the solid was extracted with ether (3X 100 ml.). The extracts were combined, dried over anhydrous magnesium sulfate and the ether removed in *vacuo*. The red oil was dissolved in absolute ethanol (500 ml.) and hydrazine hydrate (30.0 g., 100%) and three teaspoons of Raney nickel were added. The mixture was slowly brought to reflux temperature (steam bath) and maintained there for 1 hour. This was cooled, filtered, and the filtrate evaporated on a flash evaporator leaving a red-brown oil. Distillation of this oil at reduced pressure gave pure *o*-amino-β-phenylethanol (13.3-14.7 g., 67.5 - 74.6%) b.p. 125-128°/0.65 mm. Bennot and Hafez (20) report b.p. 155°/5 mm. for this compound. The above represents a yield of 42.7 - 47.2% of the amine based on *o*-nitrotoluene as starting material. The picrate was prepared and on cyrstallization from ethanol, yellow needles m.p. 181.5 - 183.5° were obtained. Calc. for $C_8H_{11}ON$: $C_6H_3O_7N_3$: C,45.90; H,3.85%. Found: C,46.19; H,3.97%.

2-(2-Hydroxyethyl) phenylhydrazone of Ethylpyruvate.

A stirred solution of α-methylethylacetoacetate (3.60 g.) in absolute ethanol (25 ml.) was cooled to 0° and treated with 8.5 ml. of 50% aqueous potassium hydroxide and 10 ml. of ice-cold water followed immediately by the diazonium salt solution prepared from o-amino-β-phenylethanol (3.20 g.), concentrated hydrochloric acid (10 ml.), and sodium nitrite (1.60 g.). This mixture was stirred at 0° for 1 hour, placed in a refrigerator overnight, and then extracted with ether. The ether was evaporated and the tarry residue taken up in a small amount of chloroform and put on "Merck" alumina. The desired material was eluted from the column with 20% chloroform in petroleum ether (b.p. 60-100°). The eluate on evaporation gave a solid which was crystallized from petroleum ether (b.p. 60-100°) containing a small amount of ethanol. Colorless needles (2.14 g; 36.7%) m.p. 96-97.5° were obtained. Calc. for $C_{13}H_{18}O_3N_2$: C,62.38; H,7.25%. Found C,62.33; H,7.30%.

2-(2-Hydroxyethyl)phenylhydrazone of Diacetyl.

α-methylethylacetoacetate (3.00 g.) in water (30 ml.) containing sodium hydroxide (.80 g.) was shaken mechanically at room temperature overnight. The solution was cooled in an ice-bath, stirred, and treated with the diazonium chloride solution, prepared from o-amino-β-phenylethanol (2.85 g.), concentrated hydrochloric acid (4.5 ml.), and sodium nitrite (0.90 g.). The mixture was immediately adjusted to pH 5 by the addition of cold, 40% aqueous sodium acetate. Stirring was continued at 0° for 1 hour, and then the mixture was placed in a refrigerator overnight. The mixture was ether extracted, the ether evaporated, and the tarry residue taken up in a small amount of chloroform and placed on "Merck" alumina. Elution with 40% chloroform in petroleum ether (b.p. 80-100°) followed by evaporation of the solvent and crystallization of the residue from petroleum ether (b.p. 80-100°) gave pale yellow needles (2.60 g., 50.8%) m.p. 98-99°. Several crystallization from the same solvent gave an analytical sample. Calc. for $C_{12}H_{16}O_2N_2$: C, 65.43; H, 7.32%. Found C, 65.79, 65.88; H, 6.92, 7.32%.

Attempted Preparation of 2-Nitro-3-Carboxymethylphenylacetic Acid.

To a well stirred mixture of potassium metal (7.90 g.) in anhydrous benzene (120 ml.) was added absolute ethanol (24 ml.) and the whole was heated under reflux until all the potassium had reacted. The solvent was then removed in *vacuo* and to the solid potassium ethoxide was added dry ether (240 ml.) ethyloxalate (29.4 g.) and 1,3-dimethyl-2-nitrobenzene (15.1g.). The deep red solution was boiled under reflux (drying tube) for 22 hours, cooled, and filtered. The red solid was washed with ether, then dissolved in water (50 ml.), heated to 70°, and maintained at that temperature for 10 minutes. The cooled solution was acidified with 2% hydrochloric acid and extracted with ether. The ether on evaporation gave a yellow solid (7.55 g.) which was not characterized but used directly as follows: the solid was dissolved in water (130 ml.) containing sodium hydroxide (2.1 g.) and cooled to 10° in an ice-bath. The stirred solution was treated dropwise with dilute hydrogen peroxide (6 ml. of 30% hydrogen peroxide in 14 ml. of water) at such a rate that the temperature did not exceed 15°. This solution was allowed to stand at room temperature overnight and then carefully acidified with concentrated hydrochloric acid.

The precipitate was removed by filtration, dried and then crystallized from aqueous ethanol. Colorless needles (5.28 g.) m.p. 154-155° not identical with the desired material were obtained. Several crystallizations from the same solvent system gave an analytical sample m.p. 155.5 - 157.5°. It was thought to be 2-nitro-3-methylphenylacetic acid on the basis of its analysis and equivalent weight. Calc. for $C_9H_9NO_4$: C, 55.38; H, 4.65%; Eq. wt. 195.2. Found: C, 55.44; H, 5.01%; Eq. wt., 196.

1,2,3,4-Tetrahydroquinoline.

A mixture of quinoline (83.0 g.), copper chromite (8.3 g.) in absolute ethanol (200 ml.) was subjected to high pressure hydrogenation (initial hydrogen pressure of 1600 p.s.i) at 180° for 1 hour. The cooled mixture was filtered to remove the catalyst, the ethanol evaporated and the residue distilled at reduced pressure. The fraction (70.0 g., 85.3%) b.p. 113-116°/10 mm. was collected. Adkins and Billica (61) report b.p. 85-86/2 mm. for this compound.

1,2,3,5,6,7-Hexahydrobenzo [ij] quinolizine (Julolidine).

A mixture of tetrahydroquinoline (10.0 g.) and 1,3-dibromopropane (70.0 g.) was heated at 160° for 8 hours. The cooled mixture was made acidic with 20% hydrochloric acid and steam distilled to remove excess 1,3-dibromopropane. The cold residue was made basic with 40% sodium hydroxide, extracted with ether, the ether evaporated and the residue fractionall distilled at reduced pressure. The fraction (6.65 g.) b.p. 135-140°/10 mm. was collected. This material solidified on cooling giving a colorless solid m.p. 39°. Glass and Weissberger (20) report m.p. 39-40° for this compound.

Its pK_A was found to be 3.65 in 50% aqueous ethanol. The ultraviolet spectrum of this compound is given in Table II, p. 36.

1-Chloroacetyl-1,2,3,4-tetrahydroquinoline.

A solution of 1,2,3,4-tetrahydroquinoline (24.3 g.) in acetone (50 ml.) was mixed carefully with a solution of chloroacetyl chloride (20.7 g.) in acetone (50 ml.). When the vigorous reaction had subsided the solution was poured into saturated sodium acetate solution (200 ml.), and shaken mechanically for ½ hour. The organic phase was then decanted and combined with an ether extract of the aqueous phase. This was extracted with 20% hydrochloric acid (2 x 50 ml.) and the organic phase was evaporated and the residue distilled at reduced pressure. The fraction (25.4 g., 66.4%) b.p. 157-160°/0.17 mm. was collected. Sugimoto (62) reports b.p. 163-166°/3.5 mm. for this compound.

2-oxo-1,2,5,6-Tetrahydro-1H-pyrrolo [3,2,1-ij] quinoline.

An intimate mixture of 1-chloroacetyl-1,2,3,4-tetrahydroquinoline (21.5 g.) and aluminum chloride (45.0 g.) was heated to 150° and maintained at that temperature for 15 minutes. The cooled material was carefully treated with 500 g. of crushed ice, the white solid removed by filtration and dried. This material was crystallized from petroleum ether (b.p. 60-80°) giving a white solid (14.3 g., 80.5%) m.p. 88-91°. Sugimoto (62) reports m.p. 91-92° for this compound

1,2,5,6-Tetrahydro-1H-Pyrrolo [3,2,1-ij] quinoline (Lilolidine).

A suspension of lithium aluminum hydride (2.0 g.) in dry ether (60 ml.) was treated rapidly with a solution of the above lactam (5.00 g.)

in dry ether (150 ml.). This mixture was boiled under reflux for 14 hours and the excess hydride then carefully decomposed with water. The ether was decanted and the slurry washed with two 50 ml. portions of ether. The ether was extracted with 20% hydrochloric acid (2 x 50 ml.) and on evaporation gave 0.70 g. of starting material. The acid layer was made alkaline with concentrated potassium hydroxide, extracted with ether, the ether removed *in vacuo* and the residual oil distilled at reduced pressure. The fraction (2.63 g; 68.3% based on starting material consumed) b.p. 112-115°/6mm. was collected. Redistillation gave a colorless oil b.p. 81-82°/0.45mm. Sugimoto (62) reports b.p. 112°/4 mm. for lilolidine. The pK_A was found to be 5.08 in 50% aqueous ethanol. The ultraviolet spectrum of this compound is given in Table II p. 36.

Lithium Aluminum Hydride Reduction of Some Sterically Hindered Aromatic Nitro Compounds.

The lithium aluminum hydride reductions were carried out in one of two ways depending on the solubility of the starting material in ether.

(i) When the nitro compound was ether soluble, its ether solution was added in a dropwise manner to a suspension of a half-molar excess of the hydride in anhydrous ether. When the addition was complete, the mixture was boiled under reflux for 6 hours. Amines formed were extracted with 10% hydrochloric acid and identified as their picrates (melting points and mixed melting points). The azo compounds were crystallised from the appropriate solvent and identified by comparing their properties with those given in the literature.

(ii) If the nitro compounds (1,3-di(methoxycarbonyl)-2-nitrobenzene and 1,3-di(methoxycarbonylmethyl)-2-nitrobenzene) were only slightly soluble in ether, they were introduced to the hydride suspension (over a period of 24 hours) by the Soxhlet extractor technique. No azo compounds were formed in these cases and the amines were isolated by filtration of the organic layer, evaporation to dryness, and crystallization of the solid residue from the appropriate solvent system.

The product yields are tabulated in Table 1 p. 31. The physical constants of the products obtained and of some of their derivatives are given below.

TABLE VIII

Physical constants of the reduction products of some sterically hindered aromatic nitro compounds.

Nitro Compound	Azo derivative M.p. °C	Amine M.p. °C	Picrate, M.p. °C.
Nitrobenzene	67-68[a]	———	———
o-Nitrotoluene	53-54[a]	liquid	213[a]
o-Nitro-β-Phenylethanol	138-139[b]	liquid	181.5-183.5
1,3-Dimethyl-2-Nitrobenzene	44.5-45[c]	liquid	189-190[a]
Nitromesitylene	73-75[d]	liquid	189-190[a]
1,3-Di(methoxycarbonyl)-2-Nitrobenzene	———	120-121[e]	———
1,3-Di(methoxycarbonylmethyl)-2-Nitrobenzene	———	101-102	———

a. These melting points are in agreement with those stated in reference 83.

b. Recrystallized from ethanol-petroleum ether (b.p. 80-100°). Calc. for $C_{16}H_{18}O_2N_2$: C, 71.09; H, 6.71%. Found: C, 71.38; H, 6.70%

c.
    Adsord (64) reported m.p. 46-47°.

d.
    Grammaticakis (65) reported m.p. 76°.

e.
    Recrystallized from ethanol-petroleum ether (b.p. 80-100°). Calc. for $C_8H_{11}O_2N$: C, 62.72; H, 7.24%. Found: C, 63.13; H, 7.22%

<u>2-Nitroisophthalic Acid.</u>

This acid was prepared by a method slightly modified from that of Noelting and Gachot (66).

Potassium permanganate (510 g.) was added in small portions over a period of 2 hours to a well stirred boiling mixture of 1,3-Dimethyl-2-nitrobenzene (100 g.) and water (2l) containing sodium carbonate (100 g.). When all the potassium permanganate had been added, water was added to bring the total volume to approximately 4l. and the vigorously stirred mixture was boiled under reflux for 15 hours. At the end of this time excess permanganate was destroyed by addition of sodium bisulfite, and the mixture was filtered hot. The residue was washed several times with hot water and the filtrates were combined and allowed to cool. The pale yellow solution was carefully acidified with concentrated hydrochloric acid, the flocculent precipitate removed by filtration and dried yielding 79-88 g. (56-63%) of a white solid. Recrystallization from dilute methanol gave beautiful white needles m.p. 312-313°d. Noelting and Gachot (66) report a melting point of 310-312°.

<u>2-Nitroisophthalyl Chloride</u>

A solution of 2-nitroisophthalic acid (10.0g.) in purified thionyl chloride (17.5 ml.) containing 1 drop of pyridine was boiled under reflux overnight. The brown solution on cooling yielded a solid mass which was broken up, filtered and washed with ice cold carbon tetrachloride. This resulted in 10-10.8g (85-92%) of a pale yellow crystalline solid. Crystallization of the acid chloride from benzene gave colorless rhombs m.p. 132-133°. Anet and Nishizawa (17) report a melting point of 128-130°.

<u>1,3-Bisdiazoacetyl-2-Nitrobenzene.</u>

A solution of 2-nitroisophthaloyl chloride (20.0 g) in tetrahydro--furan (100 ml.) was added dropwise to 800 ml. of ethereal diazomethane (prepared from 85 g. of nitrosomethylurea) cooled in an ice-bath. After standing overnight the mixture was filtered giving 18.8-20.3 g. (89-96%) of a cream colored powder. This material is extremely heat sensitive and a serious explosion resulted when it was rapidly heated in a small amount of methanol. The crude material was twice crystallized from 1:1 chloroform-benzene giving cream colored needles, m.p. 115° d. Anet and Nishizawa (17) report a melting point of 105°.

<u>1,3-Di(methoxycarbonylmethyl)-2-Nitrobenzene.</u>

To a stirred boiling solution of the above diazoketone (5.00g) in absolute methanol (150 ml.) was added dry silver benzoate in small portions until nitrogen evolution ceased (about 1.5 g. of silver benzoate was required). The mixture was then boiled under reflux for the ½ hour, the hot solution filtered and allowed to cool. Pale brown flakes (3.15-3.60 g., 62-70%) were obtained on filtration. Two further crystallizations from methanol (charcoal) gave colorless, flat, needles m.p. 145.5-147.5°. Anet and Nishizawa (17) report a melting point of 144-145°.

7-Carbomethoxymethyloxindole.

A solution of the above di-ester (10.0 g.) in methanol (100 ml.) containing acetic acid (2 ml.) and 1 teaspoon of Raney nickel was hydrogenated at an initial pressure of 70 p.s.i and room temperature overnight. The solution was filtered, evaporated to about 30 ml. and allowed to cool, whereupon pink needles (6.16-6.64 g., 67-69%) were deposited. Crystallization from ethanol-petroleum ether (b.p. 80-100°) gave beautiful pink needles, m.p. 157-158°. Several recrystallizations from the same solvent system (charcoal) gave colorless needles having m.p. 157-158°. Anet and Nishizawa (17) report a melting point of 163-164° for this compound.

Reduction of 7-Carbomethoxymethyloxindole.

The oxindole (1.0 g.) in dry tetrahydrofuran was added dropwise to lithium aluminum hydride in ether (0.4 g. in 10 ml.) at a rate sufficiently rapid to keep the ether boiling under reflux. When the addition was complete the stirred mixture was boiled under reflux for ½ hour, cooled, carefully treated with water and finally with cold 20% sulfuric acid to dissolve the aluminum salts. The organic layer was separated and the aqueous layer extracted with chloroform. The organic phases were combined and evaporated to dryness. The residue was taken up in chloroform and placed on a column of alumina. Various colored impurities were eluted with chloroform and the mixture of the oxindole alcohol and the indole alcohol was eluted with chloroform ethanol (20:1). The eluent containing the desired material was evaporated to dryness, the residue taken up in hot ethanol-petroleum ether (b.p. 80-100°) and on cooling 0.266 g. of a white powder consisting of the two alcohols was obtained.

The aqueous acid layer was made strongly alkaline with sodium hydroxide and extracted with ether (3 x 20 ml.), the ether was removed *in vacuo*, the pale yellow oil taken up in ether and added to a saturated solution of picric acid in ether. Upon standing the picrate of the indoline alcohol (0.083 g.) separated as yellow needles m.p. 154-155°. Anet and Nishizawa (17) report a melting point of 154-155° for this picrate. The above represents a 4.4% yield of the fully reduced base.

2,6-Di(2-hydroxyethyl) aniline.

1,3-Di(methoxycarbonylmethyl)-2-nitrobenzene (4.5 g.) was continually extracted for 24 hours into dry ether (400 ml.) containing lithium aluminum hydride (4.0 g.). At the end of this time the excess hydride was decomposed with ethylacetate and water. The organic layer was removed and the gummy residue twice extracted with ether-ethanol (3:1). The combined organic layer and extracts were evaporated to dryness, extracted with hot acetone, the acetone removed *in vacuo*, and the solid residue taken up in boiling ethanol-petroleum ether (b.p. 60-100°). Cooling gave colorless needles (1.60-1.70 g., 51-54%). Several crystallizations from the same solvent system gave an analytical sample, m.p. 101-102°. Calc. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34%. Found: C, 66.06; H, 8.33%.

7-(2-bromoethyl) indoline Hydrobromide.

A solution of 2,6-di(2-hydroxyethyl) aniline (1.00g.) in constant boiling hydrobromic acid (10 ml.) was boiled under reflux overnight. The cooled solution was evaporated to dryness in *vacuo*, the solid residue taken up in ethanol-petroleum ether (b.p. 60-100°), treated with charcoal, filtered and cooled. Pale pink plates (1.19-1.46 g; 70-85%) were deposited on cooling. Several crystallizations from the same solvent system gave the pure hydrobromide, m.p. 203-205°d. The melting point was undepressed on admixture with an authentic sample. Amet and Nishizawa (17) reported a melting point of 188-190° for this compound. Calc. for $C_{10}H_{13}N\ Br_2$: C, 39.11; H, 4.27; Br, 52.05%. Found: C, 38.91, 38.86; H, 3.80, 3.96; Br, 51.78%.

1,2,4,5-Tetrahydropyrrolo [3,2,1-hi] indole.

7-(2-Bromoethyl) indoline hydrobromide (4.00 g.) was dissolved in water and made basic with aqueous sodium hydroxide. The liberated base was extracted with ether (3 x 50 ml.) and the ether was removed under vacuo. The bath temperature was raised to 70° (10 mm.) to insure complete removal of water. The base was immediately taken up in dry xylene (150 ml.) and added over a period of 1 hour to boiling xylene (350 ml.) containing sodium hydride (2.0 g., 50% in mineral oil). The stirred mixture was boiled under reflux an additional hour, cooled, and carefully treated with water. The xylene layer was extracted with 20% hydrochloric acid (3 x 50 ml.), the acid extract was made strongly basic with sodium hydroxide and steam distilled until a clear distillate was obtained. The steam distillate was extracted with ether, and the ether removed under vacuo leaving a pale yellow oil. This oil was taken up in a small volume of ether and added to a saturated solution of picric acid (3.00 g.) in ether. The picrate (0.86 - 1.17 g.) crystallized immediately as yellow needles m.p. 191-192° d. The above represents a 17.7-24% yield of the free base. The extremely insoluble picrate was crystallized from acetone-alcohol giving yellow needles, m.p. 194-195°d. Calc. for $C_{10}H_{11}N\cdot C_6H_3O_7N_3$: C, 51.34;

H, 3.77%. Found : C, 51.80; H, 4.00%.

The free base was obtained by dissolving the thrice crystallized picrate (0.660 g.) in acetone and decomposing it on basic alumina. The base was eluted with methanol, the methanol removed *in vacuo* and the remaining oil distilled. A colorless oil (0.214 g., 80.4%) b.p. 40–43/0.1 mm. (air-bath temperature) which rapidly solidified m.p. 32–33° was obtained. Calc. for $C_{10}H_{11}N$: C, 82.72; H, 7.64. Found : C, 83.07; H, 7.42. Molecular weight calc: 145.2. Found: 143 (Rast). The pK_A (in 50% aqueous ethanol) was 4.1. The ultraviolet spectrum of this compound is given in Table II p. 36.

Attempted Catalytic Hydrogenation of 1,2,4,5-Tetrahydropyrrolo [3,2,1-hi] indole.

A solution of the above base (0.030 g.) in ethanol (50 ml.) containing 5% palladized charcoal (0.004 g.) was shaken at room temperature under a hydrogen pressure of 1 atmosphere for 4½ hours. No hydrogen was absorbed during this time. The base was recovered after filtration by evaporation of the ethanol. Addition of a saturated solution of picric acid in ether to the base in ether gave quantitative recovery of the starting material as its picrate, m.p. and mixed m.p. 104–105°.

Attempted Acidic Cleavage of 1,2,4,5-Tetrahydropyrrolo [3,2,1-hi] indole.

A solution of the above base (0.030 g.) in constant boiling hydrobromic acid (5 ml.) was boiled under reflux overnight. The hydrobromic acid was then removed *in vacuo* and the residue dissolved in water and the solution made basic with sodium carbonate. Ether extraction of the aqueous solution followed by evaporation of the ether gave a colorless oil whose infrared spectrum was practically superimposable with authentic starting material. Evaporative distillation of the base (40° and 0.1 mm.) gave a colorless oil (0.012 g.) which solidified at room temperature and was identical in every respect with the starting base.

<u>Dihydroindole</u>

Dihydroindole (indoline) was prepared by two methods.

(a) Amalgamated zinc and hydrochloric acid reduction of indole.

Amalgamated zinc was prepared by shaking a mixture of zinc dust (240 g.), mercuric chloride (24 g.), water (200 ml.), and concentrated hydrochloric acid (10 ml.) for 5 minutes. The solid was washed with water (3 x 100 ml.) by decantation.

To the amalgamated zinc in a 5l. round-bottomed flask was added water (100 ml.), indole (58.5 g.), and concentrated hydrochloric acid (200 ml.). An efficient water cooled condenser was connected to the flask and the reaction mixture was shaken vigorously. In a short while a violent reaction (sometimes necessitating external cooling of the reaction flask with ice-water) set in. When this subsided a further 150 ml. of concentrated hydrochloric acid was added through the top of the condenser, and the mixture was boiled under reflux for 24 hours. Concentrated hydrochloric acid (50 ml.) was added to the reaction mixture at 3 hour intervals. The hot mixture was filtered through glass wool, and the cooled filtrate was made basic first with concentrated ammonium hydroxide and then with 50% aqueous sodium hydroxide. The resulting slurry was filtered through celite, the celite washed several times with substantial volumes of ether and this was combined with the ether extract of the filtrate. The combined ether extracts were concentrated on a flash evaporator, and the residual oil was distilled at reduced pressure. The fraction b.p. 94-96°/7 mm. was collected. Yield 21.0 - 24.6 g (35.3 - 41.4%).

(b). <u>Catalytic Hydrogenation of Indole.</u>

Indole (100 g.) in purified dioxan (150 ml.) was placed in a hydrogenation bomb along with copper chromite (10 g.). The above mixture was subjected to high pressure hydrogenation (1500 p.s.i., initial pressure) for 4 hours at 170°. The cooled mixture was filtered, the filtrate was concentrated on a flash evaporator leaving a viscous oil. The residue was taken up in ether (300 ml.) and extracted with 10% hydrochloric acid (5 x 200 ml.). Evaporation of the ether layer and crystallization of the residue from petroleum ether (b.p. 30-60°) gave indole (30.6 g.). The acid extract was made basic with concentrated sodium hydroxide and extracted with ether (4 x 200 ml.). The ether was removed and the pale yellow oil remaining was distilled at reduced pressure given a colorless product b.p. 80 - 85°/5 mm. Yield 46.5 g (72.3% based on indole consumed). The above is essentially the method of Adkins and Burks (40) who report b.p. 110°/24 mm. for indoline.

<u>N-Nitrosoindoline.</u>

A stirred solution of indoline (10.5 g.), concentrated hydrochloric acid (12.0 ml.) and crushed ice was treated with a cold solution of sodium nitrite (6.3 g.) in water at such a rate that the temperature did not rise above 0° (external cooling with an ice-salt bath). After the addition was completed the mixture was stirred at 0° for ½ hour then allowed to warm to room temperature and the solid was removed by filtration at the pump. The pale yellow solid was dried (13.0 g.) and used directly in the next preparation.

Indoline Hydrazine (1-aminoindoline).

1-Aminoindoline was prepared by two methods, both of which gave satisfactory yields.

(a). Lithium Aluminum Hydride Reduction of 1-Nitrosoindoline.

A stirred solution of Lithium aluminum hydride (3.0 g.) in ether (50 ml.) was treated with a solution of the nitroso compound (10.0 g.) in dry ether (300 ml.) at a rate sufficiently rapid to keep the ether boiling under reflux. When the addition was complete the mixture was boiled under reflux for 6 hours, the cooled mixture carefully treated with water, and the organic layer decanted. The solid slurry was extracted with ether and the combined organic layers evaporated at the pump. The residual oil was distilled at reduced pressure giving a colorless oil (6.4 - 7.7 g., 71-85%) b.p. 104 - 106°/1.5 mm; reported (15) b.p. 110 - 112°/12 mm.

(b) Zinc and Acetic Acid Reduction.

A well stirred suspension of zinc dust (50 g.) in 90% aqueous methanol (250 ml.) containing the nitroso compound (13.0 g.) was cooled to 10° in an ice-bath. This mixture was treated dropwise with glacial acetic acid (50 ml.) at such a rate that the temperature did not rise above 15°. When all the acetic acid had been added the stirred mixture was allowed to come to room temperature overnight. The unreacted zinc was removed by filtration and the filtrate was made basic first with concentrated ammonium hydroxide and then strongly basic with 30% aqueous sodium hydroxide. This was filtered through glass wool, the solid washed several times with ether and the filtrate extracted with five 75 ml. portions of ether. Evaporation of the ether and distillation of the residue at reduced pressure gave 8.7-9.8 g (74-83%) of a colorless oil b.p. 86 - 83°/0.6 mm.

