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THE UNIVERSITY OF ALBERTA

A MECHANISTIC STUDY OF THE FISCHER INDOLE SYNTHESIS

Isolation and Indolization of the Dienone-imine Intermediate

by

© GURDIP SINGH BAJWA, M.Sc. (Hons).

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE

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DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

OCTOBER, 1968

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FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled A MECHANISTIC STUDY OF THE FISCHER INDOLE SYNTHESIS

Isolation and Indolization of the Dienone-imine Intermediate

submitted by GURDIP SINGH BAJWA, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

To obtain the dienone-imine intermediate proposed in the Robinson mechanism of the Fischer indole synthesis, the reaction of cyclohexanone with N'-alkyl-2,6-dialkylphenylhydrazine and its hydrochloride was studied. When the above reactants were heated in refluxing dry benzene and water removed azeotropically, 8,9-dialkyl-1,2,3,4-tetrahydrocarbazole could be obtained in good yield. Only two other products could be isolated from this reaction. They were ammonium chloride and alkylamine hydrochloride. The latter arose through the elimination of the alkyl group at the nitrogen atom and not from the alkyl group attached to the aromatic ring of the hydrazine. Although neither the enehydrazine nor the dienone-imine intermediate could be isolated, the products of the reaction could be explained only through their intermediacy.

When the reaction of N'-methyl-2,6-dimethylphenylhydrazine with cyclohexanone was conducted at room temperature through the azeotropic removal of water under vacuum, an oil was obtained which gave an indication of the presence of the expected enehydrazine in it. All attempts to isolate this enehydrazine in pure form were unsuccessful. Further, when this oil was treated in benzene with maleic anhydride, no Diels-Alder adduct of the expected dienone-imine could be isolated. The inability to isolate or trap the dienone-imine intermediate was ascribed to the presence of an enolizeable hydrogen at a carbon atom α to the imine carbon of the former cyclohexanone ring.

When such an enolizeable hydrogen in the dienone-imine intermediate was eliminated by the use of isobutyraldehyde, and the latter allowed to react with N'-methyl-2,6-dimethylphenylhydrazine hydrochloride, a stable dienone-imine hydrochloride was obtained. This could be purified and converted to the free dienone-imine. This dienone-imine reacted with tetracyanoethylene and maleic anhydride to give the reactions of secondary amines rather than to form the corresponding Diels-Alder adducts. The reaction with acetyl chloride gave N-acetylation. However, this dienone-imine could not be converted to the corresponding indole. When a mixture of propionaldehyde and N'-methyl-2,6-dimethylphenylhydrazine hydrochloride was heated in refluxing dry benzene for 20 hours, 1,3,7-trimethylindole (31%) was obtained. The latter was contaminated with 3,7-dimethylindole (~ 9%). When the above reactants were heated in refluxing dry benzene for only 10-12 minutes, a solid dienone-imine hydrochloride containing isomeric contaminants was obtained. When this material was again heated in refluxing dry benzene for 19 hours, the reaction mixture gave a 35% yield of 1,3,7-trimethylindole also contaminated with 3,7-dimethylindole (~ 9%).

The isolation of a dienone-imine and its conversion to the corresponding indole supports the mechanism proposed by Robinson for the Fischer indole synthesis.

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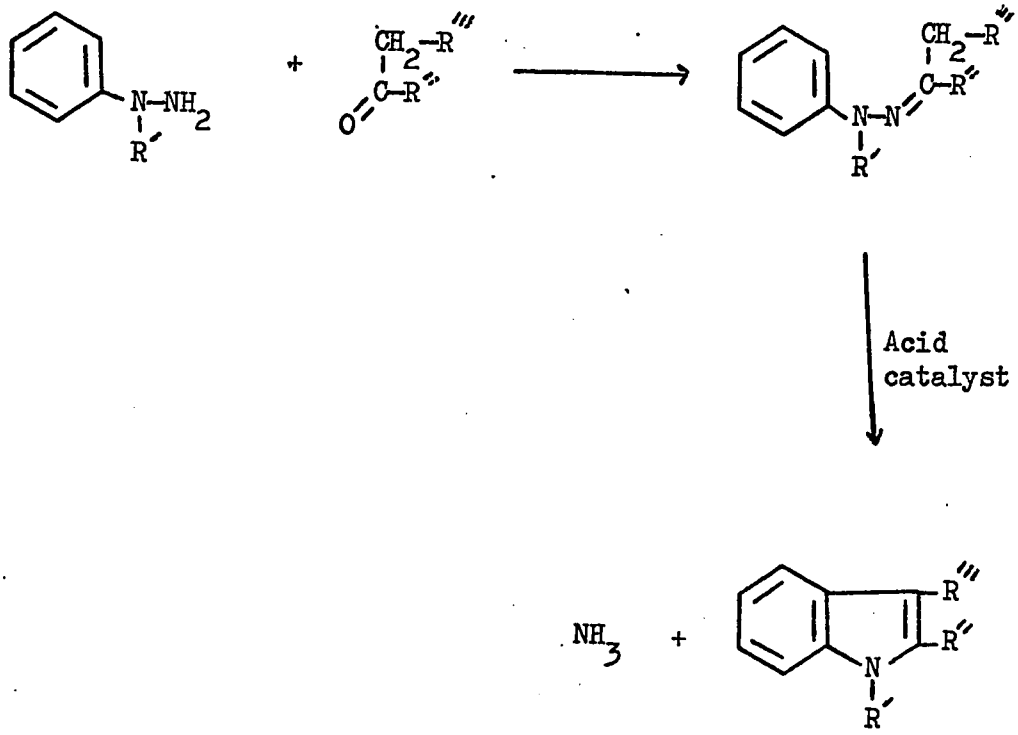
INTRODUCTION

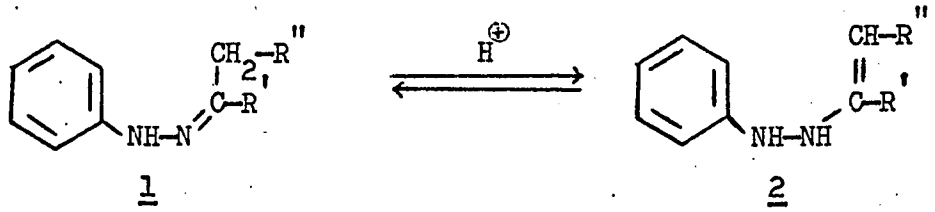
A. THE PROBLEM.

In 1883, Fischer (1, 2) developed an easy and pliant approach to the synthesis of indoles from arylhydrazones. This synthesis, known as the Fischer indole synthesis, is shown by the following general equation.

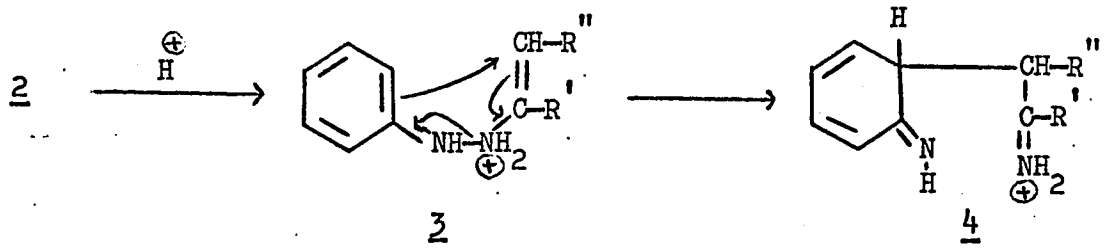


The currently accepted mechanism to account for this reaction was first proposed by Robinson (27 a, b) in 1918. This is illustrated below in Scheme I, divided into three stages (10).