1,2,6,7,8,9-Hexahydropyrrolo [3,2,1-jk] carbazole.

A mixture of 1-aminoindoline (1.00 g.), cyclohexanone (1.0 g.), ethylene glycol (20 ml.) and 1 drop of concentrated hydrobromic acid was heated at reflux temperature for 4 hours. The hot solution was poured into 100 ml. of water and extracted with ether (4 x 20 ml.). The ether layer was extracted first with 20% hydrochloric acid (4 x 15 ml.) then with water (4 x 15 ml.). The ethereal solution was evaporated to dryness and the solid residue was taken up in hot petroleum ether (b.p. 60-100°). Cooling gave colorless plates (0.76 g., 51.7%). Several crystallizations from the above solvent gave an analytical sample m.p. 154-155°. Lions and Ritchie (5,6) report a melting point of 154° for this compound. Calc. for $C_{14}H_{15}N$: C, 85.23; H, 7.66 %. Found: C, 85.46; H, 7.72 %. See table III P. 40 for the ultraviolet spectrum of this compound.

4,5-Dimethyl-1,2-Dihydropyrrolo [3,2,1-hi] indole.

This compound was prepared in 40.5 - 40.7% yield from methylethyl ketone and 1-aminoindoline in a manner analgous to that used for the previous compound. A sample crystallized from petroleum ether (b.p. 30-60°) gave colorless needles m.p. 116-117°. Calc. for $C_{12}H_{13}N$: C, 84.17; H, 7.65%. Found: C, 84.40; H, 7.58%. See Table III P.40 for the ultraviolet spectrum of this compound.

<u>1,2,6a,6,7,8,9,9a-Octahydropyrrolo [3,2,1-jk] carbazole.</u>

A mixture of granulated tin (4.0 g), concentrated hydrochloric acid (6 ml.), ethanol (10 ml.) and the dihydro derivative (1.260 g.) was boiled under reflux for 22 hours. The unreacted tin was removed by decantation and the cooled solution was treated with concentrated ammonium hydroxide until alkalinity was achieved. This slurry was then treated with 50% potassium hydroxide (100 ml.) and filtered through celite. The filtrate was extracted with ether, the celite washed several times with chloroform and the organic phases were combined and evaporated on a flash evaporator. The residual oil was dissolved in a small amount of ether and allowed to stand in the refrigerator for several days. At the end of this time the precipitated solid was separated by filtration and recrystallized from petroleum ether (b.p. 60-100°) giving colorless needles (0.104 g) m.p. 133°. This was thought to be either 7-(2-hydroxycyclohexyl)indoline or 7(1-hydroxycyclohexyl)indoline. Calc. for $C_{14}H_{19}ON$: C, 77.38; H, 8.82%. Found: C, 77.79; H, 8.65%. I.R. spectrum (CCl_4): 3402, 3603 cm^{-1}. The ether solution from the above crystallization was evaporated and the oil evaporatively distilled at 85-95/0.2 mm to give 0.700 g (65.1%) of a colorless pleasant smelling oil. The pure material possessed b.p. 84-87°/0.14 mm. Calc. for $C_{14}H_{17}N$: C, 84.37; H, 8.60%. Found: C, 84.59; H, 8.73%. For the ultra violet spectrum of this base see Table II P. 36. The picrate was prepared and on several crystallizations from ethanol yellow-orange needles m.p.155-156° were obtained. Calc. for $C_{14}H_{17}N$: $C_6H_3O_7N_3$: C, 56.07; H, 4.71%. Found: C, 56.01; H, 4.75%.

__1,2-Dimethyl-1,2,4,5-Tetrahydropyrrolo [3,2,1-hi] indole.__

This compound was prepared in 64% yield in a manner identical to that used for the previous compound. The pure material possessed b.p. 60-62°/0.13 mm. Calc. for $C_{12}H_{15}N$: C, 83.19; H, 8.73%. Found: C, 83.07; H, 8.81%. The ultraviolet spectrum of this compound is given in Table II P.36. The picrate was prepared in ether and on crystallization from ethanol yellow-orange needles m.p. 169-171° were obtained. Calc. for $C_{12}H_{15}N$: $C_6H_3N_3O_7$: C, 53.73; H, 4.51%. Found: C, 53.65; H, 4.61%.

__Attempted Preparation of 1,2,4,5-Tetrahydropyrrolo [3,2,1-hi] indole from Indoline and 1,2-Dibromoethane.__

A solution of indoline (5.0 g.) in 1,2-dibromoethane (40.0 g) was slowly heated to 150° in an atmosphere of nitrogen. A crystalline solid which gradually went into solution separated out. This mixture was maintained at 150° for 20 hours, cooled, poured into 100 ml. of concentrated hydrochloric acid, and steam distilled until all the 1,2-dibromoethane was removed. The residue from the steam distillation was made strongly basic with concentrated aqueous sodium hydroxide and steam distilled until a clear distillate was obtained. The distillate was extracted with ether, the ether removed _in vacuo_ and the residual oil distilled at reduced pressure. An oil (2.0g) b.p. 86 - 90°/5 mm. whose properties were identical to those of indoline, was obtained.

Catalytic Dehydrogenation of 1,2-Dimethyl, 1,2-Dihydropyrrolo-[3,2,1-hi] indole.

A mixture of the above tricyclic compound (0.502 g.), 10% palladium on charcoal (0.50 g.) and p-cymene (10 ml.) was boiled under reflux for 3 hours in a nitrogen atmosphere. The hot mixture was filtered through celite, the p-cymene removed in vacuo and the residue sublimed at 75° and 0.075 mm. The sublimate consisted of an oil and a crystalline solid. This mixture was taken up in hot petroleum ether (b.p. 30-60°) and on cooling rosettes of needles (0.193 g.) possessing properties identical to those of the starting material were obtained. Evaporation of the solvent from the above crystallization gave an oil possessing N-H absorption in the infrared spectrum. This oil was not further investigated.

Catalytic Dehydrogenation of 1,2,6,7,8,9-Hexahydropyrrolo [3,2,1-jk] carbazole.

A mixture of the above carbazole (1.005 g.), 10% palladium on charcoal (0.50 g.) and p-cymene (20 ml.) was boiled under reflux for 4 hours in a nitrogen atmosphere. The hot mixture was filtered through celite, the solvent removed in vacuo and the residue placed on a column of "Merck" alumina. Elution with petroleum ether (b.p. 80-100°) gave a small amount of starting material. Elution with 20% chloroform in petroleum ether (b.p. 80-100°) gave on evaporation of the eluate a colorless crystalline solid (0.279 g.). Recrystallization of this solid from petroleum ether (b.p. 30-60°) gave colorless needles m.p. 95° thought to be 1,2-dihydropyrro [3,2,1-jk] carbazole. Calc. for $C_{14}H_{11}N$: C, 87.00; H, 5.74%. Found: C, 87.34; H, 5.34%. Ultraviolet spectrum (in absolute ethanol): $\lambda_{max.}$ 236, 246(sh.), 260, 287, 292(sh), 297, 340, 356 mμ. Log ε: 4.66, 4.45, 4.30, 3.39, 3.93, 4.10, 3.65, 3.66.

<u>Butanone-2-phenylhydrazone.</u>

A mixture of phenylhydrazine (108 g.), methylethylketone (60 g.) and water (400 ml.) was boiled under reflux for 2 hours. After cooling the organic phase was decanted off and the aqueous layer extracted with ether, the organic phases were combined, the ether removed in *vacuo* and the residue distilled at reduced pressure. The fraction (153 g., 94.4%) b.p. 126-128/6 mm. was collected. Arnold (87) reports b.p. 150/100 mm. for this compound.

<u>2,3-Dimethylindole.</u>

Butanone-2-phenylhydrazone (150 g.), concentrated hydrobromic acid (1 ml.) and ethyleneglycol (500 ml.) were boiled under reflux for 10 hours. The hot mixture was poured into 2 l. of water and when cool the brown precipitate was removed by filtration. This material was melted and distilled at reduced pressure to give a pale yellow liquid b.p. 110-115°/0.05 mm. which rapidly solidified, m.p. 106°. The yield of pure material was 124.8 g. (91.1%). Marion and Oldfield (88) report m.p. 106° for 2,3-dimethylindole.

<u>1-Nitroso-2,3-dimethylindole.</u>

2,3-Dimethylindole (2.00 g.) in glacial acetic acid (20 ml.) containing water (1 ml.) was cooled to 0° in an ice-salt bath. The stirred solution was treated with solid sodium nitrite (0.97 g.) and then left at 0° for ½ hour. This solution was diluted with water, the bright yellow solid filtered at the pump and dried. Crystallization of this material from petroleum ether (b.p. 30-60°) gave yellow flakes m.p. 62° which could not be kept at room temperature for more than a few days. Wolff (69) reports m.p. 63° for this compound.

<u>Attempted Reductive Condensation of 1-Nitroso-2,3-Dimethylindole with Methylethylketone.</u>

To a stirred solution of 1-nitroso-2-3-dimethylindole (1.4 g) in 50% aqueous methanol (50 ml.) containing methylethylketone (10 ml.) was added zinc dust (5.0 g.) and the mixture cooled to 10° in an ice-bath. The stirred mixture was then treated dropwise with glacial acetic acid (5.0 ml.) at such a rate that the temperature of the reaction mixture did not exceed 15°. The mixture was allowed to come to room temperature over a period of 3 hours and then poured into a large volume of cold water. Extraction of this solution with ether after removal of the unreacted zinc by filtration gave on evaporation of the ether extract only 2,3-dimethylindole.

<u>Reduction of 2,3-Dimethylindole.</u>

2,3-Dimethylindole was readily reduced by both zinc and hydrochloric acid and tin in ethanolic hydrochloric acid. The latter method gave the most satisfactory yield of 2,3-dimethylindoline and was the one used on a large scale.

(a) <u>Zinc and hydrochloric acid reduction of 2,3-dimethylindole.</u>

A mixture of 2,3-dimethylindole (10.0 g.), ethanol (100 ml.) and granulated zinc (25 g., 30 mesh) was treated in a dropwise manner with concentrated hydrochloric acid (100 ml.) at a rate sufficiently rapid to keep the solution boiling under reflux. When all the hydrochloric acid had been added the mixture was heated until all the zinc was consumed. The cooled reaction mixture was made basic with concentrated ammonium hydroxide and then treated with 50% sodium hydroxide and filtered through celite. The filtrate was extracted with ether and combined with the ether wash of the celite. The combined ether extract and wash liquid were extracted with 20% hydrochloric acid (3 x 35 ml.). and the ether layer evaporated to dryness giving 6.7 g. of 2,3-dimethylindole. The acid layer from above was made basic with sodium carbonate, ether extracted, the ether evaporated and the residue evaporatively distilled at 140-145°/18 mm. A colorless oil (1.10 g., 32.9% based on indole consumed) was obtained. This was shown to be a mixture of 73.5% <u>cis</u>-2,3-dimethylindoline and 26.5% <u>trans</u>-2,3-dimethylindoline by G.L.P.C (Apiezon M on celite).

(b) Tin and Hydrochloric Acid Reduction of 2,3-Dimethylindole.

A mixture of 2,3-dimethylindole (50.0 g.), ethanol (270 ml.), concentrated hydrochloric acid (270 ml.) and granulated tin (410 g., 30 mesh) was boiled under reflux for 24 hours. The unreacted tin was removed by decantation and washed with ethanol. The pale yellow solution was cooled, made basic with concentrated ammonium hydroxide, and treated with 50% sodium hydroxide (300 ml.). The resulting slurry was filtered through celite, the celite washed several times with chloroform, and the chloroform combined with an ether extract of the filtrate. The organic phases were evaporated on a flash evaporator and the oil remaining distilled at reduced pressure. A colorless liquid (38.4 - 39.8 g., 75.8 - 78.6%) b.p. 109 - 113°/10 mm. was obtained. This was shown to consist of 66.0% <u>cis</u>- and 34.0% <u>trans</u>-2,3-dimethylindoline.

__cis__-and __trans__-1-Nitroso-2,3-Dimethylindoline

A stirred solution of __cis__- and __trans__-2,3-dimethylindoline (14.5 g.) in concentrated hydrochloric acid (14.6 ml.) was cooled to 0° and treated in a dropwise manner with a solution of sodium nitrite (7.1 g.) in water (60 ml.). After the addition was complete the mixture was stirred at 0-5° for ½ hour, and extracted with ether. The ether was evaporated and the remaining oil distilled at reduced pressure. A yellow oil b.p. 106 - 107°/0.35 mm. was obtained. Yield 16.5 g. (95.1%). Calc. for $C_{10}H_{12}ON_2$: C, 68.16; H, 6.86%. Found: C, 68.13; H, 6.80%.

__cis__-and __trans__-1-Amino-2,3-Dimethylindoline.

A suspension of lithium aluminum hydride (7.0 g.) in dry ether (100 ml.) was treated with a solution of the nitroso compounds (26.6 g.) in dry ether (300 ml.) at a rate sufficiently rapid to maintain the ether at reflux temperature. When the addition was complete the stirred mixture was boiled under reflux for 4 hours, the cooled mixture treated carefully with water and the organic layer decanted. The solid residue was extracted with ether and the combined organic layers evaporated. The residue was distilled at reduced pressure yielding a colorless oil (21.4 g., 87.4%) b.p. 81-82°/0.5 mm. Calc. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70%. Found: C, 73.99; H, 8.61%.

__cis__-and __trans__ __1,2,4,5-Tetramethyl-1,2-Dihydropyrrolo [3,2,1-hi] indole.__

A mixture of __cis__-and __trans__-1-amino-2,3-dimethylindoline (16.5 g.) methylethylketone (15.5 g.), ethylene glycol (200 ml.) and a few drops of concentrated hydrobromic acid was boiled under reflux for 6 hours and poured into 500 ml. of cold water. This was extracted with ether (3x 100 ml.) the ether extracted with 20% hydrochloric acid (4 x 50 ml.), then water (3 x 50 ml.), and finally evaporated on a flash evaporator. The residual oil was distilled at reduced pressure to give a pale yellow oil (11.6 g., 60.6%) b.p. 100-102/0.20 mm. which slowly solidified on standing. This material was shown to be a mixture of <u>cis</u>- and <u>trans</u>-isomers by N.M.R. However repeated crystallization of this mixture from ethanol-water gave colorless flakes m.p. 56-58° which were shown to be isomerically pure by N.M.R. and later assigned the <u>cis</u>-configuration. Calc. for $C_{14}H_{17}N$: C, 84.37; H, 8.60%. Found: C, 84.09; H, 8.31%. See Table III p. 40 for the ultraviolet spectrum of this compound.

<u>1,2,4,5-Tetramethylpyrrolo [3,2,1-hi] indole.</u>

A mixture of <u>cis</u> and <u>trans</u>- 1,2,4,5-tetramethyl-1,2-dihydropyrrolo [3,2,1-<u>hi</u>] indole (2.130 g.), 10% palladium on charcoal (2.15 g.) and <u>p</u>-cymene (15 ml.) was boiled under reflux for 5 hours in a nitrogen atmosphere. The hot solution was filtered, the <u>p</u>-cymene removed in <u>vacuo</u> and the residue taken up in petroleum ether (b.p. 80-100°) and placed on a column of "Merck" alumina. A mixture of starting material and product was rapidly eluted with petroleum ether (b.p. 60-100°). These materials were easily separable since the starting material was very soluble in absolute ethanol while the product could be crystallized from this solvent. 0.496 g. Of starting material was recovered and 0.370 g (23.2% based on starting material consumed) of product was obtained. Several crystallizations of the product from ethanol gave colorless needles m.p. 110-111°. Calc. for $C_{14}H_{15}N$: C, 85.23; H, 7.66%.

Found: C, 83.23; H, 7.01%. Ultraviolet spectrum (in absolute ethanol) λ_{max}: 267, 274, 297(sh.), 304(sh.), 310 mμ; log ε, 4.21, 4.19, 3.73, 3.80, 3.66. This material gave an intense purple color with tetracyanoethylene.

<u>Attempted Catalytic Hydrogenation of 1,2,4,5-Tetramethylpyrrolo [3,2,1-hi] indole.</u>

The above tricyclic compound (0.0878 g.) in ethanol (25 ml.) containing 10% palladium on charcoal (0.010 g.) was shaken mechanically at room temperature under a hydrogen pressure of 1 atmosphere for 22 hours. An ultraviolet spectrum of the filtered solution indicated only starting material was present.

<u>1-Benzenesulfonyl-cis-2,3-Dimethylindoline.</u>

<u>cis</u>-and <u>trans</u> 2,3-Dimethylindoline (10.0 g., obtained from tin and hydrochloric acid reduction of 2,3-dimethylindole), benzenesulfonyl chloride (15.0 g.), and 10% sodium hydroxide (300 ml) were shaken mechanically for ½ hour and then heated to 60° for 10 minutes. The mixture was cooled, and extracted with ether, the ether washed with 10% hydrochloric acid (3 x 30 ml.), then water (3 x 30 ml.) and finally evaporated. The residue was carefully fractionally crystallized from petroleum ether (b.p. 80-100°) giving two sharp melting crystalline solids. Fraction 1 (parallelograms, 11.5 g.) was isomerically pure as shown by N.M.R. and possessed m.p. 100°. Fraction 2 (flakes—5.0 g.) m.p. 76-77° was shown to be a 1-1 complex of the <u>cis</u> and <u>trans</u> compounds by N.M.R.

Several crystallizations of the high melting material from petroleum ether (b.p. 60-100°) gave pure 1-benzenesulfonyl-<u>cis</u>-2,3-dimethylindoline as beautiful colorless parallelograms m.p. 113-114°. Calc. for $C_{16}H_{17}O_2NS$: C, 66.88; H, 5.96%. Found : C, 66.93; H, 6.10%.

<u>Equilibration of cis- and trans-2,3-Dimethylindoline.</u>

<u>cis</u>-and <u>trans</u>-2,3-Dimethylindoline (4.00 g., from tin and hydrochloric acid reduction of 2,3-dimethylindole), polyphosphoric acid (5.0 g., prepared from 2.5 g. 85% phosphoric acid and 2.5 g phosphorous pentoxide), and 2,3-dimethylindole (0.50 g.) were heated in a nitrogen atmosphere at 280° for 12 hours. The above mixture was cooled and decomposed with 20% sodium hydroxide. This material was extracted with ether (3 x 30 ml.), and the ether was extracted with 30% hydrochloric acid (3 x 30 ml.), then evaporated giving 2,3-dimethylindole (0.75 g.). The acid layer was made alkaline with solid sodium carbonate, extracted with ether, the ether evaporated, and the residue distilled at reduced pressure. The fraction (2.73 g.) b.p. 103-108°/8 mm. was collected. This was shown to be largly isomerized by N.M.R.

<u>1-benzenesulfonyl-trans-2,3-Dimethylindoline.</u>

The benzene-sulfonamide was prepared in the usual manner from the equilibrated indolines and on careful fractional crystallization from petroleum ether (b.p. 80-100°) two crystalline sharp melting solids were obtained. The main product m.p. 101° was shown to be isomerically pure by N.M.R. and was assigned the <u>trans</u>-configuration. The minor low melting material (m.p. 76-77°) was shown to be a 1:1 complex of <u>cis</u>-and <u>trans</u>-benzenesulfonamides by N.M.R.

The high melting solid was recrystallized several times from petroleum ether (b.p. 60-100°) giving lustrous stubby white needles m.p.103°. Bader, Bridgewater and Freeman (63) report m.p. 101-103° for this compound.

<u>cis-2,3-Dimethylindoline</u>

A mixture of pure 1-benzenesulfonyl-<u>cis</u>-2,3-dimethylindoline (4.00 g.), reagent grade phenol (6.0 g.) and constant boiling hydrobromic acid (60 ml.) was boiled under reflux for 4 hours. The cooled mixture was made basic with 30% sodium hydroxide (90 ml.), ether extracted (4 x 50 ml.) the ether extracted with 20% hydrochloric acid (3 x 30 ml.), the acid layer made alkaline with 30% sodium hydroxide, extracted with ether, and the ether evaporated. Evaporative distillation of the residual oil (125-130°/18 mm) gave 1.78-1.76 g. (88.4 - 89.7%) pure <u>cis</u>-2,3-dimethylindoline. The pure material possesses b.p. 94-95°/3 mm. and n_D^{24} 1.560 Calc. for $C_{10}H_{13}N$: C, 81.58; H, 8.90 %. Found: C, 81.29; H, 9.07 %.

<u>trans-2,3-Dimethylindoline.</u>

Pure trans-2,3-dimethylindoline was prepared in 89.2-92.7% yield from its benzene sulfonamide in a manner identical to that used for the recovery of pure <u>cis</u>-2,3-dimethylindoline from its benzenesulfonamide. The pure material possesses b.p. 92-94/3 mm. and n_D^{24} 1.554 Bader, Bridgewater and Freeman (63) report b.p. 253°/760 mm. and n_D^{25} 1.551 for trans-2,3-dimethylindoline.

<u>1-Nitroso-cis-2,3-Dimethylindoline.</u>

A stirred solution of <u>cis</u>-2,3-dimethylindoline (2.01 g.) in concentrated hydrochloric acid (2 ml.) and crushed ice was cooled to 0° and treated dropwise with a solution of sodium nitrite (1.0 g) in water (5 ml.) at such a rate that the reaction temperature did not exceed 5°. After the addition was complete the mixture was stirred at 0-5° for ½ hour, extracted with ether, the ether evaporated and the residue evaporatively distilled at 90-100°/0.05 mm. A yellow oil (2.26 g., 93.9%) was obtained which contained 10% of the trans-isomer as shown by N.M.R. This material was therefore not characterized.

1-Nitroso-trans-2,3-Dimethylindoline.

This material was prepared from trans-2,3-dimethylindoline (2.00 g) in a manner identical to that used for the cis-compound. Work up in the usual manner followed by evaporative distillation at 90-100°/0.075 mm. gave 1-nitroso-trans-2,3-dimethylindoline (2.24 g., 93.6%) as a yellow oil containing about 10% of the cis-isomer as shown by N.M.R. It was not characterized further.

1-Amino-cis-2,3-Dimethylindoline.

A suspension of lithium aluminum hydride (0.6 g.) in dry ether (20 ml.) was treated in a dropwise manner with a solution of the 90% pure cis-nitroso compound (1.70 g.) in dry ether. The stirred mixture was boiled under reflux for 3 hours and worked up in the usual manner giving a pale yellow oil. This oil was evaporatively distilled at 80-90°/0.1 mm giving a colorless oil (1.50 g., 91.0%) which was not further characterized.

1-Amino-trans-2,3-Dimethylindoline.

This material was prepared from the 90% pure trans-nitroso compound (2.14 g.) in a manner identical to that used for the reduction of the cis-nitroso compound. The usual workup and evaporative distillation at 80-90°/

0.1 mm gave a colorless oil (1.76 g., 50.8%) which was not characterized further.

<u>1,2,4,5-Tetramethyl-cis-1,2-dihydropyrrolo [3,2,1-hi] indole.</u>

A mixture of 1-amino-<u>cis</u>-2,3-dimethylindoline (1.50 g), methylethylketone (1.50 g.), ethylene glycol (50 ml.) and 2 drops of constant boiling hydrobromic acid was boiled under reflux for 8 hours. This was poured into water and ether extracted. The ether was extracted with 10% hydrochloric acid (3 x 15 ml.) and then with water (3 x 10 ml.). The ether was evaporated and the residue was taken up in chloroform and placed on "Merck" alumina. The desired material was readily eluted with petroleum ether (b.p. 60-100°). Concentration of the eluate gave 0.78 g of compound which was isomerically pure as shown by N.M.R. Crystallization of this material from ethanol-water gave colorless flakes m.p. 55-56° (mixed m.p. undepressed) identical in every respect to that compound which had previously been isolated from a mixture.

<u>1,2,4,5-Tetramethyl-trans-1,2-dihydropyrrolo [3,2,1-hi] indole</u>

A mixture of 1-amino-<u>trans</u>-2,3-dimethylindoline (1.76 g.), methylethylketone (2.0g.), ethylene glycol (50 ml.) and 2 drops of concentrated hydrobromic acid was boiled under reflux for 8 hours. Workup in the usual manner followed by elution of the desired material from "Merck" alumina with petroleum ether (b.p. 60-100°) gave pure 1,2,4,5-tetramethyl-<u>trans</u>-1,2-dihydropyrrolo [3,2,1-hi] indole (1.28 g.) as a colorless low melting solid. This material was shown to be isomerically pure by N.M.R. and differed in its properties from the cis-isomer. It was purified by sublimation at room temperature and 0.1 mm pressure. The analytically pure material possessed m.p. 38-40°. Calc. for $C_{14}H_{17}N$: C, 84.37; H, 8.60% Found: C, 84.22; H, 8.67%. See Table III p.40 for the ultraviolet spectrum of this compound.

P A R T II

Attempted Synthesis of 3,8-Dimethylindiazene

and

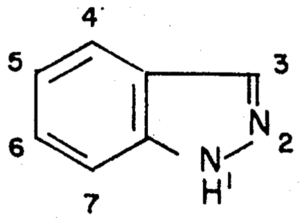
Fourteen-membered Hydrogen-bonded Dimers of some *m*-Substituted Phenols

INTRODUCTION

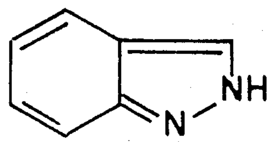
Indazole, the 2-aza analogue of indole, is theoretically capable of existing in three tautomeric forms, I, II, and III. Structure I has been referred to as isoindazole, structure II as indazole, and III as indiazene. Several types of systematic nomenclature have been applied to the various forms of indazole, however, the most generally used is that wherein I, II, and III are called 1H, 2H and 3H-indazole respectively (91). The 1-substituted indazoles must of necessity be derived from structure I, just as 2-substituted indazoles must be derived from structure II. The only authenticated derivatives of III are those bearing two groups at position 3 of the indazole moiety. It should be noted that whereas derivatives of I and II are bicyclic aromatic compounds, those of III are not.