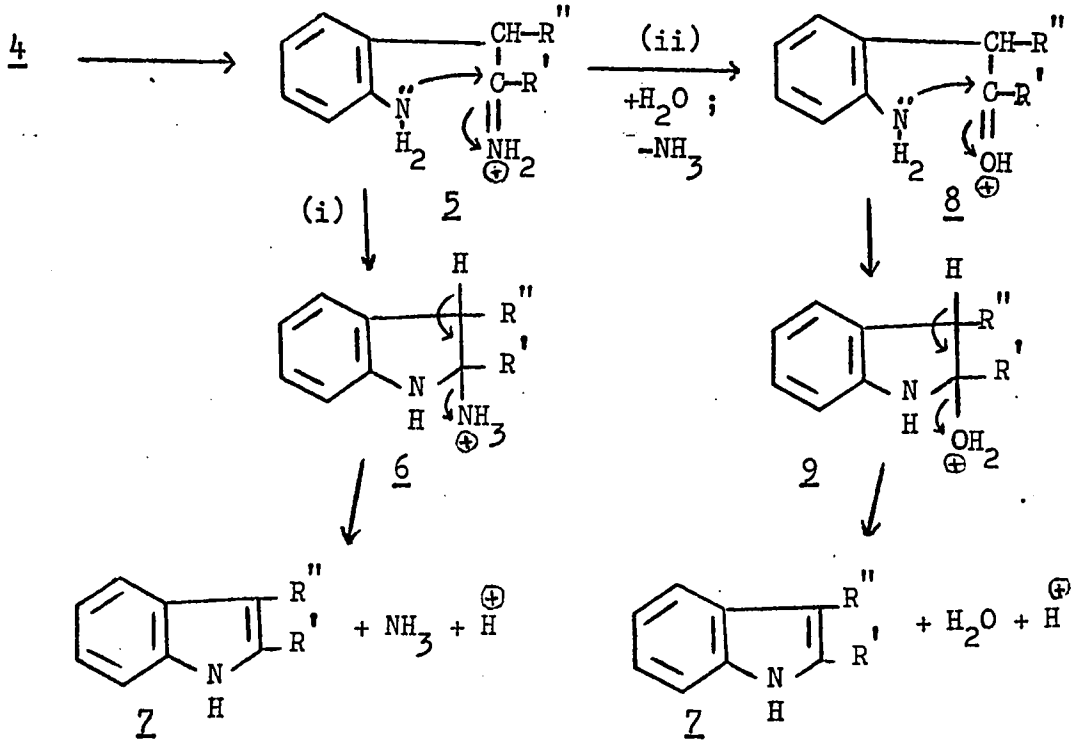
Stage a. Hydrazone–enehydrazine equilibrium (1 ⇌ 2).



Stage b. Formation of new C – C bond (3 ⟶ 4).



Stage c. Loss of ammonia (by either pathway (i) or (ii)).



Scheme I

The above mechanism offers a plausible explanation for all the experimental observations.

However, in spite of extensive research in this field, one step of this mechanism still lacks direct experimental support. The dienone-imine intermediate 4 as yet has not been isolated although indirect evidence for its intermediacy has been presented (25, 70-72, 74, 75).

Furthermore, although Suvorov (51, 52) has isolated the N,Ń-diacetyl derivative of the enehydrazine 2, the enehydrazine itself has not been obtained. In addition, the factors determining the fate of the nitrogen atoms of the arylhydrazine are not completely clarified.

One purpose of the present investigations was to isolate the enehydrazine 2.

The second, and probably more important goal was to isolate or trap the dienone-imine intermediate 4 and then effect its conversion to the corresponding indole derivative 7.

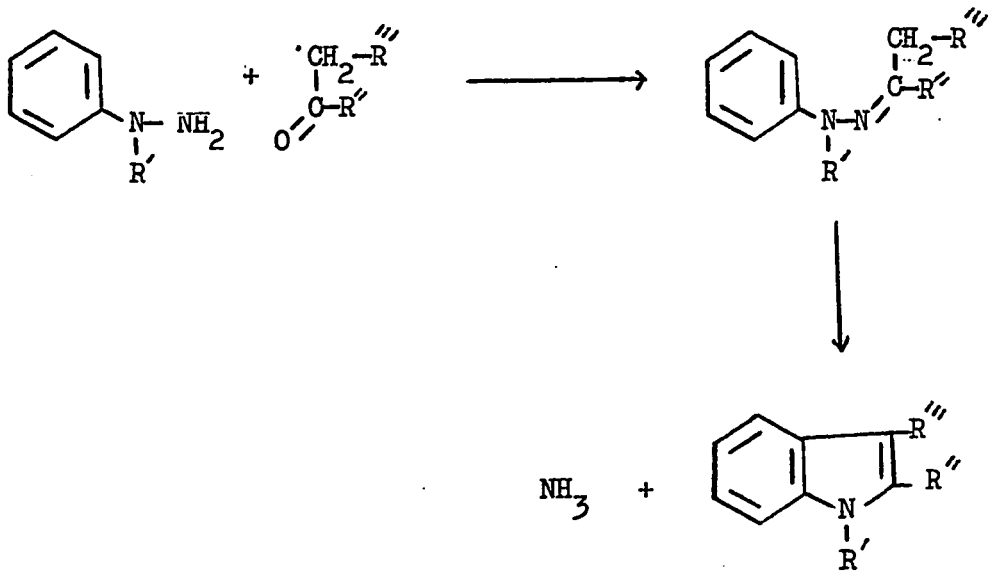
The third purpose of this work was to obtain information concerning the fate of the nitrogen atoms of the hydrazine.

B. THE DEVELOPMENT OF THE FISCHER INDOLE SYNTHESIS.

Excellent reviews (3a, 11, 32b, 32d, 50, 105b) have appeared dealing with the Fischer reaction and its use in organic synthesis. However, salient features of the development of the mechanism of the Fischer indole synthesis will be presented here as background for an understanding of the present work.

In 1883, E. Fischer and F. Jourdan (1) isolated a compound, $C_{10}H_9NO_2$ from the hydrogen chloride-catalyzed reaction of pyruvic acid with 1-methylphenylhydrazine. In the subsequent year, this compound was identified as 1-methylindole-2-carboxylic acid (2). This reaction was followed by several similar cyclizations and is now known as the Fischer indole synthesis.

Briefly, this transformation (3a) can be represented in the following manner.

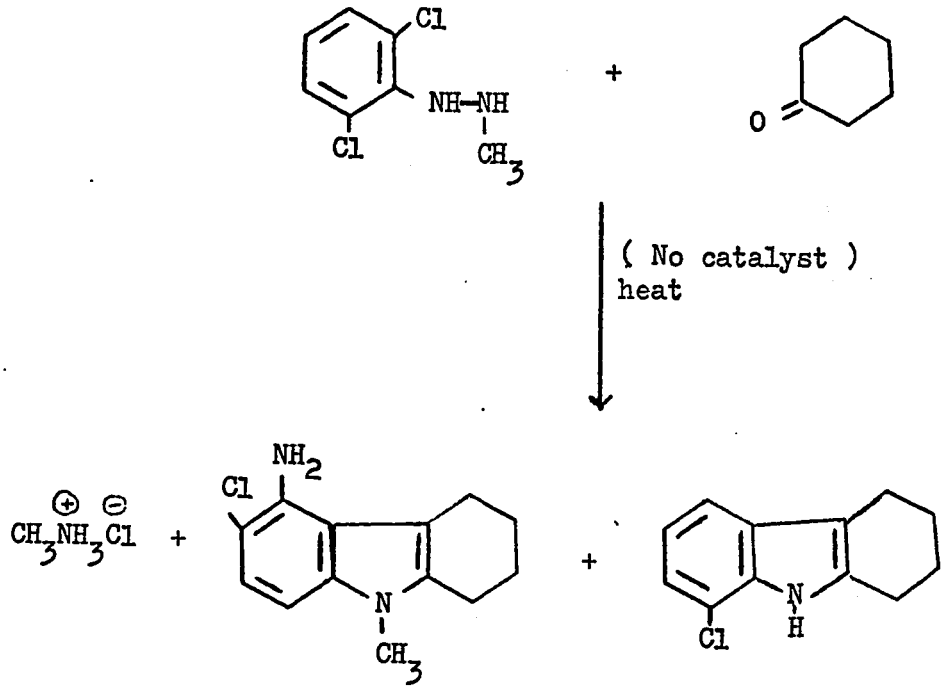


Later on, Fischer (4) reported that anhydrous zinc chloride was a better catalyst than hydrogen chloride and obtained various indole derivatives in better yields than had been possible with hydrogen chloride.