The chemistry and properties of indazoles and isoindazoles have been extensively studied, and there are several reviews on the subject (92-4). Derivatives of indiazene, which in some respects are the most interesting members of the indazole family, have received only a negligible amount of attention. The majority of papers dealing with this latter class of compounds are of an early nature, and from this standpoint alone merit reinvestigation.

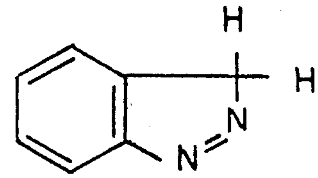
The earliest reported investigations in the field of indiazene chemistry were published in a series of papers by Duval (95-8). Warming solutions of tetrazotized 2,2'-diaminodiphenylmethanes bearing substituents at the 4- and 4'-poistions (IV) gave compounds to which Duval assigned the bis-azo structure (V) on the basis of their analyses, chemical properties, and the mode of synthesis. Electronegative groups in the 4- and 4'- positions favoured formation of the bis-azo compounds, while other substituents gave in



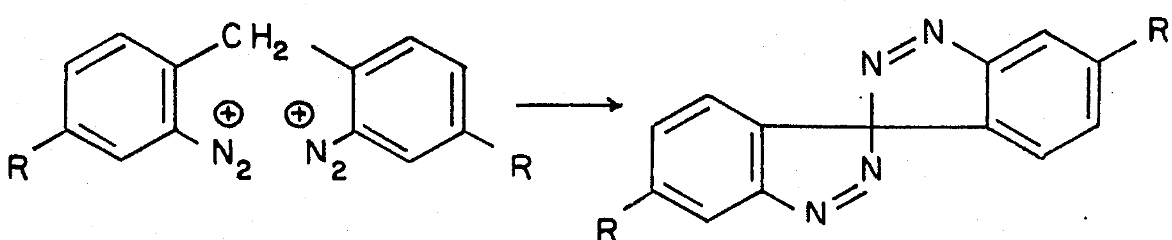
I



II

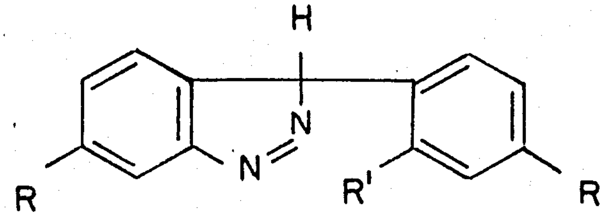


III



IV V

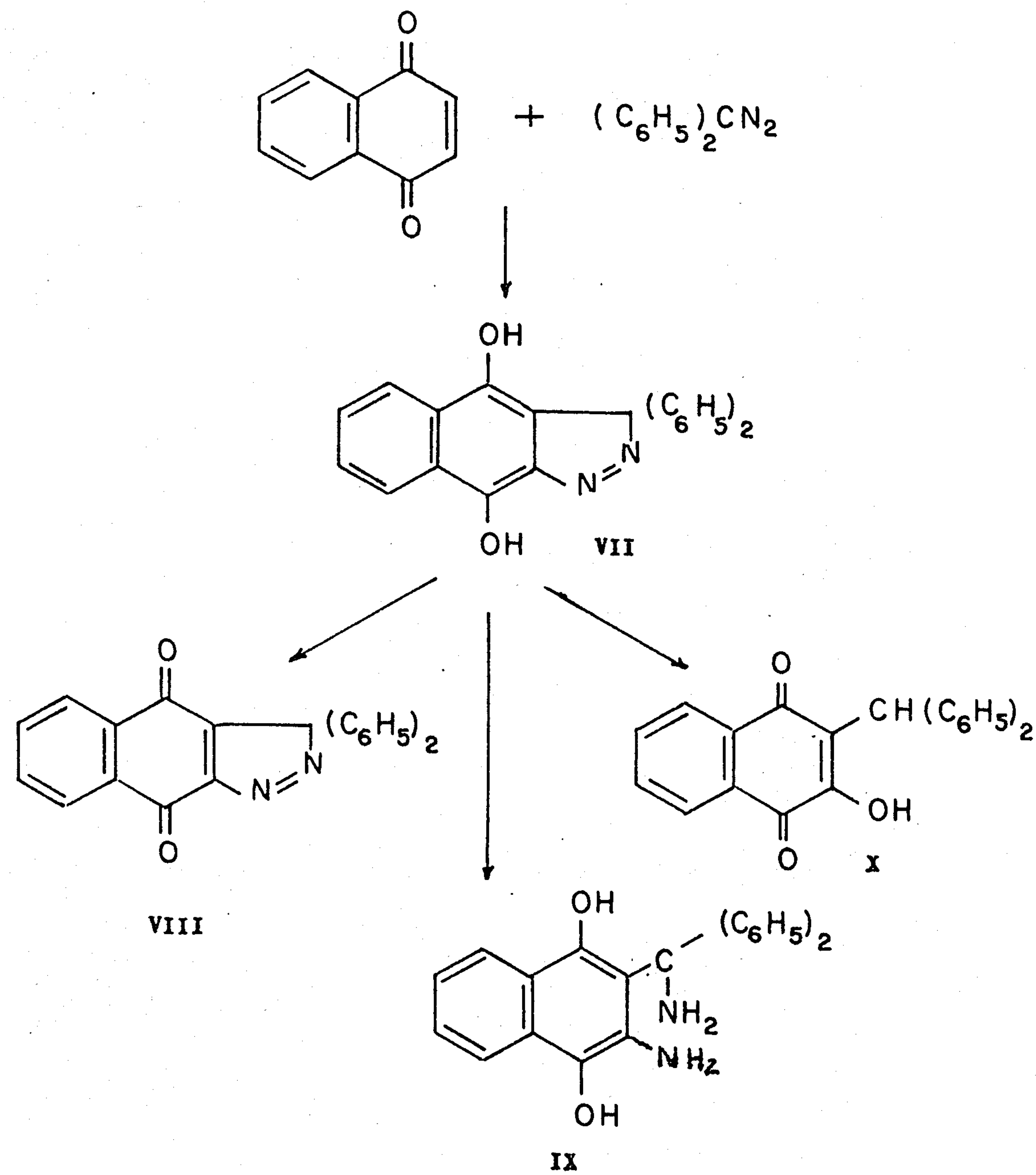
R=H, Cl, CN, CO_2H, $CO_2C_2H_5$, CH_3CO, or CH_3CONH



VI

addition, varying amounts of phenolic products. The azo compounds were neutral (except where R = CO_2H), high melting solids, insoluble in most organic solvents. They were readily reduced with stannous chloride giving colorless products, from which the azo compounds could be easily regenerated by air or mercuric oxide oxidation. On warming with sulfuric acid one mole of nitrogen was eliminated, and phenolic compounds, to which Duval assigned structure VI (R' = OH), were formed. Hydrochloric acid gave the corresponding chloro compounds (VI, R' = Cl). The hydrolysis products possessed chemical properties typical of azo compounds, and definitely unlike those of 1H-or 2H-indazole derivatives. That indiazone formation should be preferred in this case is unusual, especially since one would expect 1H- or 2H-indazole derivatives to be appreciably more stable from a resonance point of view. Obviously, the above work must be thoroughly reexamined before any firm structural conclusions can be reached. Unfortunately, Duval's work seems to have remained entirely unnoticed except for a report by Mascarelli and Zoschi (99), who claimed the bis-azo compound (V, R = Cl) was also formed in low yield when tetrazotized 2,2'-diamino-4,4'-dichlorodiphenylmethane (IV, R = Cl) was treated with potassium iodide.

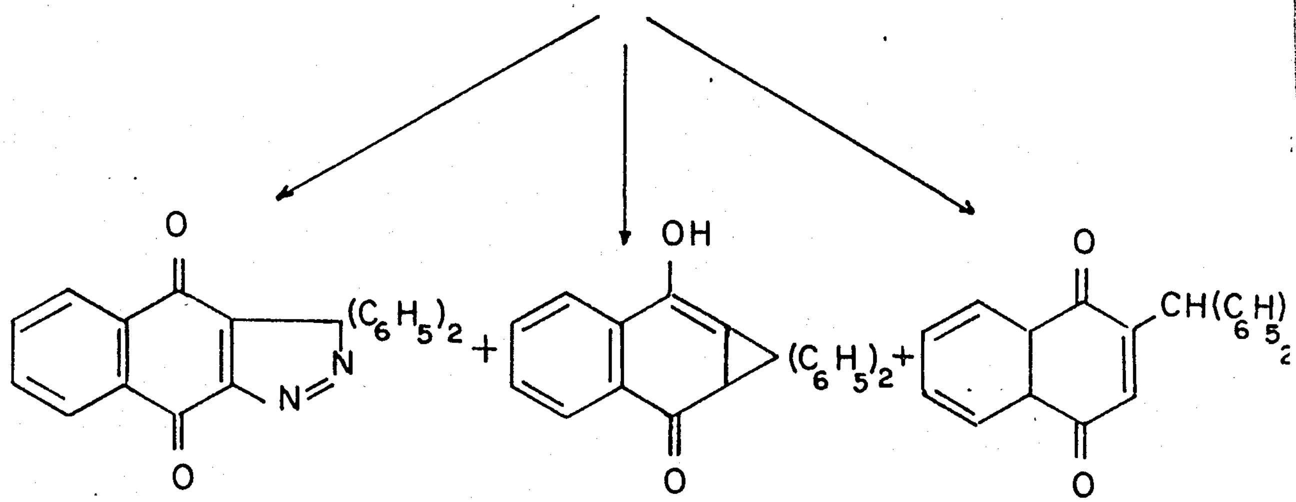
In connection with their interest in quinonoid compounds, Fieser and Peters (100) demonstrated that napthoquinone and diphenyldiazomethane reacted to form a substituted indiazone (VII). The product formed a diacetate and a dimethyl ether, and was readily oxidized to the quinone (VIII) by either mercuric oxide or nitrous acid. Reduction with zinc and acetic acid gave a diamine (IX) proving the presence of an azo group. Solution of the azo compound in alkali followed by air oxidation, resulted in elimination of one mole of nitrogen and formation of 2-diphenylmethyl-3-hydroxy-1,4-napthoquinone (X).


O
O
+ $(C_6H_5)_2CN_2$
OH
$(C_6H_5)_2$
N
N
OH
VII
O
$(C_6H_5)_2$
N
N
O
VIII
O
$CH(C_6H_5)_2$
OH
O
X
OH
$(C_6H_5)_2$
C
NH_2
NH_2
OH
IX

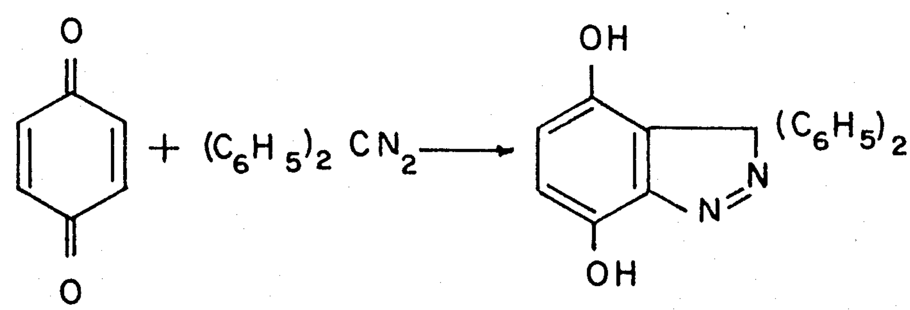
Undoubtedly the most interesting property of VII was its behavoir on thermal decomposition. Using Δ^1 pyrazolines as an analogy, Fieser reasoned this compound might also eliminate nitrogen forming a cyclopropane derivative. The indiazene decomposed at its melting point with loss of nitrogen, yielding three compounds. The first two of these were shown to be quinones VIII and XII, while the third was assigned a cyclopropane structure (XI) on the basis of observations outlined below. This substance was a fiery red solid (m.p. 274°) whose analysis was in accord with that expected. It was soluble in alkali, alkali carbonates, and concentrated sulfuric acid, giving intensely colored solutions. The compound formed a monoacetate, and quantitative reaction with Zerewitinoff's reagent revealed the presence of one active hydrogen atom and one carbonyl group. On zinc and acetic acid reduction followed by air oxidation, 2-diphenylmethyl-1,4-napthoquinone (XII) was obtained. The supposed cyclopropane derivative was not investigated further. It should be noted that structure XI is quite improbable. If this compound truly did possess a cyclopropane structure, then on steric grounds alone one should expect the ketonic form to be far more stable. Obviously this work must also be reexamined before any firm conclusions on the validity of structure XI can be made.

Like napthoquinone, benzoquinone and diphenyldiazomethane also formed an indiazene derivative (XIII). This same reaction had been observed earlier by Staudinger (101), who however, failed to investigate it further. 3,3-Diphenyl-4,7-dihydroxyindiazene (XIII) formed a diacetate and a dimethyl ether, and was soluble in both acidic and basic media giving colored solutions. Unlike VII, its alkaline solutions were not susceptible to air oxidation.

VII



VIII XI XII



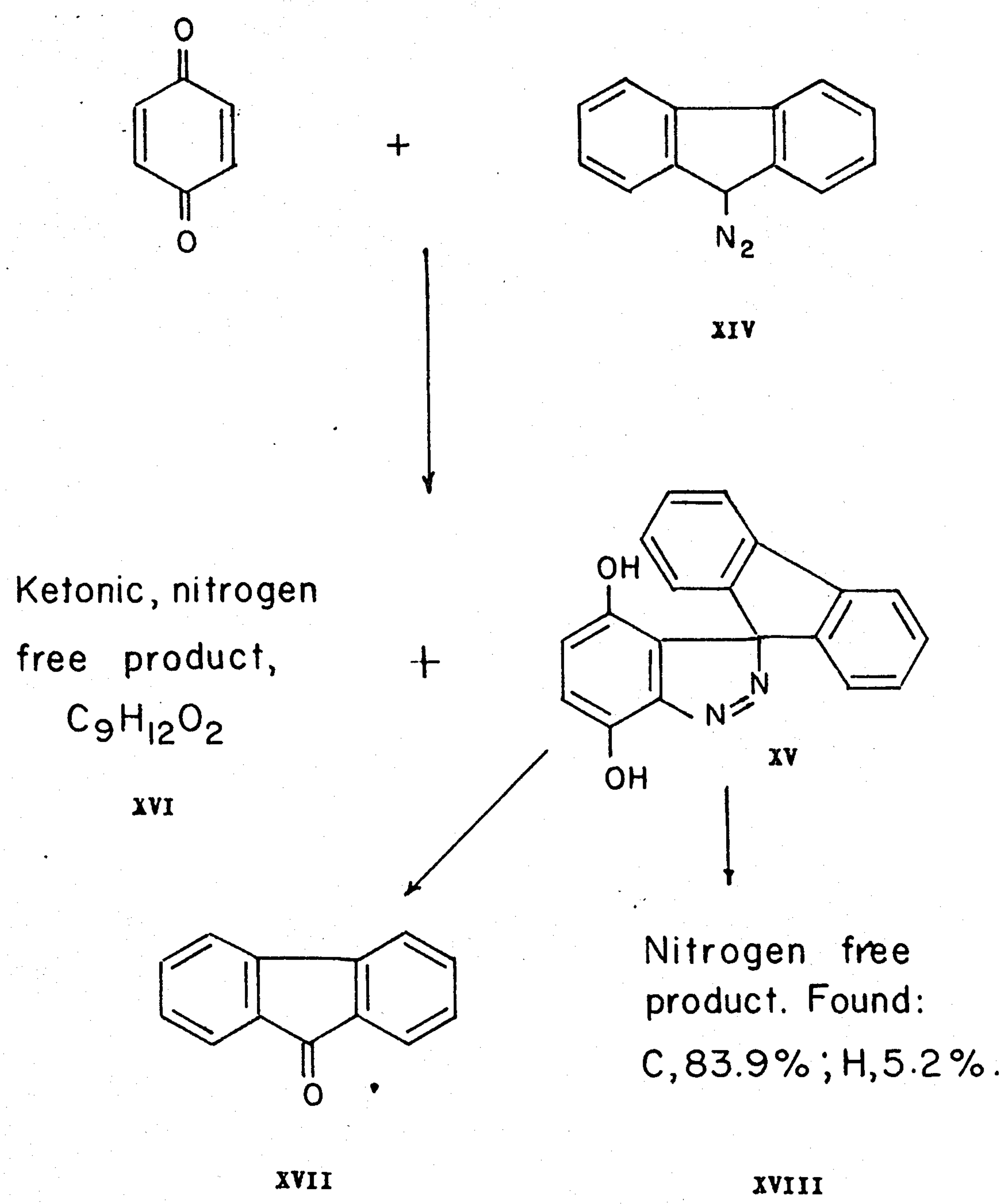
XIII

In the words of the authors, "neither this substance nor any of its simple derivatives gives good products on thermal decomposition". Similar behaviour was noted for the alkyl and acyl derivatives of VII.

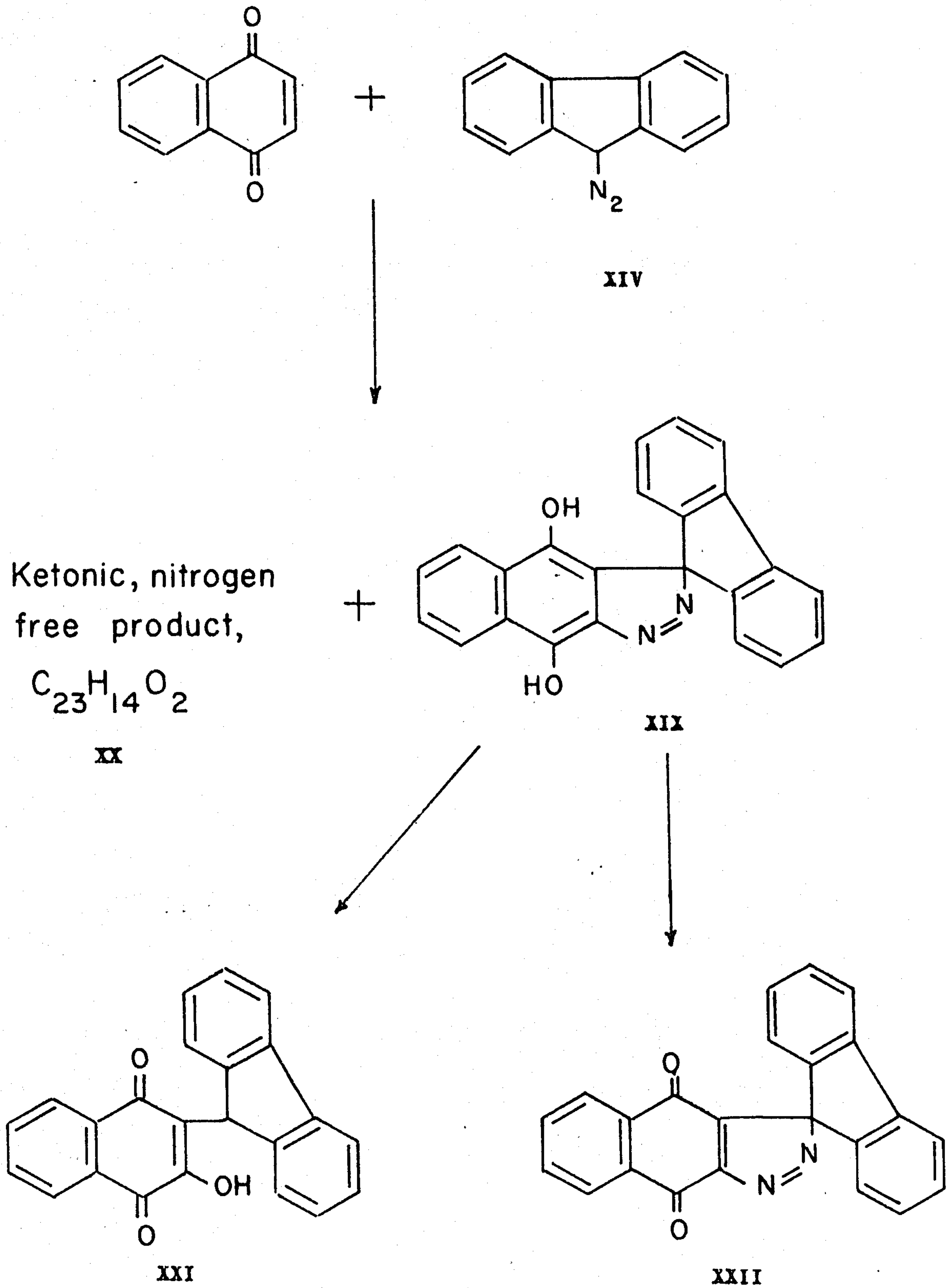
In an extension of Pieroni's work, Horner and Lingnau (102) examined the addition of 9-diazofluorene (XIV) to several p-quinones.

Two substances were isolated from the reaction of benzoquinone with 9-diazofluorene. The main product proved to be a substituted indiazone (XV), while that isolated in low yield was a compound containing no nitrogen (XVI). The nitrogen free material ($C_{19}H_{12}O_2$) possessed ketonic properties forming a hydrazone, phenylhydrazone, and semicarbazone, all of unspecified composition. The indiazone (XV) possessed two active hydrogen atoms, formed a monobenzoate, a dimethyl ether, and gave a red solution in aqueous alkali. Oxidation with chromic acid in acetic acid gave fluorenone (XVII) as the only identifiable product. Although pyrolytic decomposition even in the presence of copper powder did not effect nitrogen elimination, this could be accomplished by treating the azo compound with sodium nitrite in acetic acid. The authors do not state what relation, if any, this nitrogen free product (XVIII) bears to XVI.

9-Diazofluorene and naphthoquinone also gave the expected indiazone (XIX). In addition, a small amount of nitrogen free material, which formed a bis-phenylhydrazone, was obtained (XX). In general, this azo compound possessed properties similar to that one obtained from benzoquinone. However, unlike XV, its alkaline solution was susceptible to air oxidation, in which case a hydroxyquinone (XXI) resulted. Sodium nitrite and acetic acid did not bring about nitrogen elimination; instead the corresponding quinone (XXII) was obtained.



O
O
+
N_2
XIV
Ketonic, nitrogen free product, $C_9H_{12}O_2$
XVI
+
OH
N
N
OH
XV
O
XVII
Nitrogen free product. Found: C, 83.9%; H, 5.2%.
XVIII

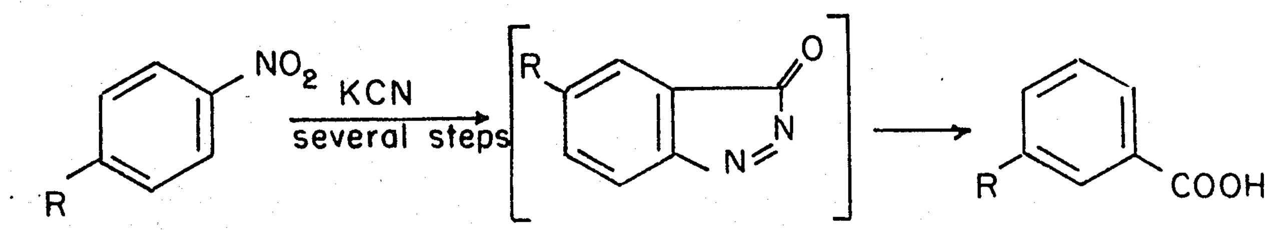

O
O
N2
XIV
Ketonic, nitrogen free product,
C23H14O2
XX
OH
N
N
HO
XIX
O
OH
O
XXI
O
N
N
O
XXII

Quinizarin (1,4-dihydroxyanthraquinone) gave products similar to those obtained from benzoquinone and napthoquinone.

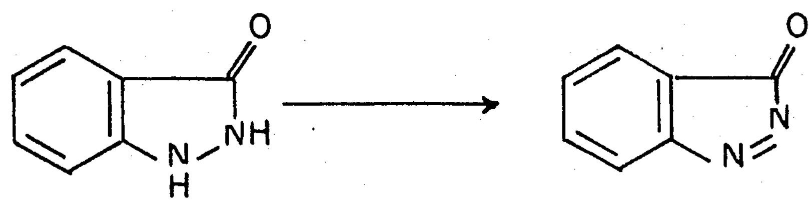
In 1960 Rosenblum (103) proposed a mechanism for the von Richter reaction (formulae XXIII-XXV) involving the intermediate formation of an oxoindiazene (XXIV) which was postulated to hydrolyze to a benzoic acid derivative under the alkaline reaction conditions. More recently, Ullmann and Bartkus (104) presented evidence for formation of 3-oxoindiazene (XXVII) when a solution of 3-indazolinone (XXVI) was subjected to lead tetra-acetate oxidation. Attempted isolation of this substance resulted in polymer formation, however its solutions were stable at -10°. Solutions of XXVII were deep red and possessed a carbonyl absorption in the infrared at 1760 cm^{-1}. Addition of cyclopentadiene or butadiene resulted in formation of the Diels-Alder adducts XXVIII and XXIX, the latter structure being proved by an independent synthesis. In agreement with the proposed von Richter reaction sequence, addition of the oxoindiazene solution to aqueous ethanolic sodium cyanide resulted in instantaneous nitrogen evolution and formation of benzoic acid in high yield. Furthermore, when water, methanol, or acetic acid were added to solutions of XXVII, benzoic acid, methylbenzoate, and acetylbenzoate respectively, were formed.

Solutions of the oxoindiazene on warming or irradiation with ultraviolet light deposited a green polymer without gas evolution.