There has been a considerable variation in the reaction conditions employed for effecting the indolizations. By the use of inert solvents like methylnaphthalene (5) and keeping the temperature below 150° (5), the yields of the indoles were improved considerably. The large excess of zinc chloride employed by Fischer (6) (in five-fold excess, w/w, over the arylhydrazone) was no longer considered to be essential because the reaction proceeded smoothly even in the presence of one per cent of zinc chloride (7, 8). Due to this discovery, this reaction has occasionally been referred to as the Fischer-Arbuzov Reaction (9).

In quest of optimum reaction conditions, several other substances have been investigated as catalysts for this reaction, and have recently been enumerated in a comprehensive review (10). They are, in general, acidic substances and compounds capable of complex-formation with organic ligands. The more common examples of these catalysts are cuprous chloride (6, 7, 11), platinum chloride (7, 12), cobalt chloride (13), stannous chloride (14), nickel chloride (13), metallic powders of cobalt, copper and nickel (13), alcoholic sulphuric acid (15), concentrated sulphuric acid (16, 17), dilute sulphuric acid (18), hydrochloric acid in acetic acid media (19), acetic acid (20), boron trifluoride etherate in acetic acid (21), hypophosphoric acid (22) and Grignard reagents (23).

Recently, it has been shown that cyclizations of the hydrazones can proceed thermally without the aid of an acid catalyst (24, 25). Thus, N-methyl-2,6-dichlorophenylhydrazine was condensed with cyclohexanone (25) without the aid of an acid catalyst, as illustrated below.



This uncatalyzed Fischer reaction under mild conditions is similar to the thermal reaction of the Claisen rearrangement.

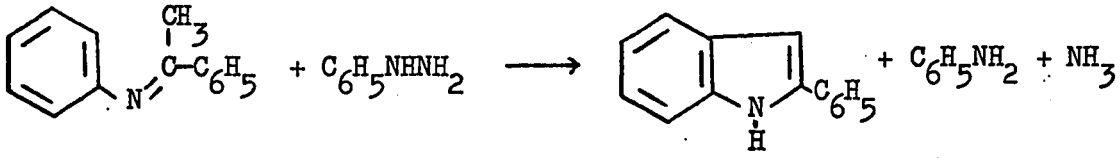
1. Mechanisms of the Fischer indole synthesis.

Exhaustive discussions of the various mechanisms proposed for this reaction have been given in several reviews (11, 50). Only a brief accound of the mechanisms other than the Robinson mechanism will be given here. More emphasis will be placed on the development

of the Robinson mechanism.

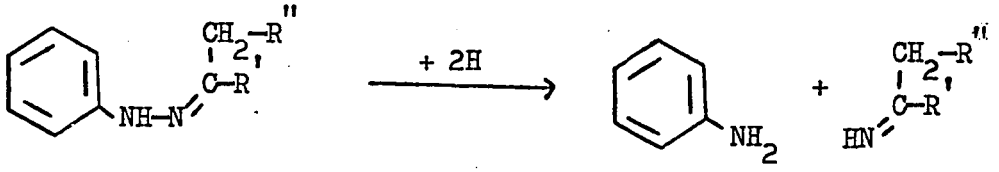
(i) Reddelien Mechanism

This mechanism was advanced in 1912 by Reddelien (26) as a result of his discovery that the anil of acetophenone is oxidized by phenylhydrazine to 2-phenylindole.

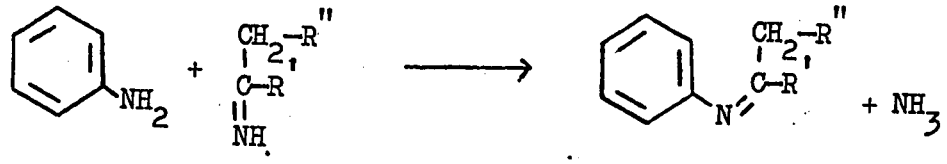


By analogy, the Fischer reaction was also believed to proceed through the formation of anil-like intermediates, and can be represent in three distinct stages.

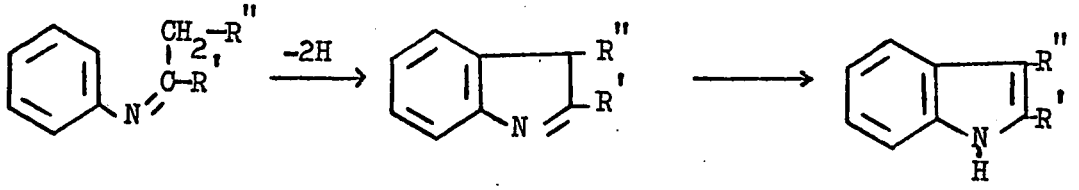
(a) Reduction of phenylhydrazone during the simultaneous oxidation in stage (c)



(b) The products of stage (a) eliminate ammonia to form the anil.



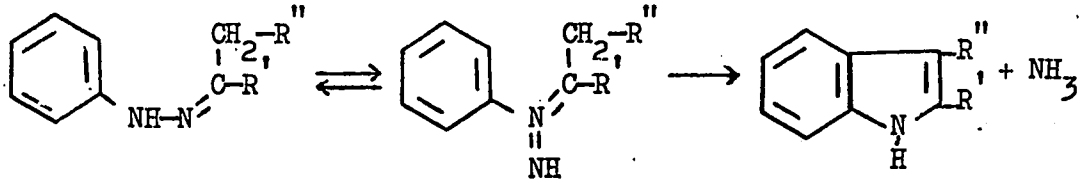
(c) Conversion of the anil to the corresponding indole.



This mechanism was severely criticised by several workers (27, 28, 29) in view of its failure to offer a plausible explanation for the formation of 1-alkyl indoles.

(ii) Landau Mechanism

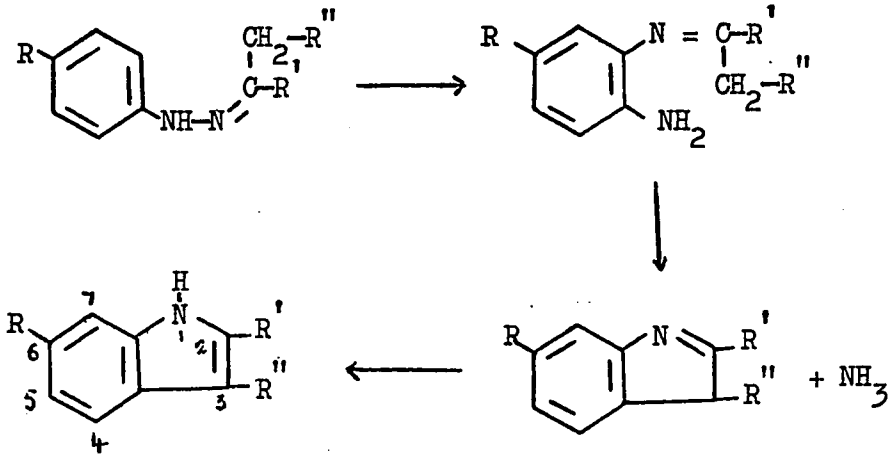
The second mechanism was suggested by Bamberger and Landau (30, footnote) and can be illustrated by the following reaction.



This mechanism does not explain the method of elimination of ammonia nor the formation of N-methylindole derivaties (25, 31) and thus could not be substantiated.

(iii) Cohen Mechanism

In a third mechanism, proposed by Cohen (32a), it was assumed that arylhydrazones undergo ortho-semidine rearrangement, with the subsequent loss of ammonia and tautomerization of the product to the corresponding indole compound. This is illustrated below.



This mechanism of indolization likewise cannot rationalize the formation of N-methylindoles (31). Moreover, it predicts the formation of 6-substituted indoles from p-substituted phenylhydrazones, whereas in actual practice, 5-substituted indoles (33) are obtained. Consequently, this mechanism has also been discarded.