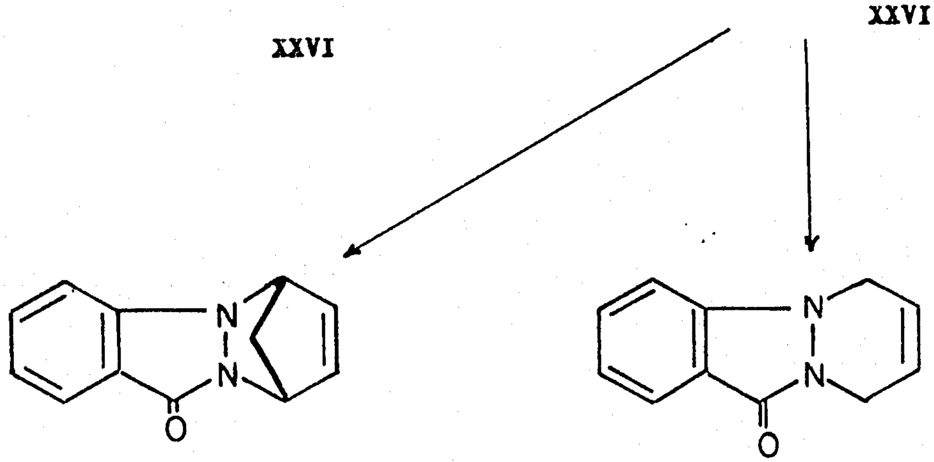
Excluding those mentioned above no other derivatives of indiazene are known. Kovach and Barnes (105) state that 7-methoxyindiazene (XXXI) was obtained by decomposition of N-nitroso-N-acetyl-2-methoxy-6-methylaniline (XXX). This structure is obviously incorrect, and must be replaced by XXXII, since



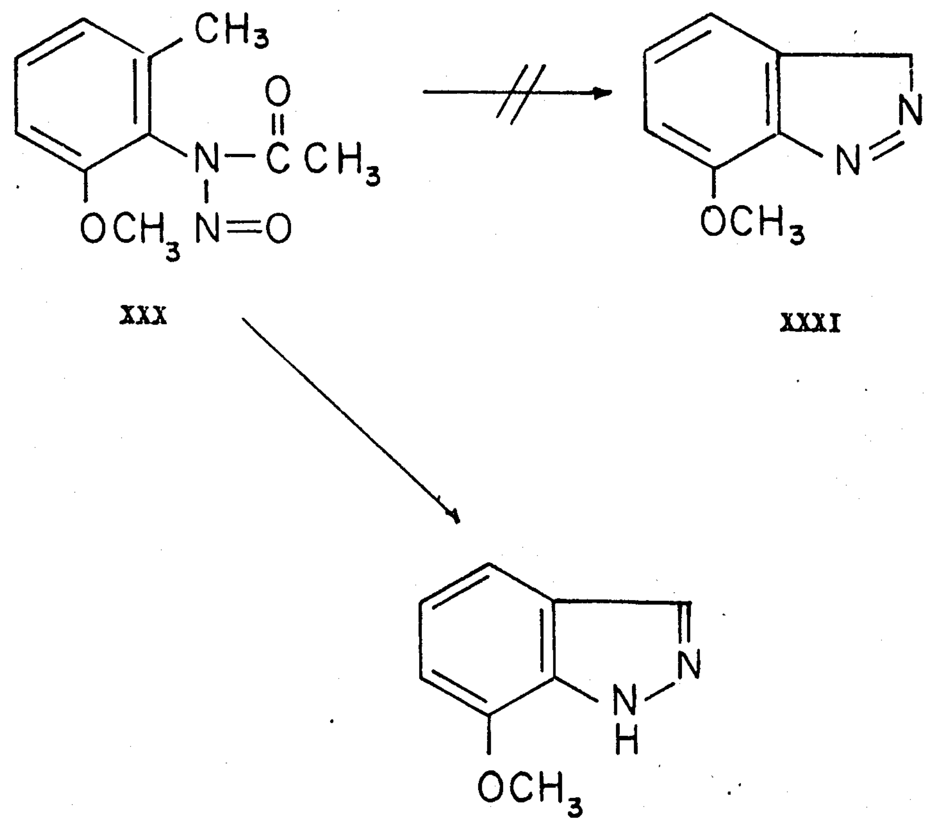
XXIII XXIV XXV



XXVI XXVII



XXVIII XXIX



XXX

XXXI

XXXII

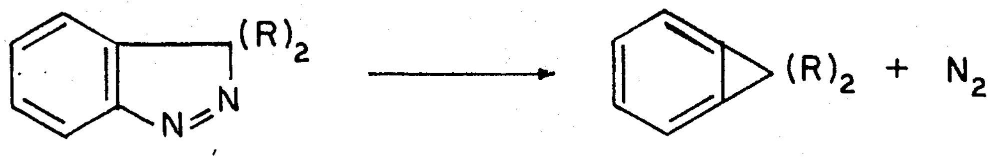
the compound could be extracted from its benzene solution with dilute hydrochloric acid, and furthermore, was precipitated from its acid solution on basification with sodium carbonate.

DISCUSSION

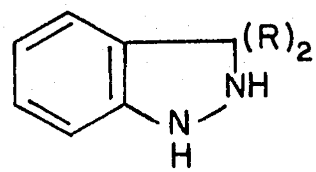
Attention has already been drawn to the almost complete non-existence of simple derivatives of indiazene. This fact prompted us to investigate the synthesis of such compounds bearing only the necessary two groups at position-3 of the heterocyclic system (I, R$\neq$H). Much of our interest in this field stemmed from the formal analogy existing between 3,3-dialkylindiazenes and substituted Δ^1-pyrazolines. These latter compounds are known to lose nitrogen, forming substituted cyclopropanes, on photolytic or pyrolytic decomposition (106), and we reasoned derivatives of indiazene might behave in similar fashion. If the above analogy held, highly strained, as yet unknown, derivatives of benzcyclopropene (II, R$\neq$H) would be formed.

The most obvious approach to derivatives of indiazene appeared to be via oxidation of a 3,3-dialkylindazoline unsubstituted at positions 1-and 2 (III). Careful scrutiny of the literature revealed indazolinone (IV) was the only known compound fitting the above requirements. Mercuric oxide oxidation of indazolinone in diglyme gave deep red solutions, presumably of the desired 3-oxoindiazene (V), however, attempted isolation gave only an isoluble deep green polymer. The nature of the red solution and the polymer obtained from it was not determined. Shortly before submission of this thesis Ullman and Bartkus (104) demonstrated V could not be isolated from solution. A complete discussion of their results has already been presented.

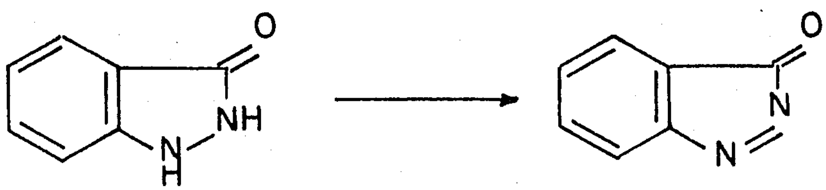
A widely applicable procedure for the preparation of 1H-indazoles involves diazotization of derivatives of o-toluidine bearing electronegative substituents (107). Although 3- alkyl-1H-indazoles have also been prepared



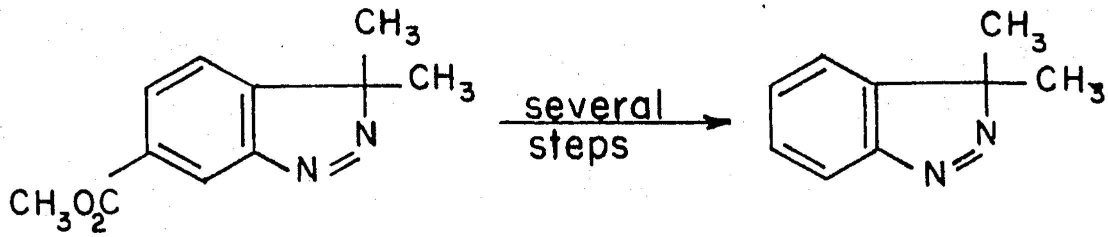
I II



III



IV V



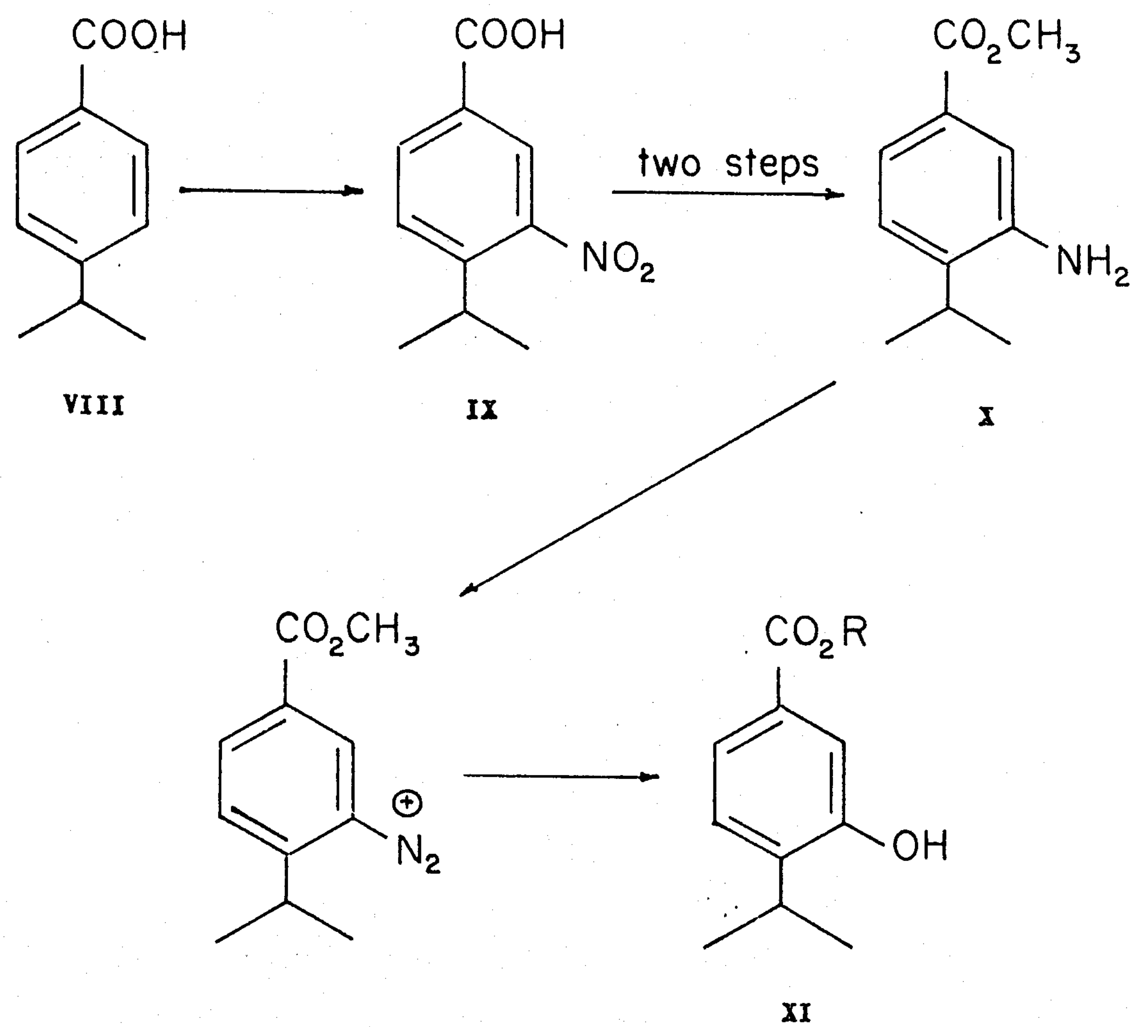
VII VI

in this way (108), the method does not seem to have been applied to those derivatives of *o*-toluidine bearing more than one substituent in the alkyl side chain (e.g. X).

For a projected synthesis of 3,3-dimethylindiazone (VI), 2-*iso*-propyl-5-methoxycarbonylaniline (X) was chosen as starting material. The predicted cyclization product (VII, R = CH_3) was expected to be easily degraded to VI via well trodden methods.

Nitration of *p*-*iso*-propylbenzoic acid (VIII), followed by Fischer esterification and catalytic reduction of the resulting nitro acid (IX), readily provided the necessary aniline. Diazotisation of this substance in glacial acetic acid and allowing the solution to remain at room temperature for two days, gave, after chromatography on alumina and saponification of the product, a carboxylic acid (m.p. 141°) which did not possess the properties expected for 3,3-dimethylindiazene-6-carboxylic acid (VII, R = H). This acid was shown to be phenolic and identical with an authentic specimen of 3-hydroxy-4-*iso*-propylbenzoic acid (XI, R = H), prepared from the diazonium salt of X. The N.M.R. spectrum of the methyl ester of this acid (XI, R = CH_3) was particularly interesting, and will be discussed in a separate section of this thesis.

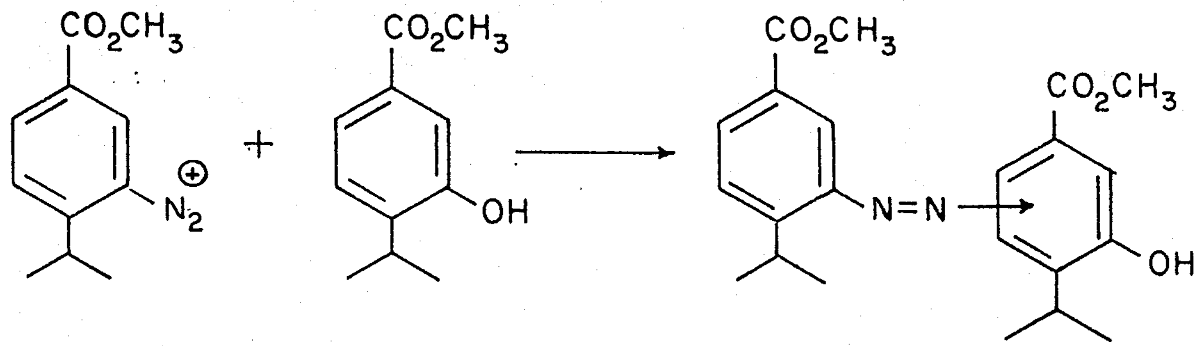
Despite its interesting properties (see below), the product resulting from attempted cyclisation of the diazonium salt (XII) was not the one originally sought for. Keith and Morgan (109) have shown that indazole formation is sometimes favoured when the diazonium salt is cyclised in alkaline medium. Consequently, a series of experiments were carried out in which the above salt was subjected to progressively greater alkaline conditions.


COOH
COOH
two steps
NO_2
CO_2CH_3
NH_2
VIII
IX
X
CO_2CH_3
CO_2R
$N_2^{\oplus}$
OH
XI

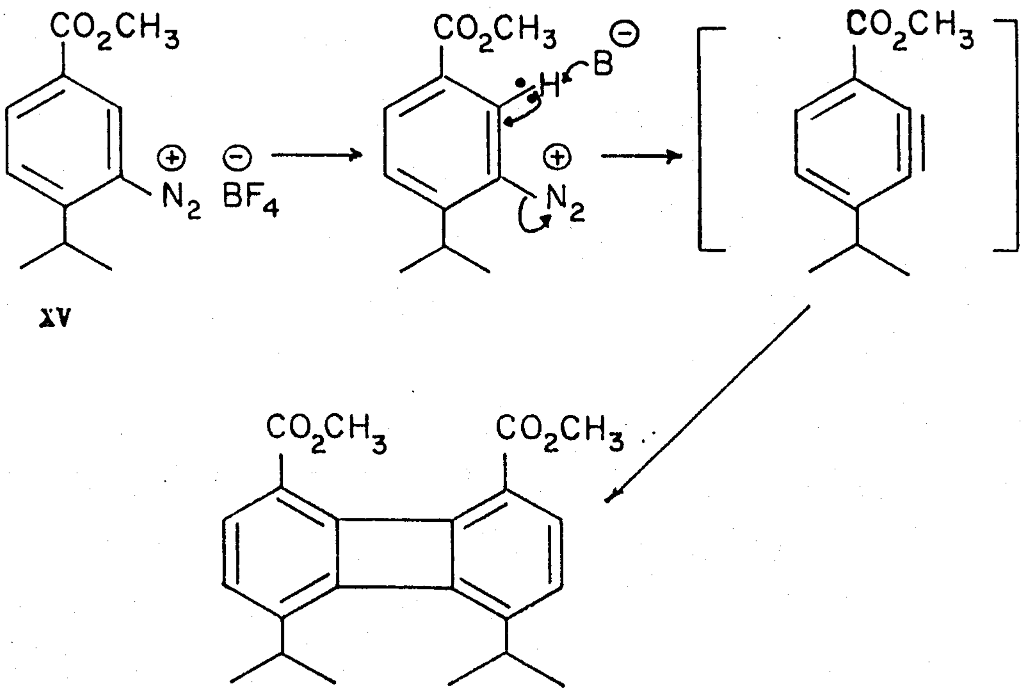
Adding the diazonium salt solution to acetate buffer ($_p$H 6) again failed to bring about cyclization; instead, a deep red solid analysing for $C_{22}H_{26}N_2O_5$ and possessing infrared (nujol) absorption bands at 3420 cm^{-1}, 1710 cm^{-1}, and 1670 cm^{-1}, was formed in low yield. The latter bands were assumed to have arisen from two methoxycarbonyl groups in differing environments, while the origin of the 3420 cm^{-1} absorption was resolved when the compound was shown to be phenolic. The evidence at hand indicated the diazonium ion had coupled with one of its decomposition products (XIII) forming an azo phenol (XIV). To determine whether the phenylazo group had coupled ortho or para to the phenolic hydroxyl, XIV was reduced (29) with hydrazine hydrate and Raney nickel. Of the two products obtained, one was shown to be the expected aniline (X). Attempted isolation of the other product (presumably one of the possible aminophenols) resulted in its decomposition. Compound XIV was not examined further and therefore its structure remains undetermined. However, on steric grounds one might expect the product to be that resulting from an attack of the diazonium ion para to the phenolic hydroxyl group in XIII.

When the cyclization was attempted in carbonate-bicarbonate buffer solution ($_p$H 9) no identifiable product could be isolated. This particular approach was as a result unhesitatingly discontinued.

Failure to achieve cyclization in the above cases led us to investigate the behavior of the benzene diazonium fluoroborate (XV) towards a strong base. When a slurry of this salt in dry *t*-butanol was treated with potassium *t*-butylate in the same solvent, there was obtained, after chromatography and saponification of the product, a small amount of an acid,



XII XIII XIV

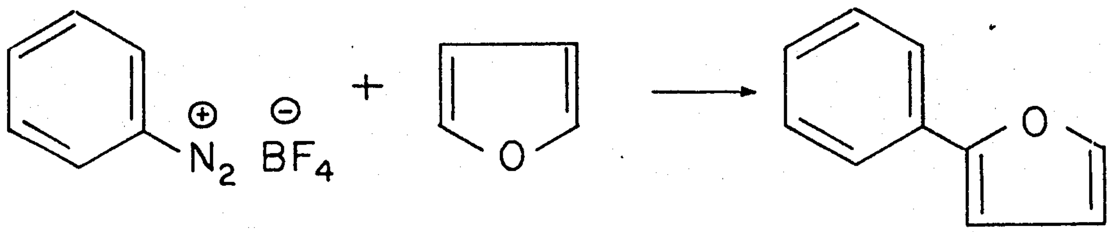


XV

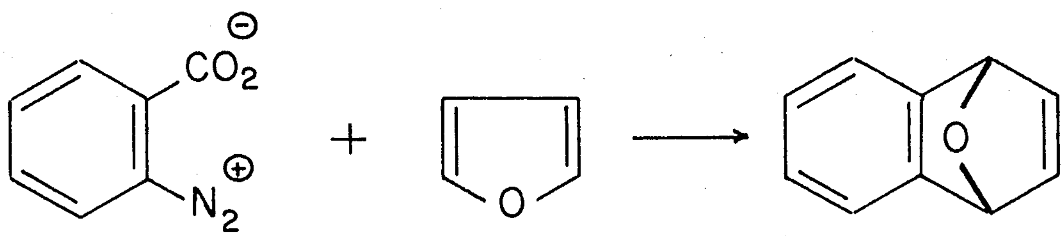
XVI

m.p. 98°. The infrared spectrum proved the absence of OH and NH functions and the presence of a carboxyl group(s) (1685 cm^{-1}). The N.M.R. spectrum showed bands for an _iso_-propyl group(s) (intense doublet and weak septet centered at 1.29 and 3.02 p.p.m. respectively), and a carboxylic acid proton(s) (12.0 p.p.m). The aromatic protons appeared as a well defined AB quartet centered at 7.22 p.p.m. The relative intensities of these bands were not determined. On the basis of this rather precarious evidence it was postulated that the proton situated between the diazonium and methoxycarbonyl groups was sufficiently acidic to be removed by the strong base present. Subsequent elimination of nitrogen, followed by dimerization of the resulting benzyne derivative would give rise to a product with the observed N.M.R. spectrum. It was considered the alternative diphenylene dimer would have a similar N.M.R. spectrum. The reaction was not repeated at this time; instead several benzenediazonium fluoroborates were subjected to the same reaction conditions in the presence of furan. If benzyne formation did occur, it would in effect, be trapped as its Diels-Alder addition product.

Benzene diazonium floroborate when decomposed under these conditions gave a colorless oil whose ultraviolet spectrum (Table IX, p. 122) was like that of 2-phenylfuran (110). Comparison of this oil with authentic napthalene-1,4-endo-oxide (XIX) prepared (111) from benzenediazonium-_o_-carboxylate (XVIII) and furan, proved the non-identity of these two compounds. The oil however, was shown to be identical in every respect with _bona fide_ 2-phenylfuran (XVIII) prepared according to Johnson (110). Despite much determined effort, no product resulting from benzyne formation could be isolated, nor could its



XVII



XVIII

XIX

presence be detected in the N.M.R. spectrum** of the crude product, indicating the above reaction was following the normal Gomberg course .

Repitition of the above reaction with 3-methoxycarbonylbenzenediazonium fluoroborate again resulted in isolation only of the corresponding substituted 2-phenylfuran. The structure of this and previously unreported substituted 2-phenylfurans is based on analyses, N.M.R. spectra, and comparison of their ultraviolet spectra with that observed for 2-phenylfuran.

Results essentially similar to those described above were also obtained with 3,5-dimethoxycarbonylbenzenediazonium fluoroborate, the only product being that resulting from a normal Gomberg reaction.

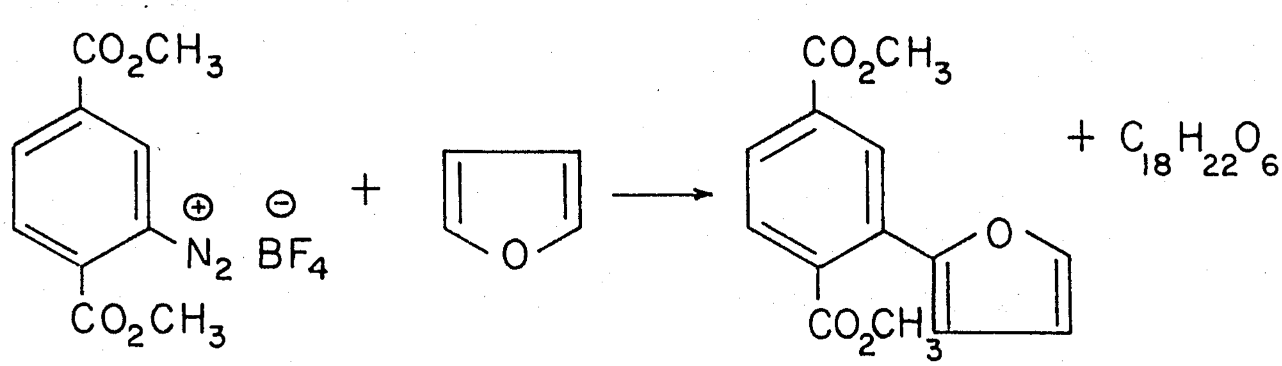
** The N.M.R. spectrum of this and the other substituted 2-phenylfurans examined possessed the same general characteristics (with reference to resonance of the furan protons) as that one shown in Figure 6 (p. 125).

TABLE IX

Ultraviolet spectra of substituted 2-phenylfurans and related compounds (in absolute ethanol).

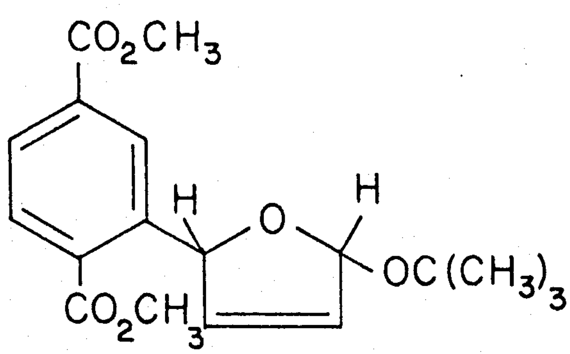
Compound	$\lambda_{max.}$ (mμ.)	log ε
2-phenylfuran	279	4.30
Naphthalene-1,4-endo-oxide	241	2.84
	263	2.68
	271	2.66
	270	2.58
2-(3-Methoxycarbonyl-phenyl)furan	241	4.22
	280	4.28
2-(3,5-Dimethoxycarbonyl-phenyl)furan	235	4.30
	280	4.23
2-(2,5-Dimethoxycarbonyl-phenyl)furan	245	4.26
	281	4.05
	319	3.55
2,5(?)-Dihydro-2(2,5-dimethoxycarbonylphenyl)-5(?)-t-butoxyfuran.	243	4.05
	294	3.30

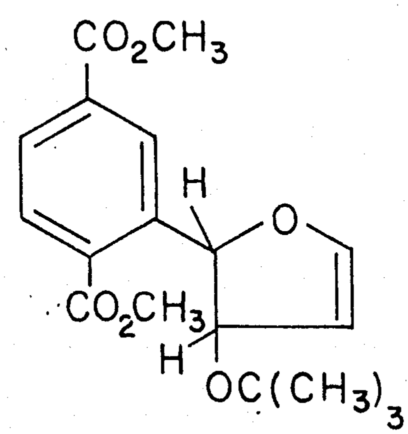
When 2,5-dimethoxycarbonylbenzenediazonium fluoroborate (XX) was decomposed with potassium t-butylate in furan, two products, separated by fractional crystallization, were obtained. The low melting substance (m.p. 85°) analysed for $C_{14}H_{12}O_5$, and possessed spectral characteristics typical of a substituted 2-phenylfuran. It could therefore be assigned structure XXI with certainty. The N.M.R. spectra of furans have been discussed in detail



XX

XXI





XXII

XXIII

by several workers (55, 112-115) and the assignments for the furan protons in XXI (see Fig 6, p.125) were made on this basis. Assignments for the benzenoid protons were determined from the expected values for ortho, meta, and para coupling constants. In both cases, the magnitude of coupling between protons was determined from first order principles.

H5 of the furan moiety (see Fig.6 p.125 for numbering system) appears as a low field doublet (7.43 p.p.m) with small spacing (1.8 c.p.s.). Under high resolution each of these bands shows additional splitting because of cross-coupling with H3. The doublet centered at 6.66 p.p.m. is due to H3 which is strongly coupled (3.3 c.p.s) to the other β (4) proton, and again at high resolution shows additional splitting because of weak 1,3-coupling with H5. The quartet centered at 6.39 p.p.m. arises from the remaining β (4) proton and is coupled weakly to H5 (1.7 c.p.s.) and strongly with H3 (3.3 c.p.s.).

H6' of the benzenoid nucleus gives rise to the lowest field signal (8.22 p.p.m.)* and is coupled (Jmeta = 1.9 c.p.s) to one meta proton. H4' Appears as part of an AB quartet, and is coupled to one ortho proton (Jortho = 8.5 c.p.s) and one meta proton (Jmeta = 1.8 c.p.s.). The other half of the AB quartet arises from H3' which is coupled to only one ortho proton (Jortho = 7.5 c.p.s.).

The evidence outlined below allows assignment of either structure XXII or XXIII to the high melting (m.p. 118°) product resulting from 2,5-

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*Coupling of para protons since very small (< 1 c.p.s.) will not considered here.

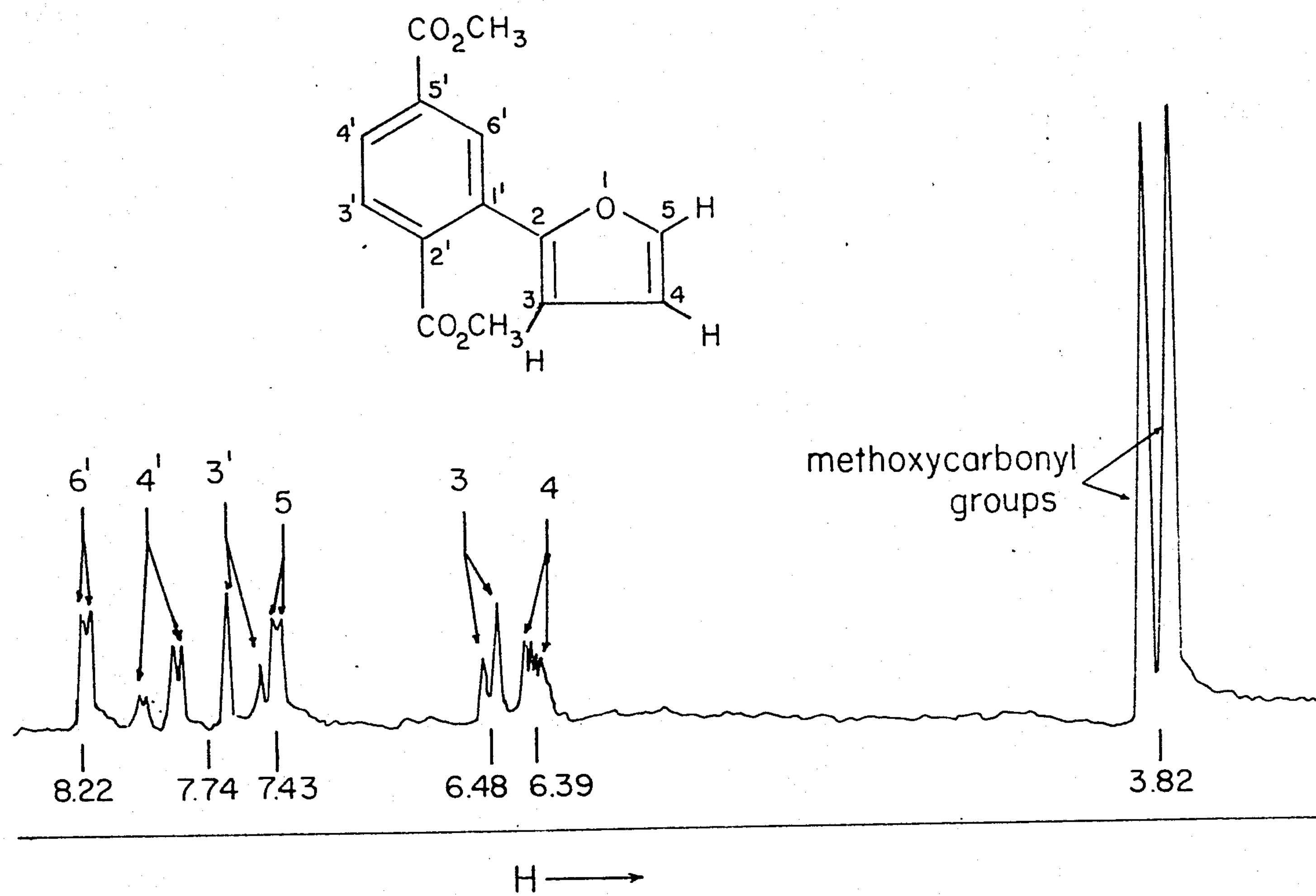


Fig.6. N.M.R. spectrum of 2-(2,5-dimethoxycarbonylphenyl)furan measured in carbon tetrachloride.

dimethoxycarbonylbenzenediazonium fluoroborate (XX) and furan. This compound analysed correctly for $C_{18}H_{22}O_6$ and its ultraviolet spectrum (Table IX, p.122) was not compatible with that expected for a substituted 2-phenylfuran or a derivative of napthalene-1,4-endo-oxide. The N.M.R. spectrum (Fig. 7, p.127) showed bands for a t-butyl group (1.39 p.p.m) and two methyls attached directly to oxygen (3.79 p.p.m.). Previous observations on the N.M.R. spectra of the above 2-phenylfurans caused us to ascribe the signal at lowest field (8.07 p.p.m.) to H6 of the aromatic ring. The signal at 7.88 p.p.m. was assigned to H3 and H4 which now had almost zero chemical shift between them. The two remaining complex multiplets (5.60 and 6.22 p.p.m.) then had to arise from the protons in the five-membered ring. Intensity measurements indicated the latter signal to be due to three and the former to one proton.

If, for the moment, structures XXII and XXIII are accepted, then treatment with acid of either should result in formation of 2-(2,5-dimethoxycarbonylphenyl) furan (XXI). This assumption was convincingly verified when a solution of the compound on treatment with dry hydrogen chloride gave XXI in 85% yield. It should be noted that cis-trans-isomerism is possible for both of the proposed structures. Although no stereochemical investigations were undertaken, the relative simplicity of the N.M.R. spectrum alone indicates only one of the two possible configurational isomers was formed.

By this time it was becoming increasingly obvious benzyne derivatives were not likely to be generated through base catalysed decomposition of the corresponding diazonium fluoroborates. Several attempts were made to repeat the results obtained originally with 2-iso-propyl-5-methoxycarbonylbenzene-

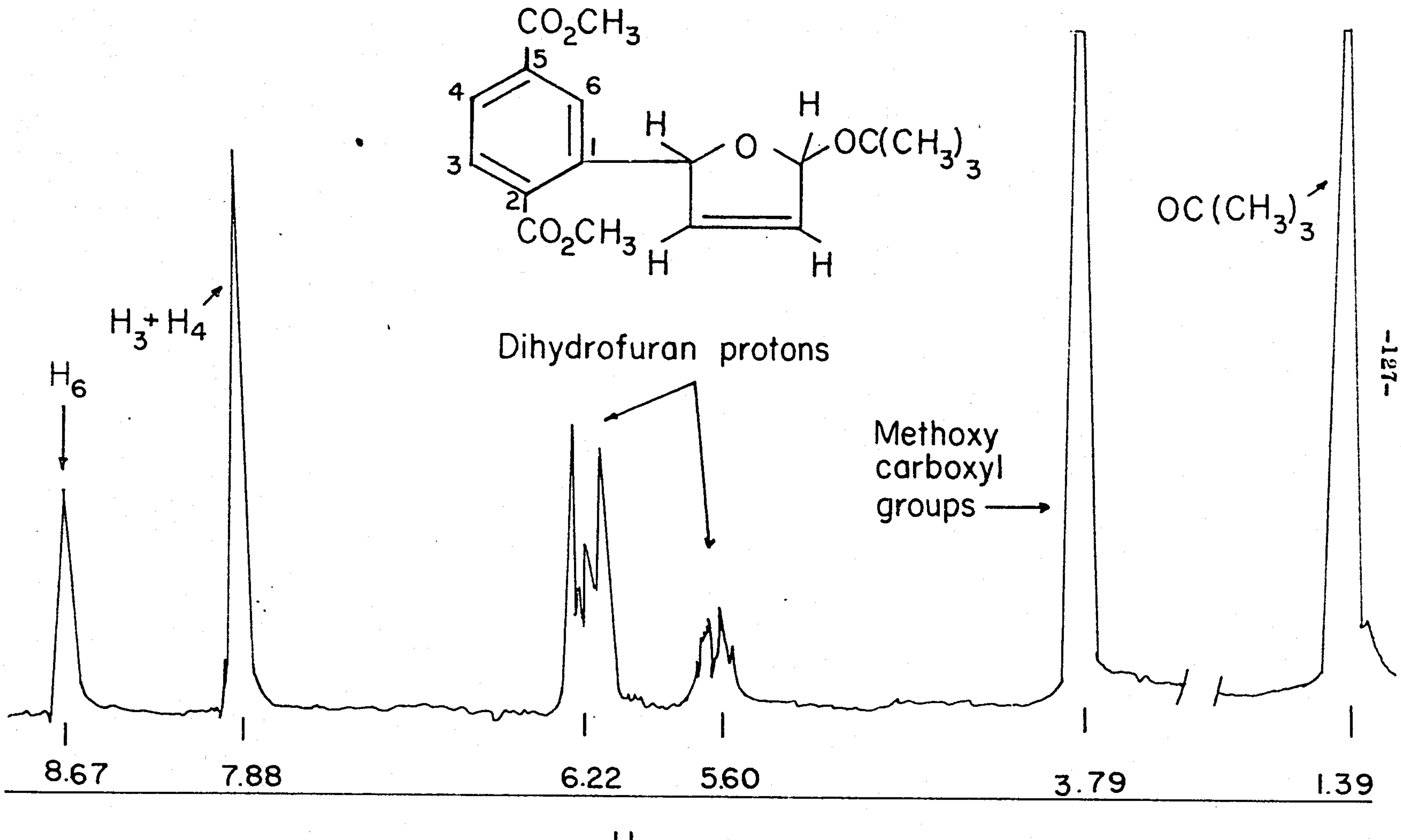


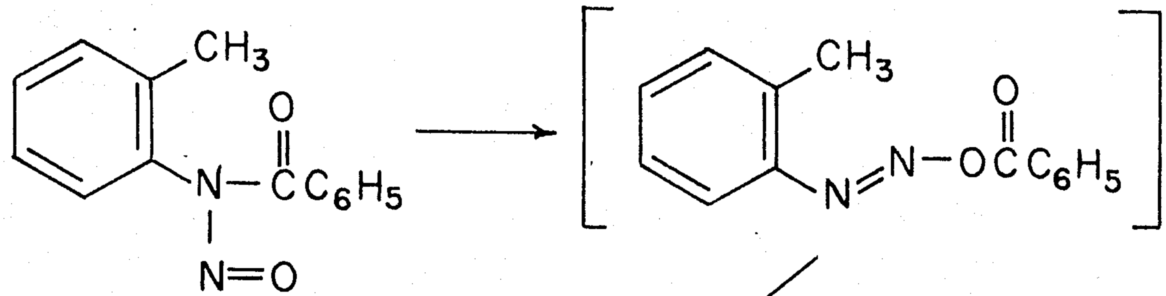
Fig.7. N.M.R. spectrum of 2,5(?)-dihydro-2(2,5-dimethoxycarbonylphenyl)-5(?)-t-butoxyfuran measured in carbon tetrachloride.

-diazonium fluoroborate. In no case was the acid (m.p. 98°) isolated. Fortunately, a small amount of this acid was still available and careful purification raised its melting point to 114°. This melting point was not depressed on admixture with authentic p-*iso*-propylbenzoic acid, and the infrared spectra of the two acids were superposable thus proving their identity. Formation of this acid from the diazonium salt can be rationalized if one assumes a small amount of methanol has resulted from ester interchange with t-butanol. The reducing action of primary alcohols is well known (116), and the yield of p-isopropylbenzoic acid is consistent with that observed if 6-10% methanol was formed in this way.

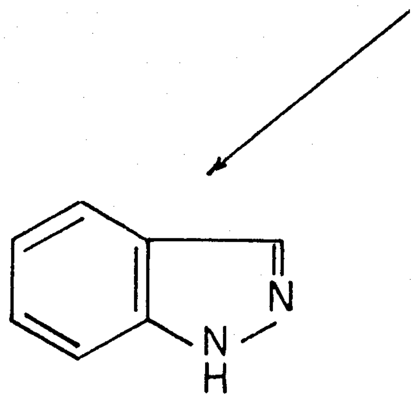
The furan derivatives prepared in the manner described above were obtained in exceptionally good yields (see Table XIII p.162). The method is superior to that used previously (110), and it is not unlikely that this same procedure should be equally applicable to other Gomberg type reactions.

Jacobson and Huber (117) have demonstrated that o-toluidines not activated by electronegative substituents are readily converted to 1H-indazoles via rearrangement of their reactive N-nitroso-N-acetyl derivatives. 1H-Indazole (XXV) itself has been synthesised by this method. Huisgen (118) has shown that improved yields of the indazoles result if N-nitroso-N-benzoyl derivatives are used and rearrangement is carried out in t-butanol at room temperature, rather than in refluxing benzene (see formulae XXIV and XXV). Despite the well known utility of the method, it does not seem to have been applied to synthesis of indiazenes.

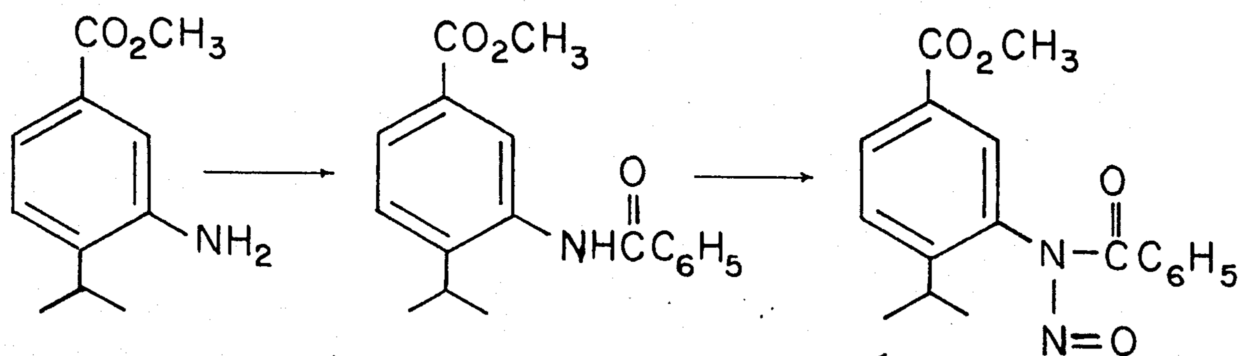
Huisgen's modification of this reaction was then applied to our system. 2-*iso*-Propyl-6-methoxycarbonylaniline (XXVI) was converted to its



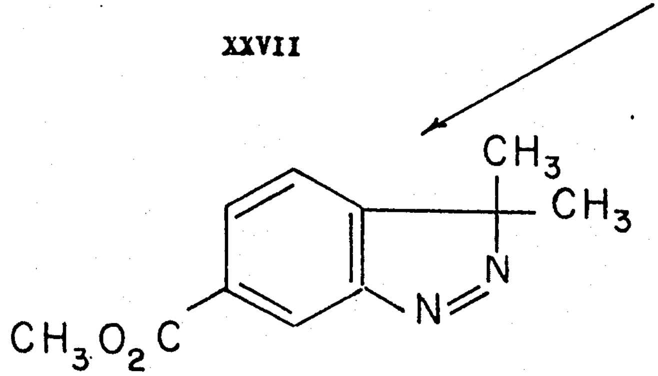
XXIV



XXV



XXVI XXVII XXVIII

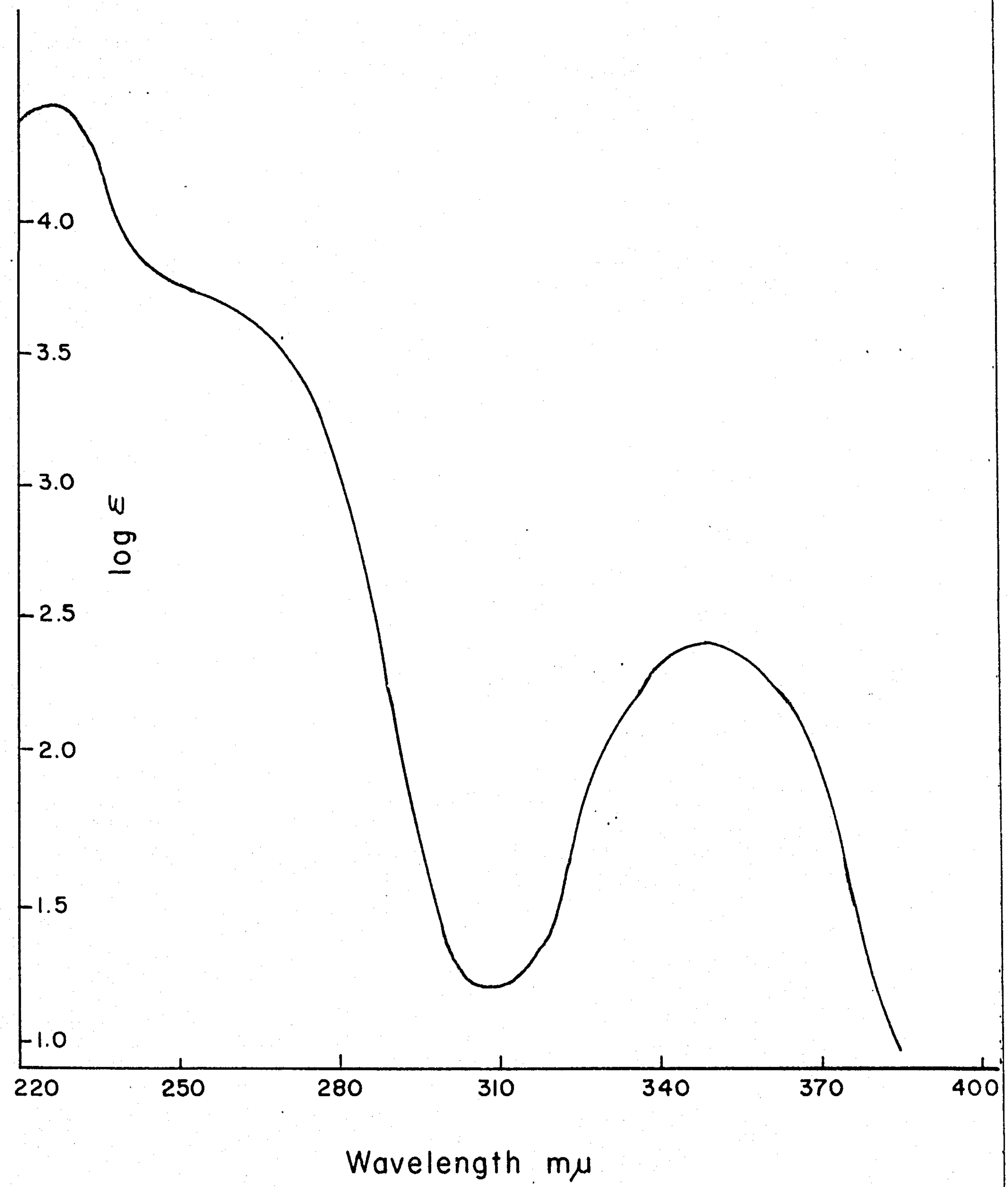


XXIX

benzoyl derivative (XXVII) and thence to the N-nitroso compound (XXVIII) in the usual manner. Rearrangement of the nitroso compound in t-butanol resulted in formation of 3,3-dimethyl-6-methoxycarbonylindiazene (XXIX) in about 50% yield. The structure of this compound was based on its molecular weight, analysis and spectral characteristics. The infrared spectrum proved the absence of OH or NH functions, and the ultraviolet spectrum (Fig 8 p.131) possessed weak long wavelength absorption not typical of 1H-and 2H-indazoles (119). The N.M.R. spectrum (Fig. 9, p.   ) conclusively demonstrated the validity of structure XXIX. The relative simplicity of this spectrum does not merit its discussion here.

Experiments of a preliminary nature directed towards thermal elimination of nitrogen from this compound (m.p 108°) were unsuccessful since it could be distilled without decomposition at atmospheric pressure. The conversion of this compound to 3,3-dimethylindiazene (XXXV) was then examined. Saponification of the above methylester gave the corresponding carboxylic acid (XXX) which was converted (formulae XXXI-XXXIII) in low yield to the 6-amino-derivative (XXXIII) following the modified Curtius degradation recently outlined by Weinstock (120). The N.M.R. spectrum of this compound is shown in Figure 10 (p.134). The assignments shown in figure 10 were made in the usual manner and are practically self explanatory. A recent deamination procedure (121) involving reduction of the corresponding aryldiazonium fluoroborate with sodium borohydride was then applied to the amine. Reduction of a methanolic solution of XXXIV gave only an unstable red oil possessing OH or NH absorption in the infrared spectrum. This oil rapidly decomposed at room temperature and was not investigated further. Since limited quantities

Fig. 8; ultraviolet spectrum (in absolute ethanol) of 3,3-dimethyl-6-methoxycarbonylindiazene.