(iv) Robinson Mechanism

The fourth mechanism was postulated by Robinson and Robinson in 1918 (27a) and is currently viewed as the accepted pathway (3b, 32b, 38, 39) for the reaction. This postulation, in contradistinction to previous hypotheses, finds considerable support from both theoretical as well as experimental observations, particularly from the work of Allen and Wilson (40) and of Carlin and Fischer(41).

Because it is quite pertinent to our work, an account will be given here of the studies dealing with the Robinson mechanism. This will be presented under the following three headings and is illustrated in the overall reaction shown in Scheme I (page 3).

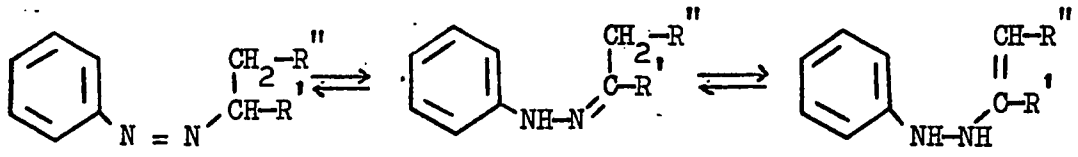
Stage a.

Evidence for the hydrazone-enehydrazine equilibrium.

The first item of evidence for this stage comes from the study of enolizations and indolizations of the various ketones and their phenylhydrazones respectively. Because there is an analogy between the keto-enol and hydrazone-enehydrazine equilibria, a correlation between the relative ease of enolizations of various ketones with the enolization of their respective phenylhydrazones should be apparent. Such a correlation, in fact, is noticed. It is

observed, in general, that the phenylhydrazones of easily enolizeable ketones like cyclohexanone, indolize with greater ease than do the phenylhydrazones of less readily enolizeable ketones such as diethyl ketone (27a). For instance, phenylacetaldehyde enolizes easily (42) (cf. the facile formation of the O-acetate of its enolic form) and its phenylhydrazone also indolizes (43) under much milder conditions. On the other hand, acetophenone (43) enolizes with difficulty and its phenylhydrazone (27, 44) also requires more vigorous conditions in order to form the indole.

The second piece of evidence for the hydrazone-enehydrazine equilibrium comes from spectroscopic studies of the hydrazones. The tautomeric equilibrium in the phenylhydrazones may be represented in the following manner.



Azo-form Hydrazone Enehydrazine

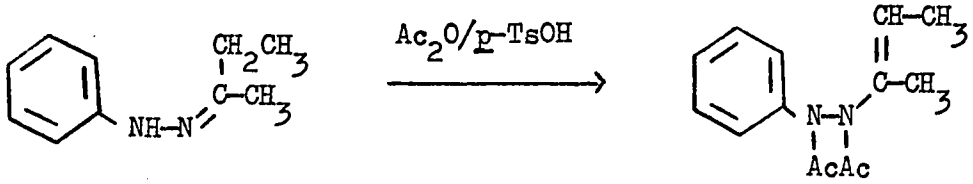
The ultraviolet studies by Grammaticakis (45) showed that phenylhydrazones, when dissolved in organic solvents under neutral conditions, do exist in equilibrium with a small amount of the azo tautomer. Polarographic investigations by Arbuzov et al (46, 47) have led to the conclusion that alcoholic solutions of phenylhydrazones of aliphatic and alicyclic ketones have the enehydrazine

structure in the free state. Arbuzov et al further contended that phenylhydrazones of aldehydes and aromatic aliphatic ketones, which exist as hydrazones in such solutions, can most likely be converted into the corresponding enehydrazine tautomers.

These results have recently been criticised by R. O'Connor (48, 49) who carried out i.r., visible, u.v. and n.m.r. spectroscopic studies of a number of phenylhydrazones, methylphenylhydrazones and benzene azoalkanes. He demonstrated that freshly prepared solutions of phenylhydrazones of aliphatic aldehydes and ketones exist as hydrazones but tautomerise rapidly into benzene azoalkanes. He further stated that no detectable concentration of the enehydrazine was found in such solutions.

However, it must be pointed out that this criticism does not rule out the formation of enehydrazine under the Fischer indolization conditions (50).

The third item of evidence for this step has been supplied by Suvorov (51, 52) who was able to trap the enehydrazine intermediate as its diacetyl derivative 10 which was subsequently converted to 2,3-dimethylindole 11 with an aqueous solution of sulphuric acid. This is illustrated below.



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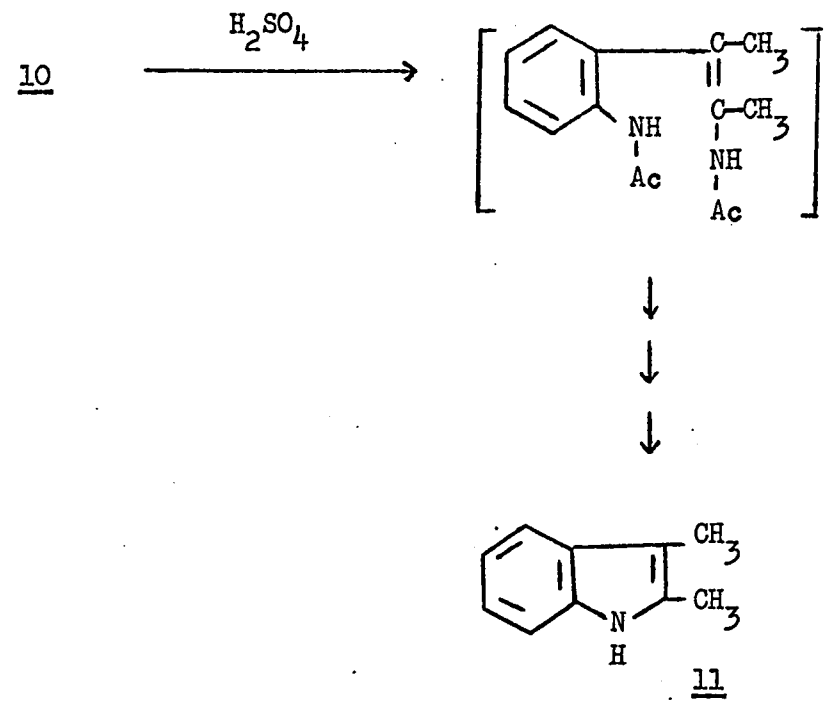


Ac_2O = acetic anhydride

p-TsOH = p-toluenesulfonic acid, monohydrate

Ac = $-\overset{O}{\overset{\|}{C}}-CH_3$

In view of the above evidence, it is obvious that the enehydrazine is quite likely one of the intermediates under the Fischer indolization conditions.

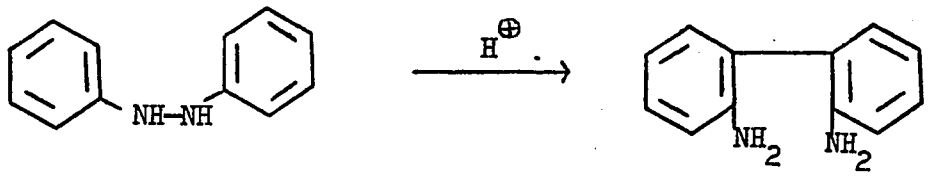
Stage b

Formation of the new C-C bond.

This stage envisages the formation of a new C-C bond and is believed to be analogous (27, 41, 53) to the ortho-benzidine rearrange-

ment and ortho-Claisen rearrangement. For the sake of comparison, these three processes are shown below.

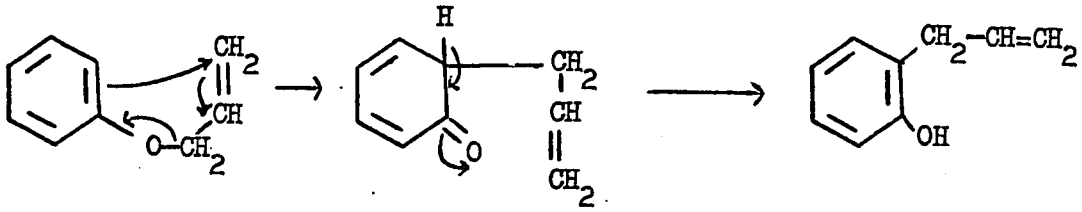
The ortho-benzidine rearrangement.



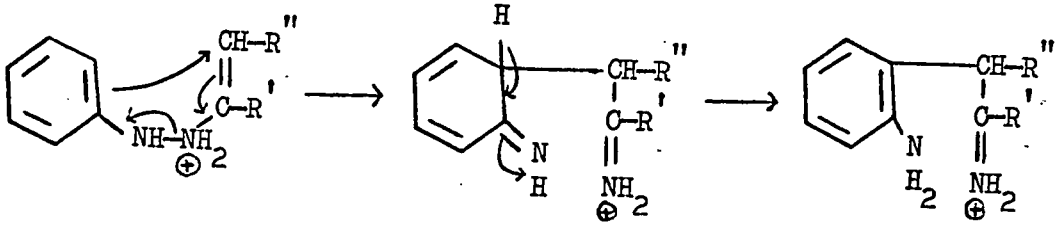
Hydrazobenzene

o-benzidine

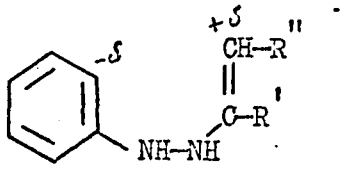
The ortho-Claisen rearrangement.



The Fischer indole synthesis.

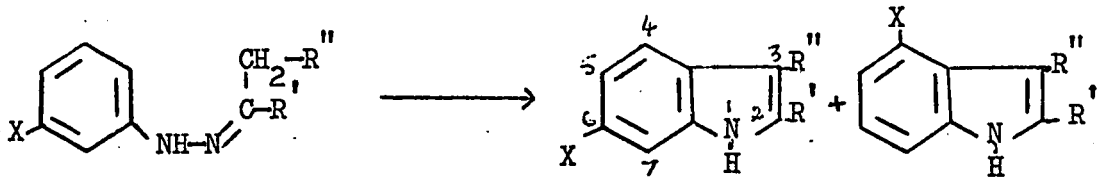


These three systems were further investigated by Arbuzov (54). After a careful consideration of the conjugation and polarization of the systems, he arrived at the conclusion that the enehydrazine intermediate is a 1,6-polarized system.



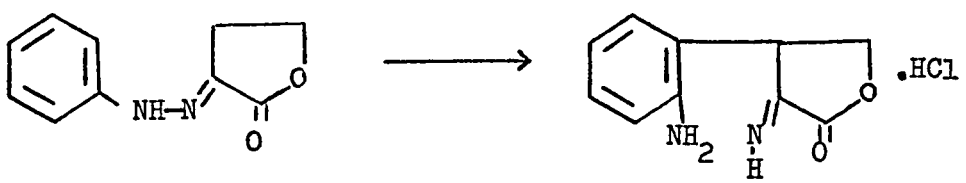
Protonation or complex-formation with a metal or metal salts further increases the polarization of this intermediate. Thus polarized, this intermediate is well-oriented for intramolecular rearrangement. Arbuzov further demonstrated that these are the only three cases of intramolecular rearrangements in polarized 1,6-conjugated systems and polarization of such conjugated systems is probably the "driving force" for the rearrangements.

The new C-C bond formation from the enehydrazine intermediate is belived to be the result of an intramolecular electrophilic substitution (33) on the aromatic nucleus. Such a conclusion is drawn (33) from the observation that in the indolization of m-substituted phenylhydrazones, the ratio of the 4-substituted indoles to the 6-substituted indoles produced is < 1 when the substituent is ortho-para directing, and it is > 1 when the substituent is meta-ortho directing (34-37). This is illustrated below.

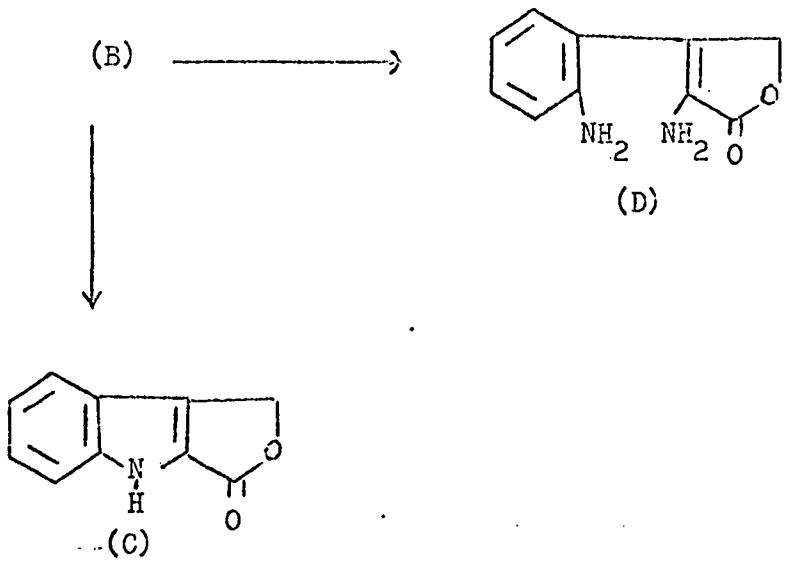


Besides these analogies, some intermediates have also been isolated under the Fischer indolization conditions which provide evidence for this stage of the mechanism. Suvorov et al (51, 52) obtained 2,3-dimethylindole 11 from 2-(N,N'-diacetyl-β-phenylhydrazino)-butene-2, 10, which suggests that the new C-C bond is formed at some stage of the reaction pathway subsequent to the enehydrazine formation.

Another intermediate isolated is due to Plieninger et al (55, 56). These workers found that when the phenylhydrazone of α-keto-γ-butyrolactone was heated in alcoholic HCl, it afforded α-imino-β-[o-aminophenyl]-γ-butyrolactone (B) in excellent yield (90%). Subsequent heating of this ketimine intermediate (B) furnished the expected indole (C), as shown below.

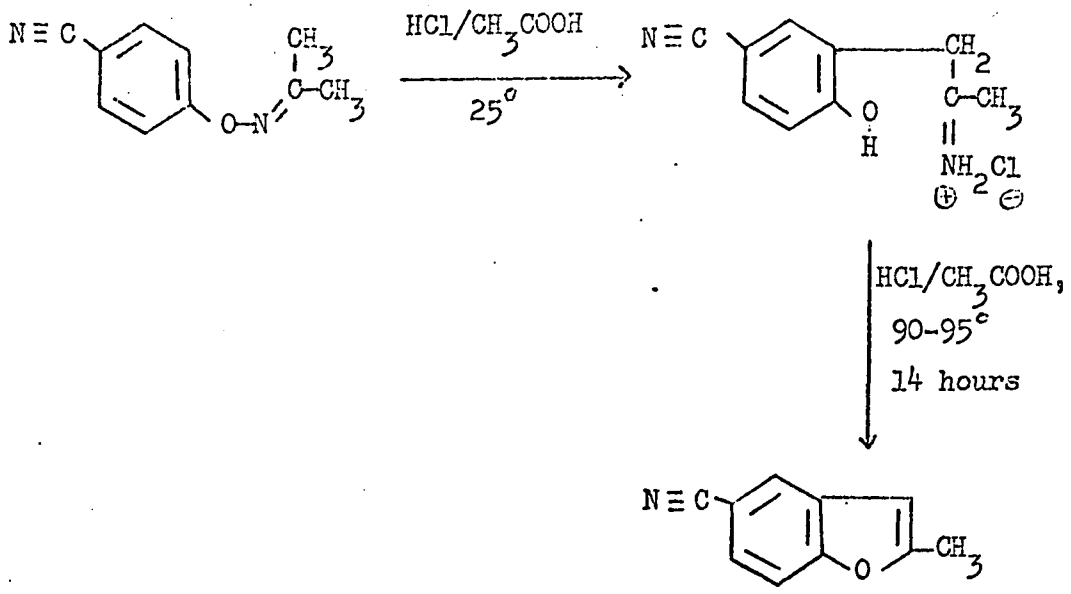


(B)



Recently, R. J. Owellen and associates (57) have examined the structure of this intermediate and by n.m.r. spectroscopy have proven it to be structure (D) rather than (B).