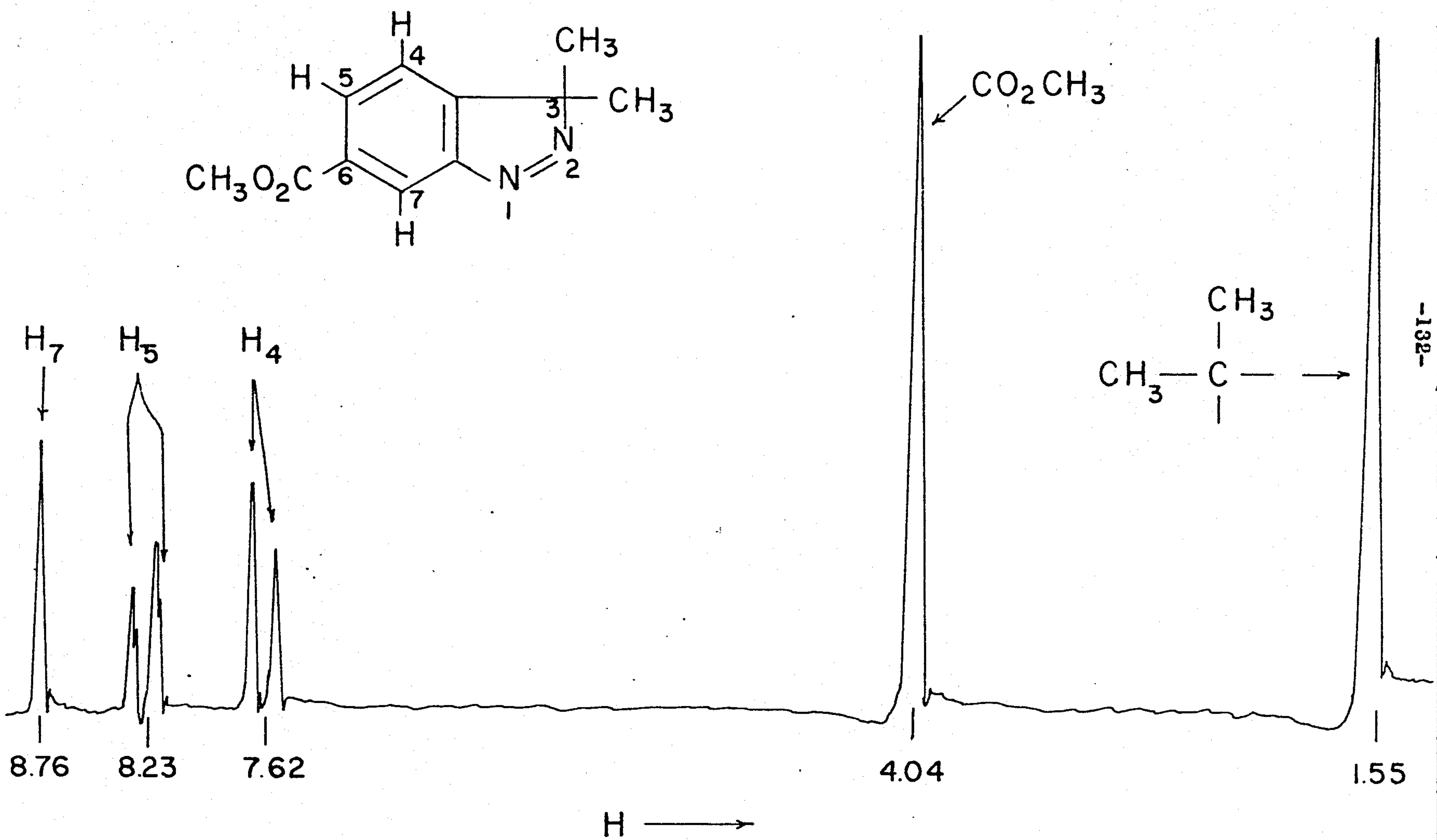
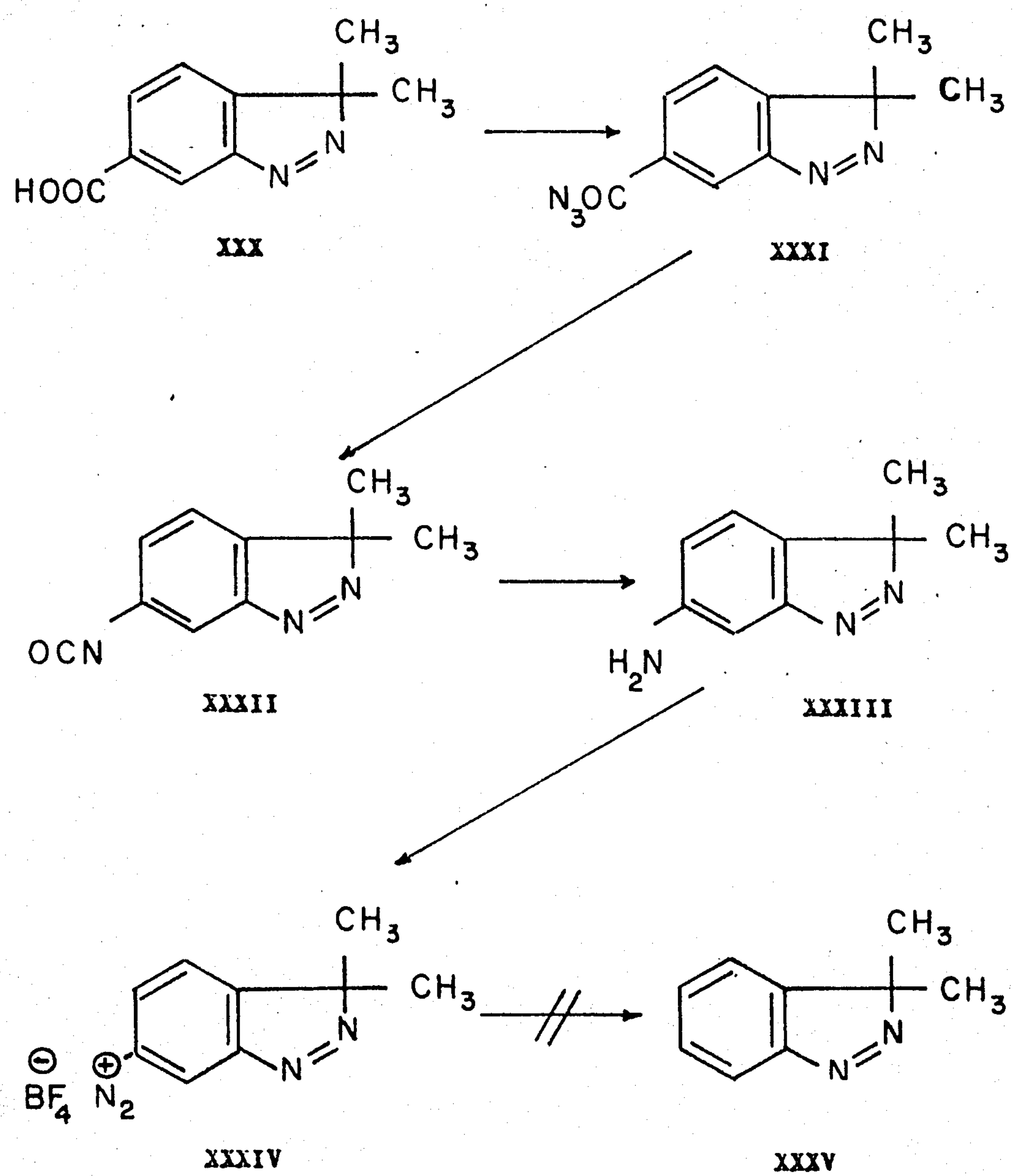


Fig.9. N.M.R. spectrum of 3,3-dimethyl-6-methoxycarbonylindiazene measured in carbon tetrachloride.



CH3
CH3
HOOC
N=N
XXX
CH3
CH3
N3OC
N=N
XXXI
CH3
CH3
OCN
N=N
XXXII
CH3
CH3
H2N
N=N
XXXIII
CH3
CH3
BF4
N2
N=N
XXXIV
CH3
CH3
N=N
XXXV

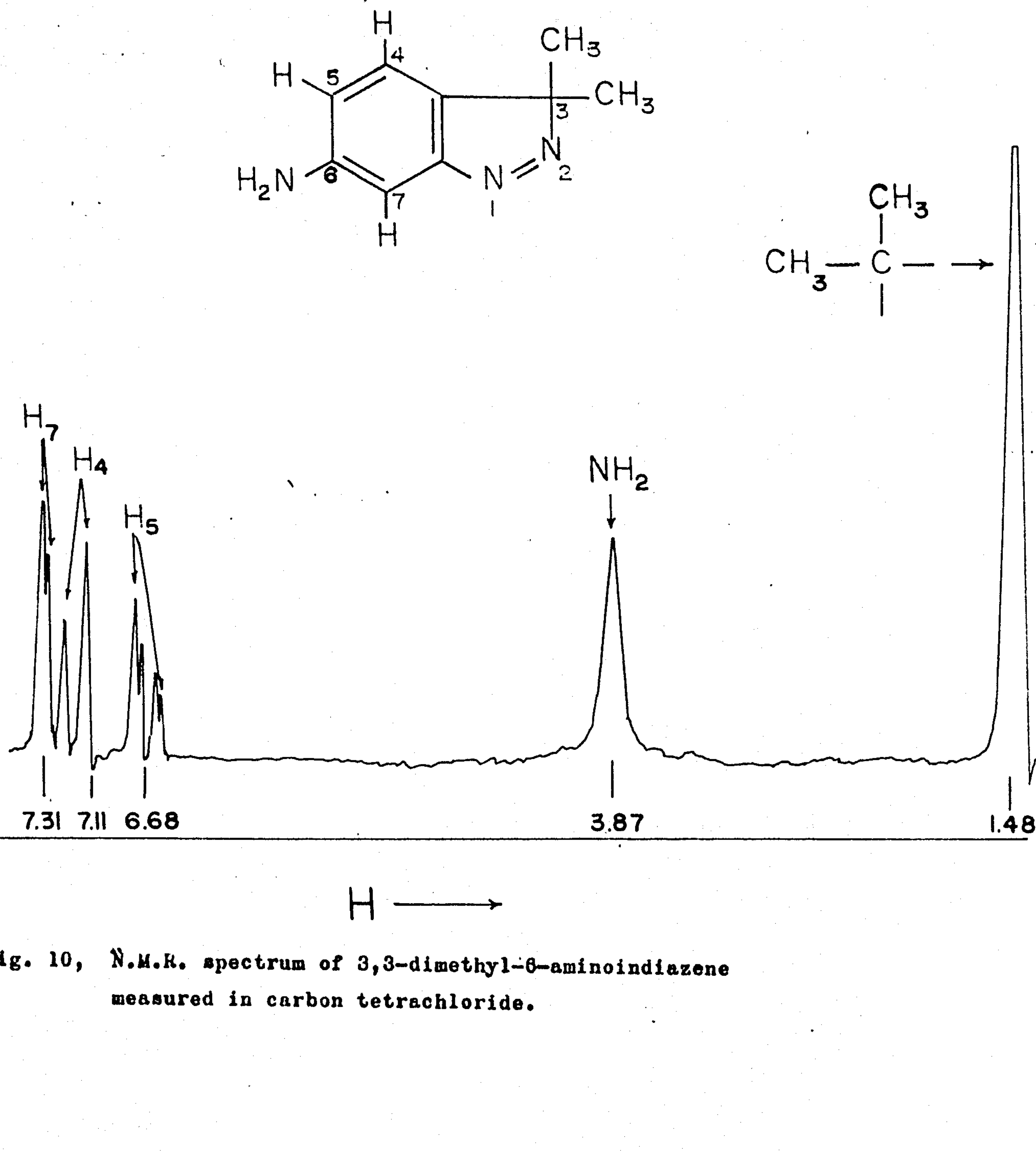
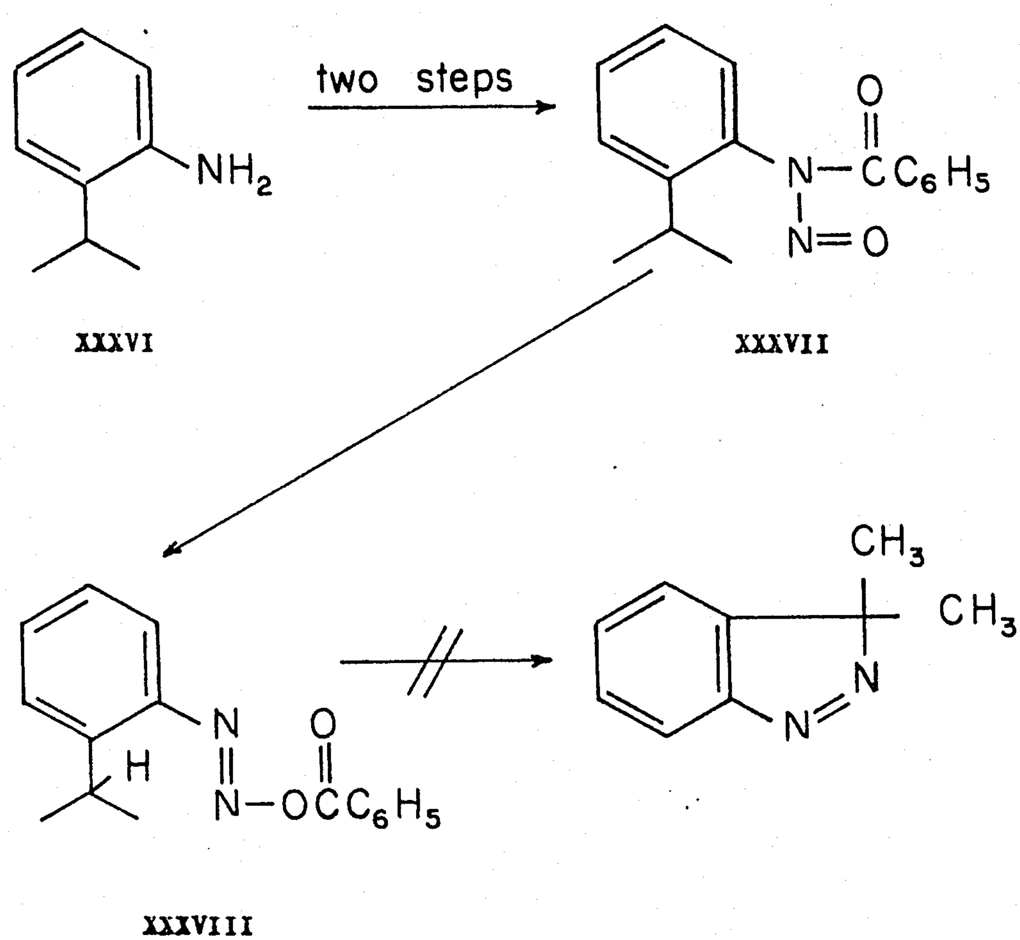


Fig. 10, N.M.R. spectrum of 3,3-dimethyl-6-aminoindiazene measured in carbon tetrachloride.



two steps
NH2
XXXVI
O
N—CC6H5
N=O
XXXVII
H
N
N—OCC6H5
O
XXXVIII
CH3
CH3
N
N

of the amine (XXXIII) were available, other deamination methods were not examined. It is felt that suitable modification of the above deamination procedure, or substitution of some other, should eventually result in the synthesis of 2,3-dimethylindiazene (XXXV).

Our failure to obtain the indiazene (XXXV) in the manner outlined above caused us to attempt a synthesis of XXXV using *p*-cumidine (XXXVI) as a starting material. This amine was benzoylated and nitrosated in the usual manner. Rearrangement of the N-nitrosamide (XXXVII) in this case, however, afforded none of the expected indiazene. The only product identified was benzoic acid, indicating that the reaction had proceeded through the diazoester (XXXVIII) stage.

Although hydrogen bonding is a phenomenon observed for most alcohols, the aggregates thus formed possess no great stability (125). Substantial evidence is presented below for formation of particularly stable hydrogen-bonded cyclic dimers.

The N.M.R. spectrum of 4-*iso*-propyl-2-methoxycarbonylphenol (XI, R = CH_3) showed the usual bands for *iso*-propyl (intense doublet and weak septet centered at 1.24 and 3.36 p.p.m. respectively) and methyl ester (singlet 3.87 p.p.m.) functions. The bands of the three aromatic protons (Fig. 11A, p. 106) were assigned on the basis of the expected coupling constants (J_{ortho} = 6-8, J_{meta} = 1.5-2, J_{para} < 1 c.p.s.) and analysis of the spectrum as an ABX system. This treatment placed H3, H6, and H5 at 7.70, 7.44 and 7.14 p.p.m. respectively. From the effects of substituents (125) it was expected that H3 and H6 would have nearly similar chemical shifts with H3 at perhaps slightly higher field, whereas the assignments made on the basis of coupling constants placed H3 at a much lower field than H6.

This effect is most simply explained if two molecules of XI (R = CH_3) are involved in a cyclic fourteen-membered hydrogen-bonded dimer as depicted in structure XXXIX. In XXXIX each H3 experiences the ring current effect (see ref. 56, p. 150) of two benzene rings, whereas in the monomer (or approximately so in a non-cyclic dimer) H3 is affected by only one benzene ring. Whether XXXIX is planar or not, the ring current effect is of the required magnitude and direction.

Further evidence supporting the above proposal was obtained from examination of the effect of dilution and addition of solvents such as methanol or acetone on the H3 resonance. It was found that the chemical shift of this

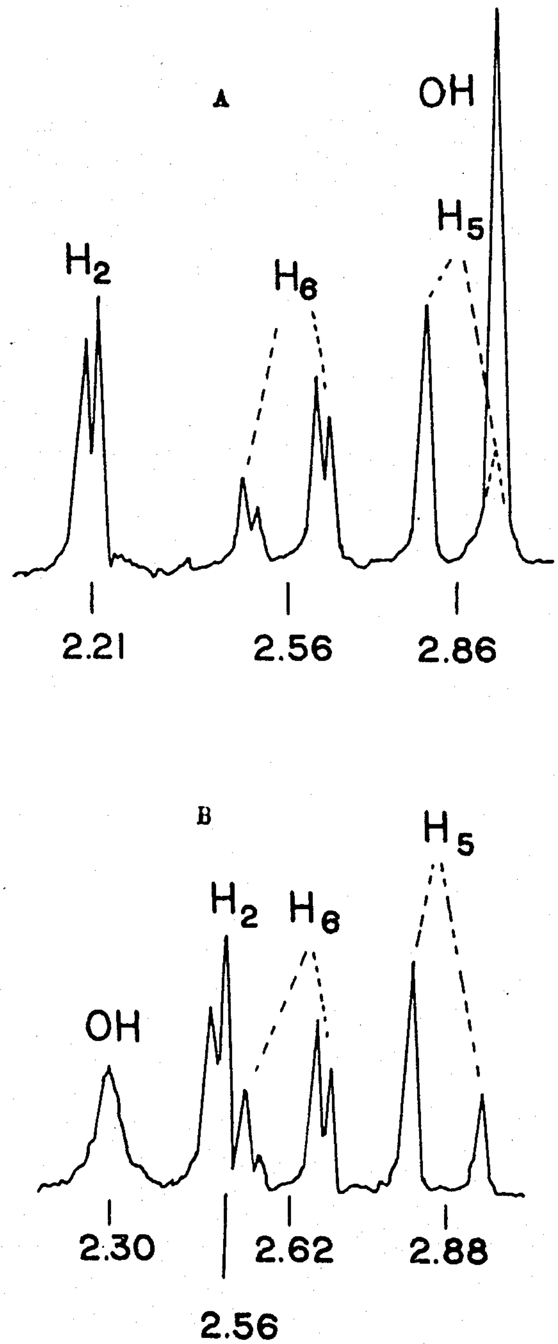
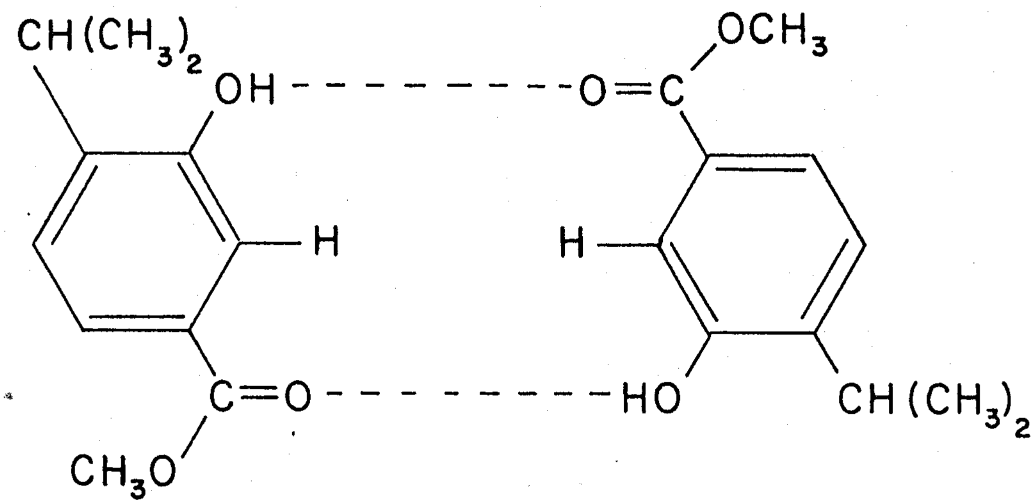


Fig. 11. N.M.R. spectra of methyl-3-hydroxy-4-iso-propylbenzoate: A, in pure carbon tetrachloride; B, in carbon tetrachloride containing 1% by volume (ie about 1 molar proportion) of methanol. The OH bands were located by O-deuteration. The high field regions of the spectra are not shown.



XXXIX

proton was strongly concentration dependent, although only at such extreme dilutions that the limit of the dilution shift could not be observed. A more satisfactory method of breaking the self-association of XI was through addition of acetone or methanol. When small increments of methanol (10% v/v in carbon tetrachloride) were added to a carbon tetrachloride solution of the dimer, the H2 resonance shifted progressively to higher field. At the point where approximately one molar proportion of methanol had been added, H2 had undergone a profound upfield shift of nearly 19 c.p.s. from its original position (Fig 11B). At the same time H6 had been affected only slighty while no significant shift in H5 was observed. The phenolic hydroxylproton had now become broad because of exchange with the methanol hydroxyl proton, and was shifted to low field because of the basicity of this solvent. The addition of more methanol now caused H2 to move slowly upfield until it became coincident with H6. The effect of methanol on H2 is shown graphically in Figure 12 (p.141) where 55 μl of 10% methanolic carbon tetrachloride corresponds to roughly one molar proportion of methanol.

Convincing evidence for the dimerization of XI was also obtained from measurement of the infrared spectrum in dry carbon tetrachloride solution at a path length of 5 cm. Except at very low concentrations ($< 10^{-4}$M) two bands (3455 cm^{-1} and 3613 cm^{-1}) were observed (see Fig 13, p.142). The feature of primary interest is the sharp band at 3613 cm^{-1}, and the variation of ε for this band (designated ε_M) with concentration. The frequency of this band varies from one alcohol to another, and has been shown in the case of aliphatic alcohols, at least, to be slightly temperature dependent (123). This band was assumed to be due only to absorption by monomers, and is in part

Figure 12

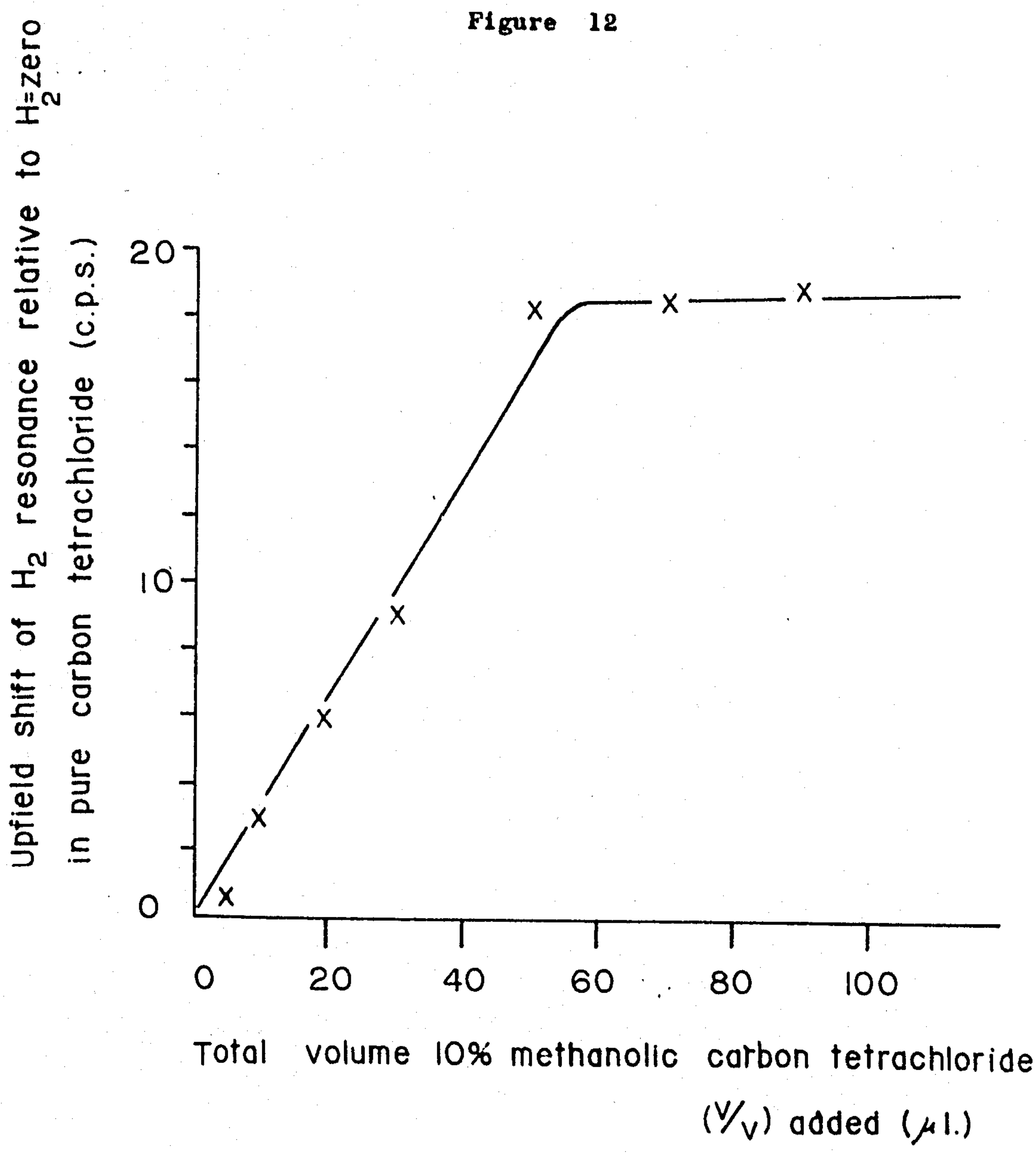


Fig. 12. Effect of addition of methanol on the H2 resonance of methyl-3-hydroxy-4-iso-propylbenzoate.