An analogous intermediate is reported (58) in the rearrangement of O-aryl oximes. Thus, p-(isopropylideneaminoxy)-benzonitrile, when allowed to stand in the presence of two equivalents of hydrogen chloride in glacial acetic acid, gave a precipitate of 3-(2-iminopropyl)-4-hydroxybenzonitrile hydrochloride. The latter afforded the corresponding benzofuran when it was heated with a hydrogen chloride-acetic acid mixture for 14 hours. This can be represented in the following manner.



The above evidence thus supports the conclusion that a new C-C bond is formed during the Fischer indolization at a stage following the enehydrazine formation.

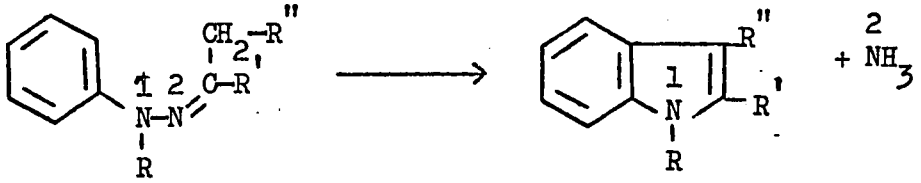
Stage c.

Loss of the Nitrogen Atom.

Determination of which nitrogen atom is eliminated from the aryl-hydrazone during indolization.

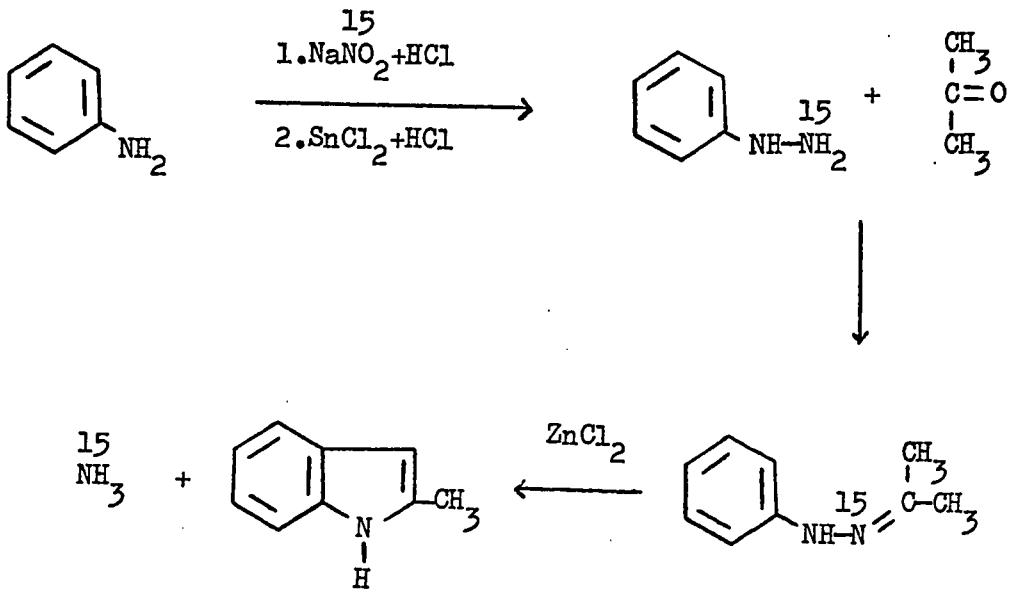
The problem of nitrogen elimination has been examined (1, 2, 6) as early as the discovery of the reaction itself. The indolization of 1-alkylarylhydrazones furnished N-substituted indoles which retained the alkyl group originally attached to the N-1 atom of the arylhydrazone. This led to the conclusion (2, 31) that it is the N-2

of the arylhydrazone which is eliminated during indolization. This is illustrated below.

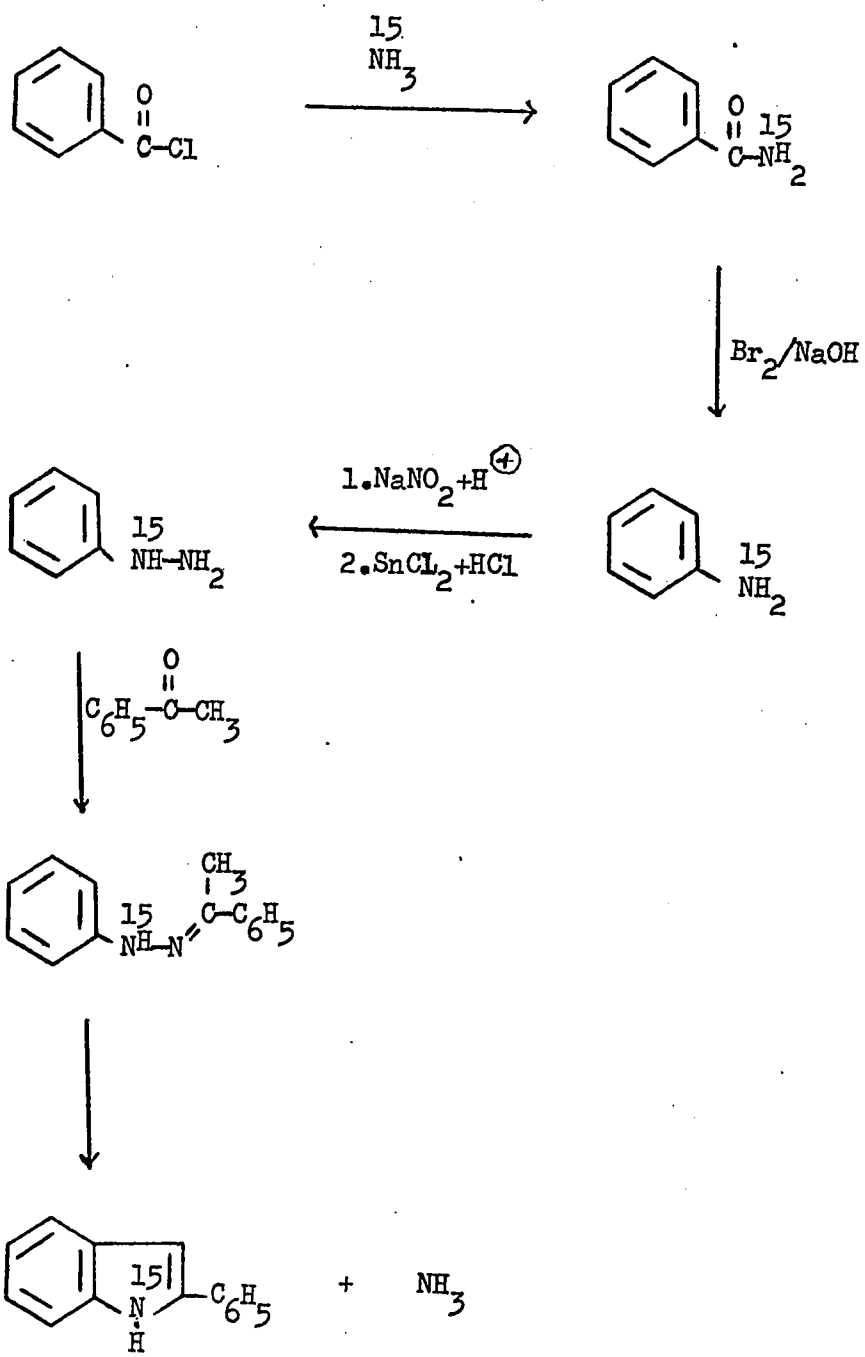


Later investigations (40, 59) with N^{15}-labelled arylhydrazones also corroborated the above postulation. These observations can be summarised in the following manner.