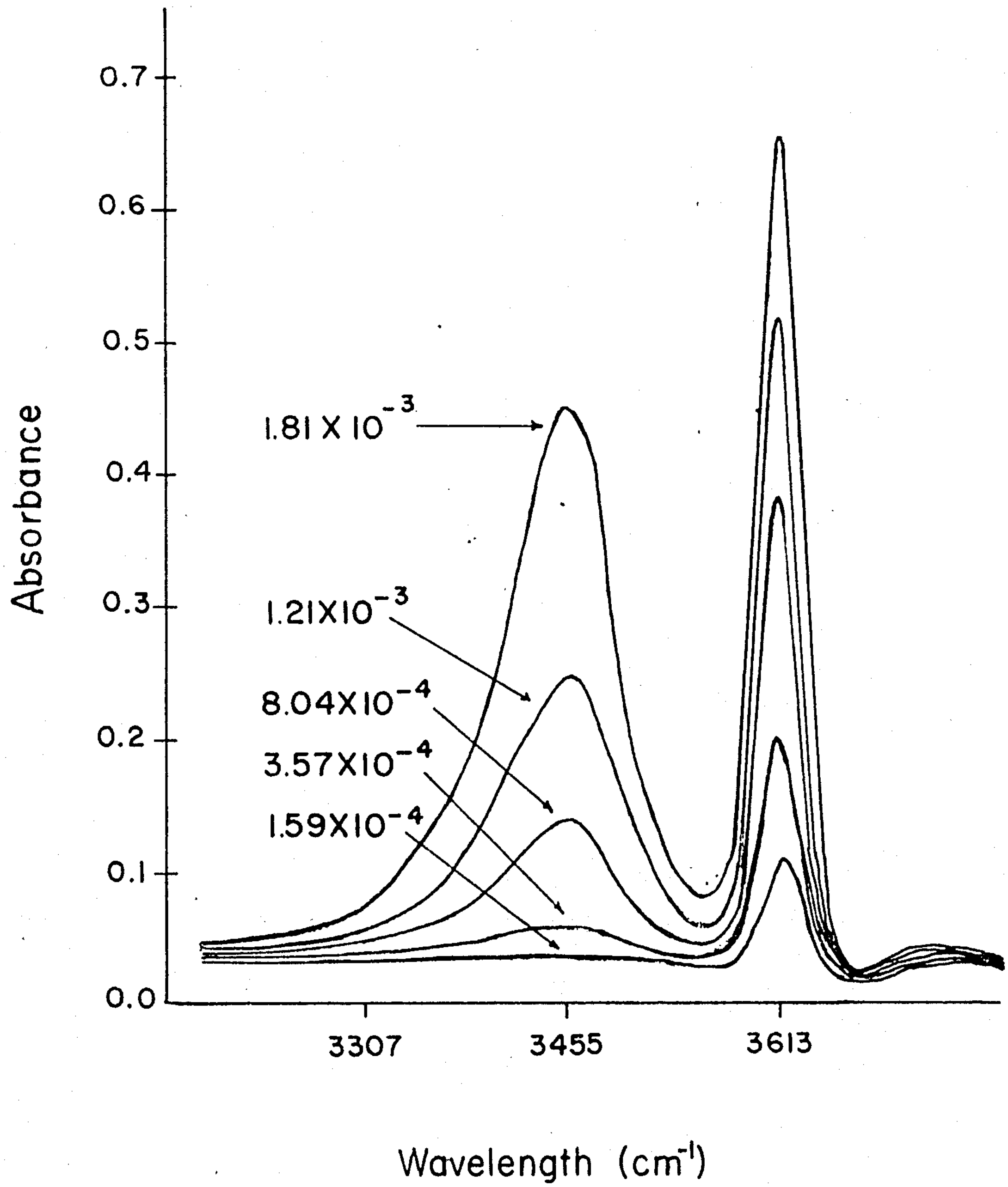


Fig. 13. Infrared absorption spectrum of 2-iso-propyl-5-methoxycarbonylphenol in carbon tetrachloride.

justified by the observed constancy of K_D over the concentration range measured (see below). Values of $\mathcal{E}_M$ vs. concentration (see table A below) were plotted, and a smooth curve drawn through the points (Fig. 16, p. 146). From the addendum* given below it is obvious that extrapolation to zero concentration

---

*The treatment outlined by Liddel and Becker (120) has been modified for our system and is essentially as follows:

If it is assumed that the alcohol molecules exist only in the form of monomer and dimer, then the concentrations C_M and C_D (in moles /ℓ.) of these two species are related by the equilibrium expression

$$K_D = C_D / C_M^2$$

where K_D is the equilibrium constant for dimer formation.

Suppose that $\mathcal{E}_M$ represents the apparent absorption coefficient due only to monomer. Then

$$\mathcal{E}_M = \mathcal{E}_M^o \, (C_M / C)$$

$$= \mathcal{E}_M^o \, (C - 2\, C_D / C)$$

where C is the total concentration of alcohol and $\mathcal{E}_M^o$ is the value of $\mathcal{E}_M$ when all alcohol molecules are in the form of monomers. Then

$$\mathcal{E}_M = \mathcal{E}_M^o \, (C - 2K_D \;\; C_M^2 / C)$$

continued on bottom of next page

gives the value ε_M^o. The value of ε_M^o determined in this way was 130. ε_M^o now being known, C_M, C_D, and K_D, were calculated for each measured point (Table XI) from the expressions

$$C_M = \frac{A_M}{\ell \varepsilon_M^o} \; ; \quad C_D = \frac{C - C_M}{2} \; ; \quad K_D = \frac{C_D}{C_M^2}$$

where A_M and ℓ represent the monomer absorbance and path length respectively. The values obtained in this way are shown in Table XI below. The value determined for K_D in this manner was 487 ± 10* ℓ/mole.

* standard deviation of the mean.

Making the approximation ** that $C_M = C$ we have

$$\varepsilon_M = \varepsilon_M^o \; (C - 2K_D \; C^2/C)$$

$$= \varepsilon_M^o \; (1 - 2K_D \; C)$$

$$d\varepsilon_M / d_c = \varepsilon_M^o \; (-2K_D)$$

$$\lim_{c \to 0} \; (d\varepsilon_M / d_c) = -2K_D \; \varepsilon_M^o$$

** See reference 124 for the justification of this approximation at low C.

TABLE X

Infrared spectral data for 2-*iso*-propyl-6-methoxycarbonylphenol.

Monomer absorbance A_M	Dimer absorbance A_D	Total alcohol concentration C (Moles/ℓ.)	Apparent monomer absorption coefficient ε_M
0.682	0.620	2.71×10^{-3}	50.2
0.644	0.430	1.81×10^{-3}	71.2
0.506	0.229	1.21×10^{-3}	83.5
0.371	0.120	8.04×10^{-4}	92.3
0.269	0.062	5.36×10^{-4}	100
0.191	0.035	3.57×10^{-4}	107
0.137	0.024	2.38×10^{-4}	115
0.095	0.016	1.59×10^{-4}	119

TABLE XI

Calculation of the equilibrium constant K_D for 2-*iso*-propyl-6-carbomethoxyphenol.

Monomer concentration C_M (moles/l.)	Dimer concentration C_D (moles/l.)	K_D (l./mole)
1.18×10^{-3}	7.65×10^{-4}	549
8.50×10^{-4}	4.80×10^{-4}	477
7.46×10^{-4}	2.30×10^{-4}	414
5.49×10^{-4}	1.29×10^{-4}	428
3.97×10^{-4}	6.95×10^{-5}	441
2.82×10^{-4}	3.75×10^{-5}	472
2.02×10^{-4}	1.80×10^{-5}	441
1.40×10^{-4}	9.00×10^{-6}	466

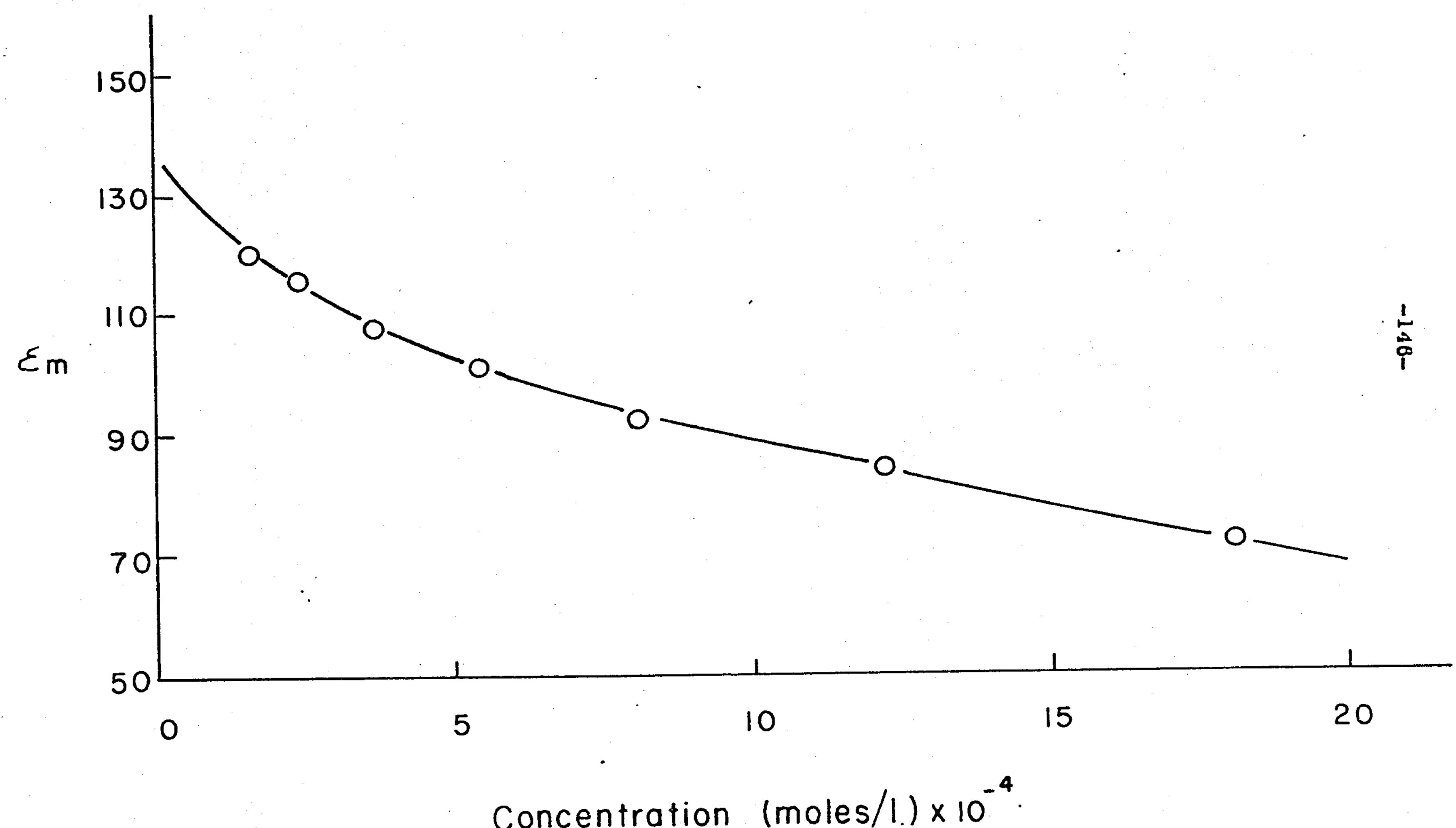


Fig.14. Apparent absorption coefficient for the 3613 cm.$^{-1}$ (monomer) band of 2-iso-propyl-5-methoxycarbonylphenol as a function of concentration.

From the appendix (see above) it is obvious that K_D can also be calculated from the slope of the $_M$ vs. C plot. K_D determined in this way was 480 l./mole, which is in good agreement with that calculated from C_M and C_D.

From the calculated dimer concentration C_D and the observed absorbance A_D, the true molar absorption coefficient $^{o}_{D}$ for the dimer was found to be 204 ± 5. This value was fairly constant in the range where A_D could be measured accurately.

Methyl-m-hydroxybenzoate also showed two bands at 3465 cm^{-1} and 3613 cm^{-1}. The appropriate values determined in exactly the same manner as described above were, $^{o}_{M}$ =133, K_D = 351 ± 25 l./mole, and $^{o}_{D}$ = 58 ± 4. In the case of m-nitrophenol and m-hydroxybenzaldehyde, hydrogen bonding was also observed to low concentrations, but K_D was not calculated. The N.M.R. spectra of these compounds were to complicated for simple analysis, although marked changes were observed on addition of small amounts of methanol.

Models show that this unusual type of hydrogen-bonded dimer formation is geometrically favourable, and the above results indicate that the aggregates thus formed possess unprecedented stability. By comparison (125), K_D for phenol in carbon tetrachloride has the value of about 1 l./mole. The results also indicate that a relatively large substituent, ortho to an H group taking part in dimer formation, has only a small effect on K_D.

EXPERIMENTAL

Unless otherwise stated all physical properties were measured as described in Part I of this thesis. Catalytic hydrogenations were also carried out as described earlier.

The infrared spectra of 2-*iso*-propyl-5-methoxycarbonylphenol and 3-methoxycarbonylphenol were measured in carbon tetrachloride (dried over phosphorous pentoxide) with a Beckman IR-2 Ratio Recording Spectrophotometer. A 5 cm. silica cell was filled with a standard solution of the phenol and the desired wavelength scanned. Dilution measurements were made by removing a known volume of solution from the sample cell and replacing it with the same volume of dry carbon tetrachloride. This procedure was continued until both bonded and non-bonded OH absorptions could no longer be detected. All solvent transfers were made rapidly to minimize absorption of atmospheric moisture.

Indazolinone

The indazolinone used (m.p. 248°) was prepared by Mrs. E. Oegorby following the method outlined by Stephenson (126).

Attempted Preparation of 3-Oxoindiazene from Indazolinone

A solution of indazolinone (2.0 g) in diglyme (200 ml.) containing yellow mercuric oxide (4.0 g.) was shaken mechanically at room temperature for 24 hours. Mercury, and unreacted mercuric oxide were removed by filtration through celite. The deep red filtrate was poured into 1 l. of water and the precipitated solid was removed by filtration. The greenish-black solid obtained after drying (1.5 g.) was insoluble in methanol and therefore not investigated further.

4-*iso*-Propylbenzoic Acid

To a stirred slurry of silver oxide prepared from silver nitrate (72.0 g.) in water (150 ml.) and sodium hydroxide (33.6 g.) in water (150 ml.) was added 4-*iso*-propylbenzaldehyde (30.0 g.) over a period of 1 hour. At the end of this time the odor of the aldehyde could no longer be detected, and the precipitated silver was removed by filtration. The filtrate was acidified with concentrated hydrochloric acid and cooled in ice. The precipitated acid was removed by filtration, dried, and recrystallized from aqueous ethanol giving lustrous needles m.p. 116° in quantitative yield. Meyer (127) reports m.p. 115-116° for this acid.

3-Nitro-4-*iso*-Propylbenzoic Acid.

A stirred solution of fuming nitric acid (150 ml., d., 1.5) in concentrated sulfuric acid (150 ml.) was cooled to 10° in an ice-bath and solid 4-*iso*-propylbenzoic acid (10.0 g.) was added at such a rate that the temperature was maintained between 0 - 10°. After the addition was completed the solution was stirred at 0 - 10° for 1 hour and then poured onto 200 g. of crushed ice. The white solid was removed by filtration and dried. Crystallization of this material from aqueous ethanol gave beautiful pale yellow needles (8.2 - 10.1 g., 64.4 - 79.2%) m.p. 155-156°, reported (128) m.p. 158-159°.

Methyl-3-Nitro-4-*iso*-Propylbenzoate.

A solution of the above acid (10.0 g.) in absolute methanol (18.0 g.)

containing concentrated sulfuric acid (1.8 ml.) was boiled under reflux for 24 hours. At the end of this time the methanol was evaporated and the residue poured into 200 ml. of water. Solid sodium carbonate was added until effervescence ceased and the mixture was extracted with ether. The ether was evaporated and the residue taken up in hot petroleum ether (b.p. 80-100°). Cooling gave beautiful pale yellow needles (9.0 - 9.7 g., 84.4 - 91.0 %) m.p. 63°. Albenius (120) reports m.p. 64° for this compound.

<u>2-iso-Propyl-6-Methoxycarbonylaniline.</u>

This compound could be prepared by two methods, both of which gave satisfactory yields.

(i) <u>Reduction with Hydrazine Hydrate and Raney Nickel in Absolute Ethanol.</u>

A solution of the above ester (10.0 g) in absolute ethanol (400 ml.) containing hydrazine hydrate (10.0 g., 100%) and 1 teaspoon of Raney nickel was slowly heated to boiling and maintained at that temperature (water-bath) for 1 hour. The cooled solution was filtered, the ethanol evaporated and the residue distilled at reduced pressure. A colorless liquid (7.3 - 7.7 g., 84.4 - 89.5 %) b.p. 117-119 /0.14 mm. which slowly solidified on cooling was obtained. Crystallization of this material from petroleum ether (b.p. 60-80°) containing a few drops of chloroform gave colorless rectangular plates m.p. 49-50°. Fileti (130) reports m.p. 51-52° for this aniline.

(ii) <u>Catalytic Reduction over Adams' Catalyst.</u>

The above nitro ester (22.8 g.) in absolute ethanol (300 ml.) containing platinic oxide (0.35 g.) was hydrogenated at room temperature and an initial hydrogen pressure of 64 p.s.i. for 1 hour. The mixture was filtered, the ethanol removed and the residue distilled at reduced pressure giving an oil (16.6 g., 88.8 %) identical in every respect to that obtained by reduction with hydrazine hydrate and Raney nickel.

<u>Attempted Preparation of 3,3-Dimethyl-5-methoxycarbonylindiazene from the Diazonium Salt of 2-iso-Propyl-5-Carbomethoxyaniline.</u>

In no case did the above diazonium salt yield the desired indiazene. The reaction conditions and media investigated are described below.

(i) <u>Glacial Acetic Acid as Solvent.</u>

The reaction conditions described here are identical to those used in the preparation of 5-nitroindazole (130a).

To a stirred solution of 2-<u>iso</u>-propyl-5-methoxycarbonyl-aniline (2.10 g.) in glacial acetic acid (50 ml.) cooled to 15° was added all at once, a solution of sodium nitrite (0.70 g.) in water (5 ml.). The deep red solution was stirred for 15 minutes and then allowed to stand at room temperature for 2½ days. At the end of this time the acetic acid was evaporated, water added to the residual oil, and the mixture made alkaline with sodium carbonate. This was extracted with ether, the ether evaporated, the residue taken up in chloroform, and placed on "Merck" alumina. Fraction 1 was an unsaponifiable red oil and was discarded. Fraction 2, also a red oil was saponified as follows: a mixture of the oil and water (25 ml.) containing sodium hydroxide (2.0 g.) was shaken at room temperature overnight. The aqueous solution was extracted with ether, and then acidified with concentrated hydrochloric acid. The precipitated solid was removed by filtration, dried, and recrystallized from water. Pale orange needles (0.73 g.) m.p. 141° were obtained. Several more crystallizations from the same solvent gave pure 3-hydroxy-4-iso-propylbenzoic acid m.p. 142 - 143°. Barth (131) reports m.p. 141 - 143° for this acid.

(ii) Sodium Acetate - Acetic Acid Buffer as Solvent.

A solution of the aniline (2.000 g.) in concentrated hydrochloric acid (2.5 ml.) was cooled to 0° in an ice-salt bath. The stirred solution was treated dropwise with a cold solution of sodium nitrite (1.00 g.) in water (20 ml.). When the addition was complete, the solution was stirred at 0° for 15 minutes, filtered, and the filtrate added to a stirred solution of 30% sodium acetate (80 ml.). Stirring was continued at 0-5° for ½ hour the mixture was then allowed to reach room temperature over a period of 2 hours, and finally placed in a refrigerator overnight. The mixture was extracted with ether, the ether evaporated, the tarry material taken up in chloroform, and placed on acid washed alumina. Elution with 15% chloroform in petroleum-ether (b.p. 80-100°) gave first a red tar which was not further investigated. The broad orange band following this was eluted with chloroform. Evaporation of the eluate, and crystallization of the solid residue from chloroform-petroleum ether (b.p. 80-100°) gave deep red rectangular plates (0.236 g.) m.p. 160-162°. This substance was thought to be 2,5'-dimethoxycarbonyl-2',5-di-iso-propyl-4-hydroxyazobenzene (see later experimental work). Several crystallizations of this material from the same solvent system gave brilliant orange rectangular plates m.p. 166.5-167.5°. Calc. for $C_{22}H_{26}O_5N_2$: C, 66.31; H, 6.58%. Found : C, 66.56; H, 6.78 %.

(iii) Carbonate-Bicarbonate Buffer as Solvent

A stirred solution of the aniline (1.000 g.) in concentrated hydrochloric acid (1.1 ml.) and crushed ice (10 g.) was treated dropwise at 0° with a solution of sodium nitrite (0.50 g.) in water (10 ml.). Stirring was continued for 15 minutes, the diazonium salt solution filtered, and added dropwise to carbonate-bicarbonate buffer solution (200 ml., $_p$H9) at 0°. When addition was completed, the solution was immediately readjusted to $_p$H9 with sodium carbonate solution (0.2 M.). Stirring was continued at 0° for ½ hour, the reaction mixture then allowed to reach room temperature over a period of 1½ hours, and the orange solid removed by filtration and dried (0.660 g.). Chromatography of this material on acid washed alumina gave a deep red oil on elution with 20% chloroform in petroleum ether (b.p. 60-100°). The infrared spectrum of this oil showed no OH or NH absorption. The N.M.R. spectrum in carbon tetrachloride was not consistent with that expected for the indiazone or any other product which could be expected from the diazonium salt. This material was not investigated further.

(iv) <u>Decomposition of 2-iso-Propyl-5-Methoxycarbonylbenzendiazonium Fluoroborate with Potassium t-Butoxide in t-Butanol.</u>

The above diazonium salt was prepared as described later in this section of the thesis.

The diazonium fluoroborate (2.030 g.) was suspended in dry t-butanol (25 ml.), and the stirred mixture, protected from moisture with a calcium chloride drying tube, was cooled to 20° in a cold water bath. The stirred suspension was then treated dropwise with a solution of potassium t-butoxide in t-butanol (prepared from potassium metal (0.80 g.) and dry t-butanol (75 ml.)) at 20-25°. When the addition was complete the deep red solution was stirred at

20-25° for ½ hour, and then poured into saturated sodium chloride solution. This mixture was extracted with ether, the ether evaporated and the oil dissolved in 50% aqueous ethanol (25 ml.) containing potassium hydroxide (1.00 g.). This mixture was shaken at room temperature overnight, then evaporated to a small volume _in vacuo_, and acidified with concentrated hydrochloric acid. The precipated solid (0.050 g. m.p. 98°) was removed by filtration and dried. Recrystallization of this solid from water gave colorless needles m.p. 114°. Eventually this compound was shown to be identical in every respect to 4-_iso_-propylbenzoic acid (see Discussion).

Methyl-3-hydroxy-4-iso-propylbenzoate and 3-Hydroxy-4-iso-propylbenzoic Acid.

A solution of _o_-isopropyl-5-methoxycarbonylaniline (3.00 g.) in concentrated hydrochloric acid (3.8 ml.) was cooled to 0° in an ice-salt bath. The stirred solution was treated dropwise with a solution of sodium nitrite (1.2 g.) in water (10 ml.). After the addition was complete, the solution was stirred at 0° for ½ hour, allowed to warm to room temperature, and then heated to 50° and maintained at that temperature until nitrogen evolution ceased. The mixture was cooled, extracted with ether, the ethereal solution extracted with cold 5% sodium hydroxide and the alkaline solution immediately acidified with concentrated hydrochloric acid. The acidic mixture was extracted with ether, the ether evaporated, and the residue crystallized from petroleum ether (b.p. 80-100°). A tan colored solid (1.01 g.) which was difficult to purify was obtained. This substance was best purified by saponification of the ester, then esterification of the resulting acid with diazomethane as described below.

The above methylester (0.204 g.) in 15% sodium hydroxide (2 ml.) and ethanol (2 ml.) was boiled under reflux overnight. The solvent was evaporated and the residue on acidification with concentrated hydrochloric acid gave a white solid which was filtered and dried. Crystallization of this acid from water gave colorless needles (0.121 g.) m.p. 142° identical in every respect to the acid prepared as mentioned previously.

A solution of the above acid (0.114 g.) in ether (20 ml.) was treated with a slight excess of ethereal diazomethane and allowed to stand overnight. Evaporation of the ether and crystallization of the residue from petroleum ether (b.p. 80-100°) gave fluffy white needles (0.092 g.) m.p. 73°. Several crystallizations from the same solvent gave white needles m.p. 74°. Calc. for $C_{11}H_{14}O_3$: C, 68.02 ; H, 7.27 %. Found : C, 67.76 ; H, 7.73 %.

<u>Reduction of 2,5'-Dimethoxycarbonyl-2',5-Di-iso-propyl-4-Hydroxyazobenzene.</u>

A solution of the above azo compound (0.520 g.) in ethanol (50 ml.) containing hydrazine hydrate (0.5 g., 100%) and a pinch of Raney nickel was slowly heated to reflux temperature on a steam bath and maintained at that temperature for 1 hour. The cooled solution was filtered, the ethanol evaporated, the residue taken up in ether and extracted with dilute hydrochloric acid. The acid solution was made basic with sodium hydroxide (10%) and extracted with ether. The ether was evaporated and the residue placed on "Merck" alumina. Elution with 30% chloroform in petroleum ether (b.p. 80-100°)

gave after concentration of the eluate 2-*iso*propyl-5-carbomethoxy aniline (0.120 g.) identical in every respect with authentic material. Attempted isolation of the supposed 2-*iso*propyl-4-amino-5-carbomethoxyphenol from the alkaline extract gave only an intractible black tarry material. This substance was not investigated further.

Methyl-3-Nitrobenzoate.

A solution of commercial 3-nitrobenzoic acid (60.0 g.) in absolute methanol (200 ml.) containing concentrated sulfuric acid (10 ml.) was boiled under reflux for 24 hours. Cooling gave beautiful pale yellow needles which on filtration and drying weighed 58.8 g. (89.8%) and possessed m.p. 77°. Kamm and Segur (132) report m.p. 78° for this compound.

3-Methoxycarbonylaniline.

Methyl-3-nitrobenzoate (15.0 g.) in absolute ethanol (250 ml.) containing platinic oxide (0.2 g.) was hydrogenated at room temperature and an initial pressure of 57 p.s.i. for 1 hour. The reaction mixture was filtered, the ethanol removed in vacuo, and the residual oil distilled at reduced pressure. A pale yellow oil (10.0 - 11.0 g., 79.9 - 87.8 %) b.p. 103 - 106°/0.25 mm. was obtained. Ungnade and Henick (133) report b.p. 152 - 153°/11 mm. for this amine.

Methyl-3-Hydroxybenzoate.

A solution of the above aniline (9.1 g.) in concentrated sulfuric acid (4.5 ml.) and water (35 ml.) was cooled to 0° in an ice-salt bath.

The stirred mixture was then treated dropwise with a solution of sodium nitrite (3.1 g.) in 10 ml. of water. The solution of the diazonium salt was warmed to room temperature over a half-hour period and then heated on a steam cone at 50-60° until nitrogen evolution had ceased. The cooled mixture was extracted with ether, the ether evaporated, and residue dissolved in chloroform and placed on "Merck" acidic alumina. Elution with 50% chloroform in petroleum ether (b.p. 80-100°) and evaporation of the eluate gave an oil which rapidly solidified at room temperature. Solution of this solid in hot petroleum ether (b.p. 80-100°) containing a trace of chloroform gave after cooling, pale yellow needles (0.97 g.) m.p. 69°; reported (134) m.p. 70°.