(i) (ref. 59)



(ii) (ref. 40)


15
NH3
O
C–Cl
O
15
C–NH2
Br2/NaOH
1.NaNO2+H⊕
2.SnCl2+HCl
15
NH–NH2
15
NH2
O
C6H5–C–CH3
CH3
15
NH–N=C–C6H5
15
N
H
C6H5
+
NH3

Mechanism of N-2 elimination.

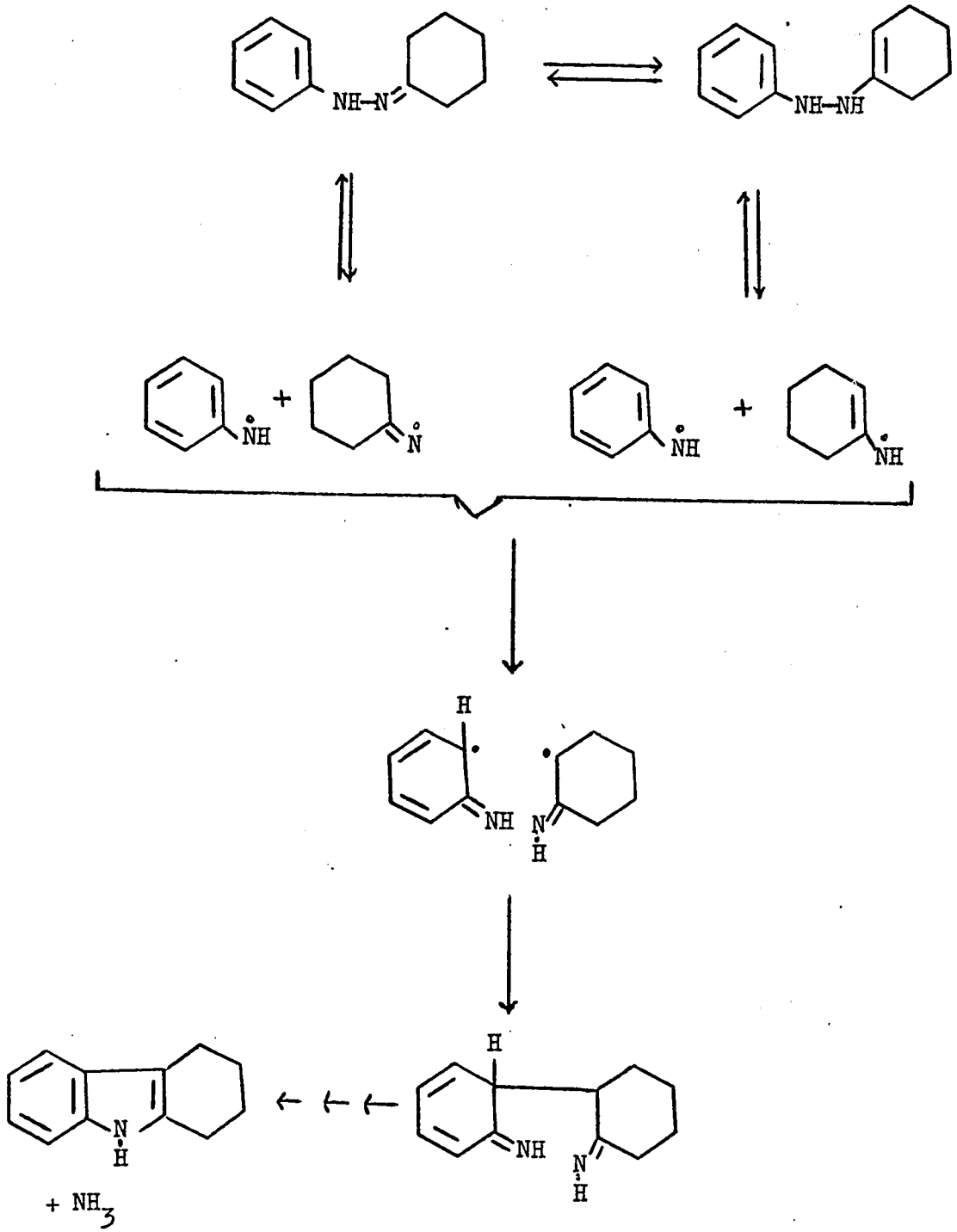
Two rival mechanisms were suggested in 1924 (27b) to account for the elimination of ammonia during the Fischer indole synthesis. One (Path i, Scheme I) was a nucleophilic attack of the amine on the ketimine while the other (Path ii, Scheme I) involved first an hydrolysis of the ketimine to the corresponding ketone and then the nucleophilic attack of the amine on the carbonyl moiety.

Pathway ii is supported by the fact that ketimines are readily hydrolyzed under aqueous acidic conditions to the corresponding carbonyl functions. However, Allen and Wilson (40) preferred path i, because many cases (60, 61, 62) are known where the ketimines are quite stable in acidic media.

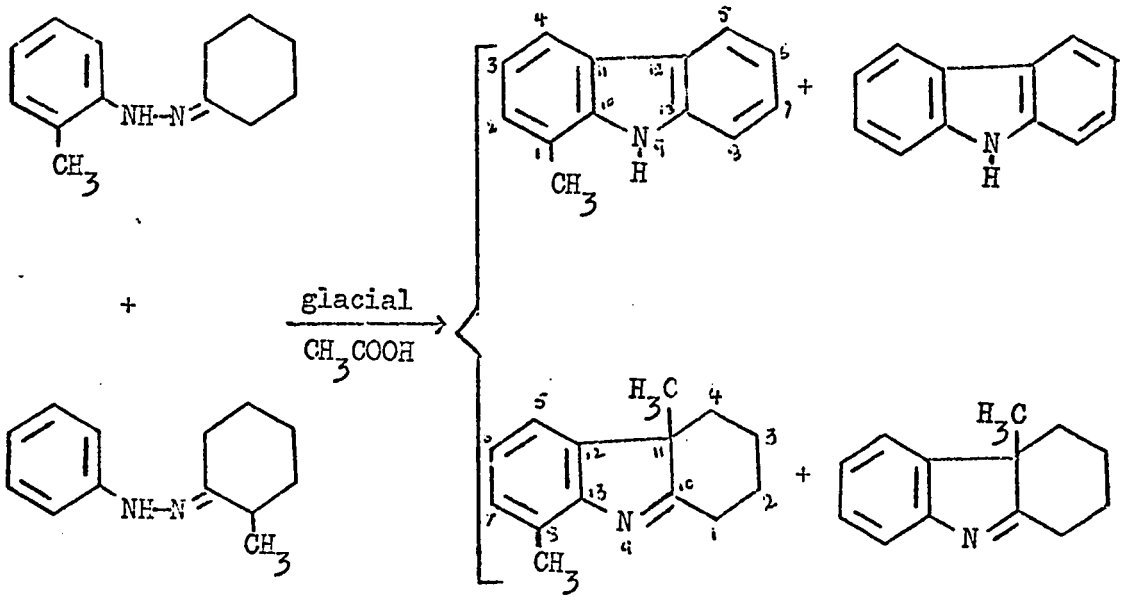
From the foregoing evidence, it appears difficult to predict the exact mechanism of ammonia elimination. Moreover, it is quite possible that both the mechanisms (i and ii, Scheme I) may be operating, depending upon the conditions employed for the indolization.

(v) Pausacker Mechanism

According to this mechanism stage b of the Robinson mechanism is considered to be free radical in nature as shown below. It comprises the homolytic dissociation of the N-N bond, either before or after the enehydrazine formation, leading to the liberation of free radicals. These free radicals then recombine to form the dienone-imine intermediate. The latter indolizes subsequently in accordance with the Robinson mechanism.


NH–N
NH–NH
NH
N
NH
NH
H
NH
N
H
H
NH
N
H
N
H
+ NH3

The evidence cited in favour of such a postulation is threefold. First is the formation of four products, carbazole, 1-methylcarbazole (both obtained after dehydrogenation of the respective tetrahydrocarbazoles), 11-methyl-2,3,4,11-tetrahydro-1H-carbazole and 8,11-dimethyl-2,3,4,11-tetrahydro-1H-carbazole from the indolization of a mixture of cyclohexanone o-tolylhydrazone and 2-methylcyclohexanone phenylhydrazone (63, 64) as shown below.