<u>5-Nitrobenzene-1,3-Dicarboxylic Acid.</u>

A mixture of isophthalic acid (20.0 g.) and fuming nitric acid (180 ml., d. 1.5) was heated to boiling and maintained at that temperature for 4 hours. At the end of 3 hours all the isophthalic acid had gone into solution. The solution was concentrated to half its original volume by distillation and diluted with an equal volume of water. This was cooled in a refrigerator overnight, the precipitate filtered, washed with ice-cold water and dried. A pale yellow product m.p. 249-252° was obtained. Meyer and Wesche (135) report m.p. 248-249° for this acid. Yield 21.2 g. (83.4%).

<u>Dimethyl-5-Nitrobenzene-1,3-Dicarboxylate.</u>

A solution of 5-nitrobenzene-1,3-dicarboxylic acid (21.2 g.) in absolute methanol (100 ml.) containing concentrated sulfuric acid (5 ml.) was boiled under reflux for 12 hours. At this time much of the product had already crystallized out and the reaction was stopped, cooled and filtered.

Colorless fluffy needles (15.0 g., 70.5%) m.p. 123° were obtained. Meyer and Wesche (135) report m.p. 123° for this compound.

3,5-Dimethoxycarbonylaniline.

The above nitro ester (18.0 g.) in absolute ethanol (250 ml.) containing platinic oxide (0.30 g.) was reduced at room temperature and an initial hydrogen pressure of 50 p.s.i. for 1 hour. The resulting slurry was evaporated to dryness and the solid dissolved in hot methanol, filtered, and cooled. Pale yellow needles (15.3 g., 92.2%) m.p. 172° were obtained; reported (136) m.p. 176°.

3-Nitrobenzene-1,4-Dicarboxylic Acid.

To a solution of fuming nitric acid (38.0 g.) in fuming sulfuric acid (56 g., 20%) was added 5.00 g. of finely ground terephthalic acid all at once. A vigorous reaction occurred and the reaction mixture soon reached reflux temperature. The solution was allowed to cool to room temperature and the resulting slurry was poured into water (200 ml.) and allowed to cool in a refrigerator. The precipitate was filtered at the pump, washed with ice cold water and dried. A cream colored solid (5.47 g., 86.2%) m.p. 268° was obtained. Soderman and Johnson (137) report m.p. 265° for this acid.

3-Nitroterphthalylchloride.

A mixture of the above acid (5.00 g.), thionyl chloride (10 ml.) and 1 drop of pyridine was boiled under reflux overnight. Thionyl chloride (excess) was removed in vacuo and the residue on distillation at reduced pressure gave a pale yellow oil (4.34 g., 78.5%) b.p. 120-125°/0.25 mm. Soderman et. al. (137) report b.p. 174°/5 mm. for 3-nitroterphthalylchloride.

Dimethyl-2-Nitrobenzene-1,4-Dicarboxylate.

A solution of the above di-acid chloride (4.34 g.) in dry benzene (30 ml.) containing absolute methanol (1.15 g.) was boiled under reflux overnight. The solvent was evaporated and the residue taken up in hot petroleum ether (b.p. 60-100°) containing a small amount of chloroform. Cooling gave beautiful transparent parallelograms (3.76 g., 87.0 %) m.p. 74-75°. Kauffman and Weissel (138) report m.p. 76° for this compound.

2,5-Dimethoxycarbonylaniline

The above nitro ester (19.6 g.) in absolute ethanol (250 ml.) containing platinic oxide (0.25 g.) was reduced at room temperature and an initial hydrogen pressure of 63 p.s.i. for 1 hour. The resulting slurry was heated until solution took place, filtered, and cooled. Yellow needles (15.5 g., 90.5 %) m.p. 132° were obtained. Kauffman and Weissel (138) report m.p. 134° for this amine.

Preparation of Benzenediazonium Fluoroborates.

These diazonium salts were prepared according to the method outlined below.

The aniline (0.1 mole) was dissolved in a solution of water (10 ml.) containing concentrated hydrochloric acid (6.0 ml.) and cooled with stirring to 0° in an ice-salt bath. The resulting stirred slurry was treated dropwise with a solution of sodium nitrite (0.8 g., 0.11 mole) in water (2 ml.), the solution temperature not being allowed to exceed 5°. When the addition was complete stirring was continued for 15 minutes. This stirred solution was then treated dropwise with a solution of sodium borofluoride (1.5 g., 0.14 mole) in water (5 ml.) at such a rate that the reaction temperature did not exceed 5°. After the addition was complete, stirring was continued for 15 minutes, the solid filtered at the pump, washed with a small volume of ice-water, then with a large amount of ether. This material was sucked as dry as possible and then dried in a current of air. The diazonium fluoborates were not characterized. Yields of these salts are given in tabular form below.

TABLE XII

Preparation of several benzenediazonium fluoroborates.

Starting material	Yield of diazonium salt (%)
Aniline	79–81
3-Methoxycarbonylaniline	84–96
3,5-Dimethoxycarbonylaniline	86
2-*iso*-Propyl-5-methoxycarbonylaniline	80–95
2,5-Dimethoxycarbonylaniline.	74–76

Preparation of Substituted 2-Phenylfurans from the Corresponding Benzenediazonium Fluoroborates and Furan.

In a thoroughly dried three-necked flask protected from moisture with a calcium chloride drying tube, and equipped with a dropping funnel (also protected from moisture), was placed the diazonium fluoroborate (0.05 mole) and dry furan (36 g., 0.53 mole). The stirred slurry was cooled to 20° and a solution of potassium *t*-butoxide in *t*-butanol (prepared from 2.0 g. of potassium metal and 100 ml. of dry t-butanol) was added dropwise over a period of 1 - 1.5 hours. During this time the bath temperature was not allowed to exceed 25°. After the addition was complete, stirring was continued at 20-25° for ½ hour. The deep red solution thus obtained was poured into a large volume of saturated sodium chloride solution, and extracted with ether. The ether was removed in *vacuo* and the residue worked up by one of the two following methods.

Method A.

If the product was a liquid (eg. 2-phenylfuran) it could be extracted from the above residue with petroleum ether (b.p. 60-100°). Evaporation of this solvent and distillation at reduced pressure gave the liquid product.

Method B.

When the product was a solid, the above residue was taken up in chloroform and placed on a column of "Merck" alumina. The crystalline product was then eluted from the column with chloroform in petroleum ether (b.p. 60-100°). Evaporation of the eluate gave material which was then crystallized from the appropriate solid.

Yields, physical constants, etc. of the 2-phenylfurans are given in Table XIII below.

TABLE XIII

Preparation of some substituted 2-phenylfurans.

Diazonium salt used	Method of workup: elution solvent.	Product %	M.p. °C	B.p. °C
Benzenediazonium fluoroborate	B: 10% Chloroform in pet. ether	2-Phenylfuran: 33	------	105-6/12 mm.
"	A	" 40	------	"
3-Methoxycarbonylbenzenediazonium fluoroborate	B: 20% Chloroform in pet. ether	2-(3-Methoxycarbonylphenyl)furan[a] 64-8	64-5	97-8/0.03 mm.
3,5-Dimethoxycarbonylbenzenediazonium fluoroborate	B: 50% Chloroform in pet. ether	2-(3,5-Dimethoxycarbonylphenyl)furan[b] 76	152-3	------
2,5-Dimethoxycarbonylbenzenediazonium fluoroborate	B: 30% Chloroform[c] in pet. ether	2-(2,5-Dimethoxycarbonylphenyl)furan[d] 38-43	84-5	------
		2,5(?)-Dihydro-2-(2,5-dimethoxy-carbonylphenyl)-5(?)-t-butoxyfuran[e] 38-40	118-9	------

a. Crystallized from petroleum ether (b.p. 30-60°). Calc. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98%. Found: C, 71.06; H, 5.10 %.

b. Crystallized from petroleum ether (b.p. 60-100°). Calc. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65%. Found : C, 64.73; H, 4.76%.

c. The products were separated by fractional crystallization from petroleum ether (b.p. 60-100°). Analytical samples of both substances were prepared by recrystallization from this same solvent.

d. Calc. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65%. Found: C, 64.54; H, 4.67%.

e. Calc. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63%. Found: C, 64.77; H, 6.63%.

__2-Phenylfuran.__

For comparison purposes 2-phenylfuran was synthesized following the method outlined by Johnson (110).

A stirred solution of aniline (23.3g.) in concentrated hydrocloric acid (60 ml.) and water (40 ml.) was cooled to 0° in an ice-salt bath, and treated dropwise with a solution of sodium nitrite (18.0 g.) in water (35 ml.) at such a rate that the reaction temperature did not exceed 5°. When the addition was complete, stirring was continued at 0° for 15 minutes, then 100 ml. of pre-cooled furan was added. To this vigorously stirred mixture was added 150 ml. of 3N sodium hydroxide solution at a rate such that the temperature did not exceed 10°. When all the aqueous alkali had been added the mixture was stirred vigorously at 0° for 5 hours. At the end of this time the organic layer was decanted and combined with an ether extract of the aqueous phase. The furan and ether were removed __in vacuo__ and the thick tarry residue distilled at reduced pressure. The fraction (2.1 g.) b.p. 103-105/12 mm. was collected. Johnson (110 reports b.p. 107-108°/15 mm. 2-Phenylfuran prepared in this way was identical to that prepared from benzenediazonium fluoborate and furan.

Benzenediazonium-o-carboxylate

This compound was prepared according to the method outlined by Hantzsch and Davidson (159).

A stirred solution of anthranilic acid (10.0 g.) in ethanol (100 g.) and concentrated hydrochloric acid (6 ml.) was cooled to 0° in an ice-salt bath and treated dropwise with iso-amylnitrite (14.0 g.). When all the iso-amylnitrite had been added a rapid stream of gaseous hydrogen chloride was bubbled through the mixture for 10 minutes. The mixture was then diluted with an equal volume of ether, the white precipitate filtered, and dissolved in a small volume of cold water. The stirred solution was then treated at 0° with freshly prepared silver oxide until a grey color indicating the presence of excess silver oxide was observed. This slurry was filtered, the solid washed with ice-cold water, and approximately 30 ml. of ethanol was added to the filtrate. Ether was then added to the cold stirred solution until a solid precipitated out. The solid was removed by filtration and dried, giving 7.1 g. of a pale pink solid. This material, when dry, was easily detonated by rubbing against a metal surface. It can be safely stored in dry tetrahydrofuran in the cold.

Naphthalene-1,4-endoxide.

A stirred slurry of benzenediazonium-o-carboxylate (14.0 g.) in furan (200 ml.) was boiled under reflux for 64 hours. The cooled mixture was filtered. The furan evaporated and the red oil taken up in chloroform and placed on "Merck" alumina. The product (8.44 g., 63.4%) was eluted from the column with 20% chloroform in petroleum ether (b.p. 80-100°).

Crystallization of this substance from petroleum ether (b.p. 60-80°) gave pale yellow malodorous needles, m.p. 55°. Stiles and Miller (111) report m.p. 55-56° for this compound.

<u>Conversion of 2,5(?)-Dihydro-2(2,5-Dimethoxycarbonylphenyl)-5(?)-t--Butoxyfuran to 2-(2,5-Dimethoxycarbonylphenyl)furan.</u>

Dry hydrogen chloride was bubbled through a solution of the t-butoxydihydrofuran (0.50 g) in carbon tetrachloride (50 ml.) for 15 minutes the solution was then warmed gently for 5 minutes, and the carbon tetrachloride removed <u>in vacuo</u>. The solid residue was taken up in hot petroleum ether (b.p. 60-100°), and on cooling, pale yellow parallelograms (0.30 g) m.p. 85°, identical in every respect to authentic 2-(2,5-dicarbomethoxyphenyl)furan were obtained.

<u>N-Benzoyl-2-iso-Propyl-5-Methoxycarbonylaniline.</u>

A solution of 2-<u>iso</u>-propyl-5-methoxycarbonylaniline (10.0 g.) in dry benzene (100 ml.) and dry pyridine (50 ml.), protected from moisture with a calcium chloride tube, was treated dropwise, with stirring, with benzoylchloride (8.0 g.) over a period of 10 minutes. The resulting solution was boiled under reflux for 1 hour and then poured into 200 ml. of water. The organic layer was decanted, and the aqueous phase was extracted with ether. The organic layers were combined, dried over anhydrous magnesium sulfate, the solvent removed in <u>vacuo</u>, and the solid residue crystallized from petroleum ether (b.p. 60-100°). White needles (14.0 g., 90.3%) m.p. 122° were obtained.

<u>N-Nitroso-N-Benzoyl-2-iso-Propyl-5-Methoxycarbonylaniline.</u>

In a 500 ml. three-necked flask equipped with a gas inlet tube and a calcium chloride tube, was placed a mixture of the above benzamide (10.0g.), glacial acetic acid (50ml.) and acetic anhydride (25 ml.). The stirred mixture was warmed until solution took place and then cooled to 0^{o} in an ice-bath. Nitrous gases, which were first passed through a calcium chloride tower, were then bubbled through the well stirred slurry until the benzamide had all gone back into solution (dry nitrogen was used as a carrier gas). By this time, the solution which was originally colorless had become deep green. Nitrous gases were then bubbled through the deep green solution for an additional half-hour. The reaction mixture was poured onto ice (about 200 g.), the precipitated solid removed by filtration, washed well with ice-cold water, and then placed in a pre-cooled vacum dessicator over sulfuric acid. The pale yellow nitroso compound was kept in a cold room under vacum overnight. The dry yellow powder thus obtained (9.6-10.2g., 87-92%) could be kept at 0^{o} for several days without appreciable decomposition. Normally, however, the nitroso compound was used directly in the next reaction.

<u>3,3-Dimethyl-6-methoxycarbonylindiazene</u>

A mixture of the above nitroso compound (10.00 g.), and t-butanol (150 ml.), protected from moisture with a calcium chloride drying tube, was stirred at room temperature until solution was complete. The above solution was allowed to stand at room temperature for 24 hours, the t-butanol removed in vacuo, the residue taken up in chloroform, and placed on a column of "Merck" alumina. Various low boiling materials and colored impurities were eluted with 5% chloroform in petroleum ether (b.p. 80-100^{o}). The product was removed from the column with 30% chloroform in petroleum ether (b.p. 80-100^{o}).

The eluate was evaporated and the residue crystallized from petroleum ether (b.p. 60-80) giving stout orange rods (3.00 g., 47.4%) m.p. 106°. Several crystallizations from the same solvent (charcoal) gave colorless stout rods, m.p. 108-109°. Calc. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92%. Found: C, 64.70; H, 6.21 %. Mol. wt., 211. Calc. for $C_{11}H_{12}O_2N_2$: 204.2 U.V. spectrum (in absolute ethanol): λ max. 226, 250(sh.), 350 mμ; log ε : 4.44, 3.75, 2.40.

3,3-Dimethylindiazene-6-carboxylic Acid.

The above methylester (501.6 mg.) in 50% aqueous ethanol (20 ml.) containing 1.5 g. of 10% potassium hydroxide solution was boiled under reflux on a water bath for 2 hours. The cooled solution was concentrated to a small volume *in vacuo*, the residual liquid acidified with 10% hydrochloric acid, the precipitated solid removed by filtration, and dried. Yield, 444.3 mg. (95.1%) m.p. 155°. Several crystallizations from water-acetone (4:1) gave colorless, stout, needles m.p. 202-203°. Calc. for $C_{10}H_{10}O_2N_2$: C, 63.14; H, 5.30%. Found: C, 63.32, 63.06; H, 5.75, 5.27%.

3,3-Dimethyl-6-Aminoindiazene.

The acid azide and isocyanate were prepared from the above acid following the general procedure recently published by Weinstock (120).

A stirred solution of the above acid (1.000g.) in acetone (15 ml.) and water (5 ml.) was cooled to 0° in an ice-salt bath. The stirred solution maintained at 0°, was treated dropwise first with a solution of triethylamine (0.63 g.) in acetone (10 ml.), then with a solution of ethylchloroformate (0.71 g.) in acetone (5 ml.). After stirring for ½ hour at 0° a solution of sodium azide (0.47 g.) in water (6 ml.) was added dropwise, the temperature being maintained at 0°. The reaction mixture was stirred at 0° for 1½ hours, and then poured into a large volume of ice-water. This mixture was extracted with ether, the ether dried over anhydrous magnesium sulfate and then removed in vacuo at room temperature leaving a semi-solid residue. This material was taken up in dry xylene (10 ml.) and heated on a steam-bath (calcium chloride drying tube) until nitrogen evolution ceased (about 1½ hours). To the above solution was added 6.0 g. of 50% aqueous potassium hydroxide solution, and heating (steam-bath) was continued for an additional 2 hours. The cooled mixture was placed in a seperatory funnel, the organic layer removed and combined with an ether extract of the alkaline layer. The combined organic layers were extracted with 10% hydrochloric acid (3 x 50 ml.), the acid extract made basic with sodium carbonate, and exhaustively extracted with ether. Evaporation of the ether and crystallization of the solid residue from petroleum ether (b.p. 60-100°) gave yellow needles (0.310 g.) m.p. 130°. Several crystallizations from the same solvent gave an analytical sample m.p. 132°. Calc. for $C_9H_{11}N_3$: C, 67.04; H, 6.88%. Found: C, 67.05; H, 6.77%.

Preparation of the Diazonium Fluoroborate of 3,3-Dimethyl-6-amino-indiazene.

This diazonium salt was prepared from the amine in a manner entirely analogous to that already described for the preparation of various substituted benzenediazonium fluoborates. From 0.50 g. of the above amine was obtained 0.356 g. (44.3%) of the corresponding diazonium fluorborate. The salt was not characterized, but used directly in the next reaction.

Attempted Preparation of 3,3-Dimethylindiazene.

Using the deamination method outlined by Hendrickson (121), the above diazonium fluoborate (0.355 g.) was suspended in methanol (15 ml.) and cooled with stirring to 0°. The stirred suspension was treated with small portions of sodium borohydride (0.055 g.) at a rate such that the reaction temperature did not exceed 5°. At the end of this time the reaction mixture was poured into ice-water, and extracted with ether. The ether was evaporated *in vacuo* at room temperature leaving a viscous red oil which rapidly decomposed giving an insoluble black solid. This material was not investigated further.

Nitration of Cumene.

Cumene (224 g.) was cooled to 30° and a solution of concentrated nitric acid (144 g.) in concentrated sulfuric acid (198 g.) was added dropwise, the reaction temperature being maintained at 30-40°. When the addition was complete the stirred mixture was maintained at 30-45° for an additional 2 hours. The mixture thus obtained was poured into 1 l. of water, the organic layer removed and combined with an ether extract of the aqueous phase, and the combined organic phases washed first with several large volumes of water, then with 2% sodium bicarbonate solution. The ethereal solution was concentrated on a flash evaporator and the residual oil was distilled at reduced pressure. There was obtained first a low boiling fraction (45.5 g.) b.p. 47-50/14 mm) which was mainly cumene, then a mixture of *o*-and *p*-nitrocumene, b.p. 115-137°/14 mm. The combined yield of *o*-and *p*-nitrocumene was 100 g. (61%). The above mixture was then twice fractionally distilled *in vacuo* using a 2 ft. Vigreux column. There was thus obtained 25.0 g. of fairly pure o-nitrocumene, b.p. 115-120/14 mm., n_D^{24} 1.5267 and 40 g. of pure p-nitrocumene, b.p. 135-137°/14 mm., n_D^{24} 1.5348. The middle fraction which consisted of a mixture of the isomeric nitrocumenes was not refractionated. Brown and Bonner (140) report b.p. 115°/13 mm. and n_D^{20} 1.5248 for o-nitrocumene, and b.p. 134°/13 mm., n_D^{20} 1.5369 for p-nitrocumene.

2- Aminocumene.

A solution of 2-nitrocumene (18.2 g.) in ethanol (200 ml.) containing platinic oxide (0.20g.) was hydrogenated at room temperature and an initial hydrogen pressure of 64 p.s.i for 1 hour. The mixture was filtered, the ethanol removed *in vacuo*, and the residual oil distilled at reduced pressure. There was obtained 12.0g. (80.3%) of a colorless oil. b.p. 88-92°/8 mm. The acetate prepared from this amine possessed m.p. 73°. v.Braun *et. al.* (141) report b.p. 214°/732 mm for 2-aminocumene and 72° for its N-acetate.

N-benzoyl-2-iso-propylaniline.

This benzamide was prepared in exactly the same manner as N-benzoyl-2-*iso*-propyl-5-carbomethoxyaniline. From 12.0 g. of the aminocumene was obtained 16.5 g. of the pure *ortho*-isomer, m.p. 144°, and 2.2 g. of a low melting solid (presumably a mixture of isomeric benzamides), after fractional crystallization from petroleum ether (b.p. 80-100°). Several crystallizations of the benzamide of 2-aminocumene from the same solvent gave an analytical sample, m.p. 149° Calc. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16%. Found: C, 79.95; H, 6.82%.

N-Nitroso-N-benzoyl-2-iso-propylaniline.

This compound was prepared in 92% yield from the above benzamide, in a manner entirely analogous to that used in preparation of N-nitroso-N-benzoyl-2-*iso*-propyl-6-carbomethoxyaniline

Attempted Preparation of 3,3-Dimethylindiazene.

The above nitroso compound (5.40 g.) was decomposed in the same manner as already described in the preparation of 3,3-dimethyl-6-carbomethoxyindiazene. Evaporation of the *t*-butanol *in vacuo* gave a black solid which was dissolved in a mixture of chloroform and petroleum ether (b.p. 60-100°). Cooling gave pale grey needles which were removed by filtration. This substance (1.0 g.) was shown to be benzoic acid by comparison with authentic material. The mother liquors from the above crystallization were evaporated *in vacuo* and the oily residue taken up in chloroform and placed on "Fluka" neutral alumina. Elution with petroleum ether (b.p. 60-100°) gave an oil (0.30 g.) whose N.M.R. spectrum indicated the presence of at least two compounds, both of which still contained an *iso*-propyl group. This material was not characterized further. A black tar was eluted from the column with 1:1 chloroform petroleum ether (b.p. 60-100°). This tar was also not further investigated.

CLAIMS TO ORIGINAL RESEARCH

1. Ortho alkyl substituted nitrobenzenes on lithium aluminum hydride reduction give rise to substantial amounts of the corresponding aniline as well as the expected azo derivative. Di-ortho substituted nitrobenzenes on lithium aluminum hydride reduction yield predominantly or exclusively, the corresponding di-ortho substituted anilines.

2. 1,2,4,5-Tetrahydropyrrolo [3,2,1-hi] indole was synthesised in three steps from 1,3-dimethoxycarbonylmethyl-2-nitrobenzene, and several of its physical and chemical properties are described. Two alkyl derivatives of this ring system have been prepared by tin in ethanolic hydrochloric acid reduction of their corresponding 3,4-dehydro derivatives.

3. 1,2,4,5-Tetramethylpyrrolo [3,2,1 hi] indole was prepared by catalytic dehydrogenation of cis-1,2-dihydro-1,2,4,5-tetramethylpyrrolo [3,2,1-hi] indole, and several of its physical and chemical properties are described.

4. The stereochemistry of the tin in ethanolic hydrochloric acid and zinc and hydrochloric acid reduction of 2,3-dimethylindole was determined. In the former case 66.0% cis and 34.0% trans-2,3-dimethylindoline was formed. The latter reduction yielded 73.5% cis and 26.5% trans-2,3-dimethylindoline.

5. In conjunction with (4) the stereoisomeric cis and trans-2,3-dimethylindolines have been fully characterized. The polyphosphoric acid catalysed equilibration of both of these indolines was examined and the equilibrium composition obtained in this way consisted of approximately 74% trans and 26% cis-2,3-dimethylindoline.

6. The N.M.R. spectra of all the stereoisomeric intermediates (including the two indolines mentioned in (4) and (5) leading to 1,2,4,5-tetramethylpyrrolo [3,2,1-*hi*] indole were measured. Coupling constants and chemical shifts for each of these compounds were determined. The coupling constants $J_{H2\,H3}$, $J_{H2(CH_3)2}$, and $J_{H3(CH_3)3}$ showed marked variation. Resonance for the methyl group at C_2 in 1-benzenesulfonyl-*trans*-2,3-dimethylindoline appeared at unexpectedly high field (0.56 p.p.m.). The upfield shift of this signal was ascribed to the magnetic anisotropic effect of the phenyl ring in the sulfonamide residue at C_1.

7. An excellent method of preparing substituted 2-phenylfurans by potassium *t*-butoxide catalysed decomposition of an appropriate benzenediazonium fluoroborate in the presence of furan was developed. The preparation of 2(3,5-dimethoxycarbonylphenyl) furan in 76% yield illustrates the utility of this method. When 2,5-dimethoxycarbonylbenzenediazonium fluoroborate was subjected to the described reaction conditions, an unusual side reaction resulting in the formation of 2(2,5-dimethoxycarbonylphenyl)-5(?)-*t*-butoxy-2,5(?)-dihydrofuran occurred. This amounted to 50% of the total product, the other product being the expected substituted 2-phenylfuran. Physical and chemical evidence for the structure of this dihydro furan is described.

8. A new type of exceedingly stable hydrogen-bonded dimer formation involving *o*-substituted phenols is described. Substantial spectral evidence for this dimer formation is presented.

9. 3,3-Dimethyl-6-methoxycarbonylindiazene was synthesized from N-nitroso-N-benzoyl-2-*iso*propyl-5-methoxycarbonylaniline using the modified Jacobson-Huber synthesis. Some properties of this and two other 6-substituted 3,3-dimethylindiazenes are described. Conversion of 3,3-dimethyl-6-methoxycarbonylindiazene to 3,3-dimethylindiazene failed, as did an attempted synthesis of this latter compound from N-nitroso-N-benzoyl-*o*-*iso*propylaniline.

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