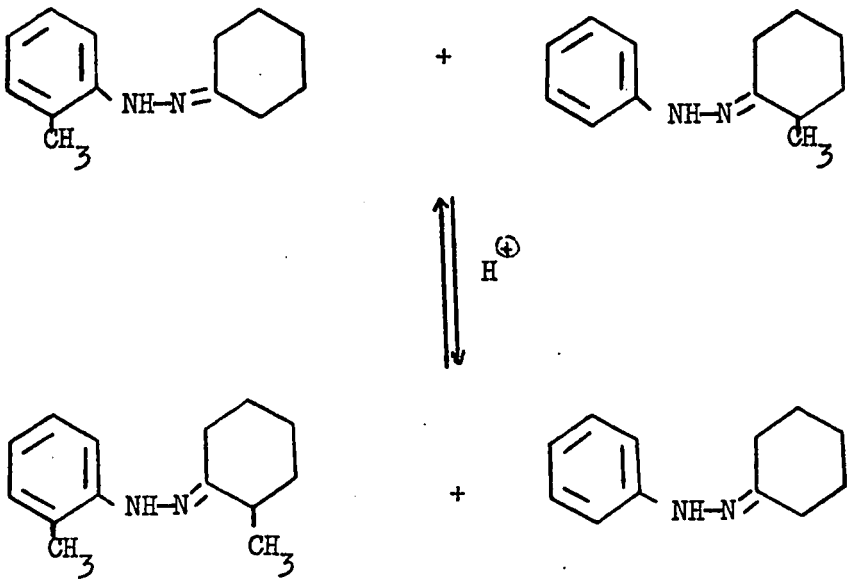
Secondly, the formation of anilines (as derivatives) and cyclohexanones (by odour), detected during the above indolization (such decompositions were observed only when sulfanilic acid or cuprous

ion was used as the catalyst), was also believed to lend a support to this hypothesis (63, 64).

Thirdly, because stage b of the Robinson mechanism is analogous to the o-benzidine rearrangement, there should occur p-rearrangement also. The fact that p-rearrangement has not been observed during indolizations so far, is also considered evidence in support of Pausacker's modified mechanism.

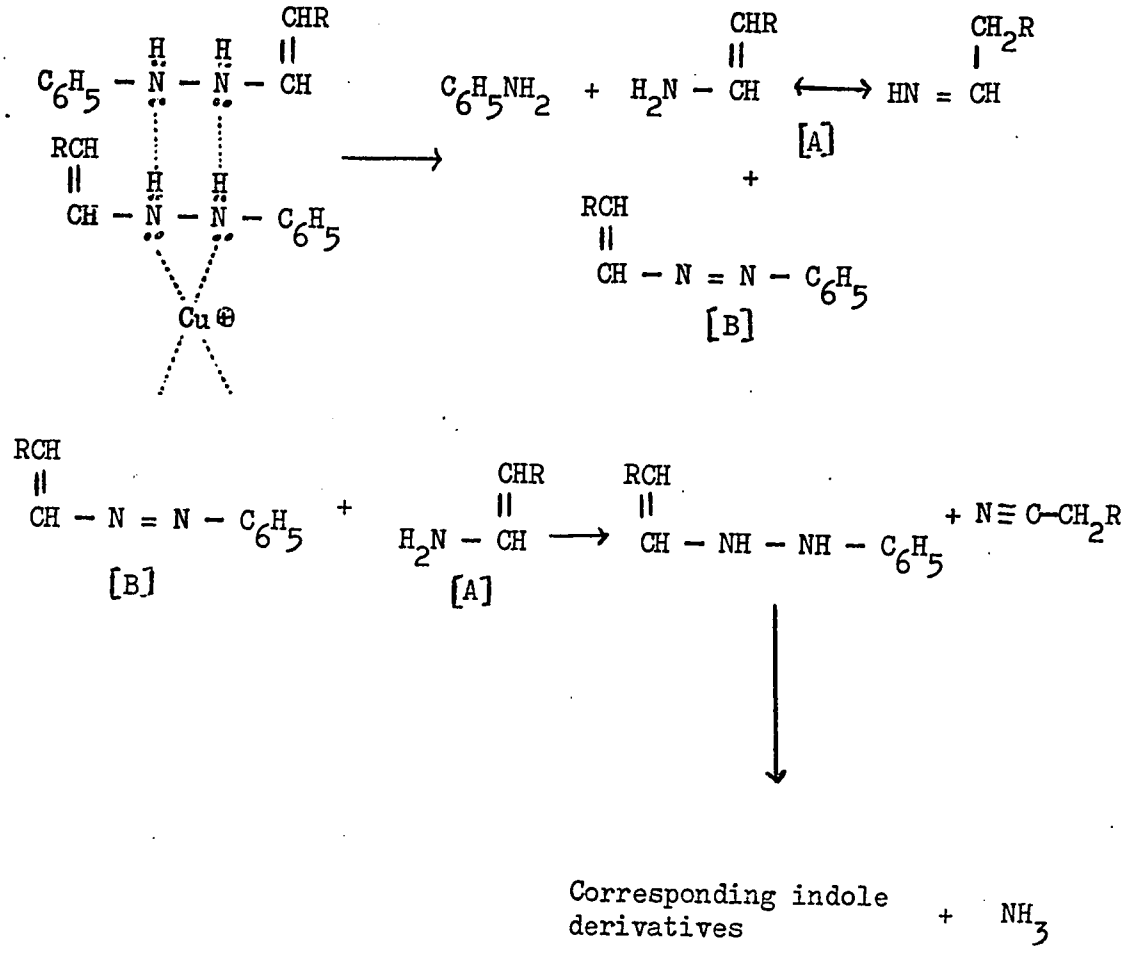
However, the points mentioned above are not sufficient to require a modification of the stage b of the Robinson mechanism since these experimental results can also be rationalized by the following alternate explanations (50).

The above indolizations of the mixture of arylhydrazones can be interpreted to have proceeded first, by hydrolysis of the aryl hydrazones to the corresponding arylhydrazines and cyclohexanones and their recombination to form the four arylhydrazones.



The latter can subsequently indolize to the four observed products (65). Alternatively (66), transhydrazonation, analogous to the transesterification, can also rationalize these experimental observations.

The formation of anilines during the indolization of the arylhydrazones (63, 64, 67) is due to an alternate decomposition of the latter and is considered to be a side reaction (68, 69). It can be explained by the fact that complexing (68) of the acid-catalysts (like sulfanilic acid, cuprous ion) with the enehydrazine tautomer of the phenylhydrazone causes weakening of the N-N bond as illustrated below.



It is believed that the diazo compound B can be reduced by the aldimine (or ketimine) A back to the original enehydrazine (68) which then indolizes to the corresponding indole derivatives as shown above.

The specificity of cuprous ion or sulfanilic acid to such decompositions is attributed to stereochemical considerations (50).

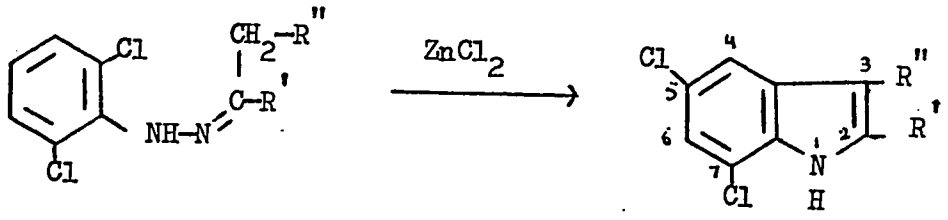
The lack of para-rearrangement is due to a greater steric hinderance to it (27b, 54) as compared to that for the ortho-rearrangement. Also the formation of tarry by-products in some Fischer indolizations may have been due to the products of the para-rearrangement (50).

In view of the above argument, Pausacker's modification does not find full support and is therefore, unlikely.

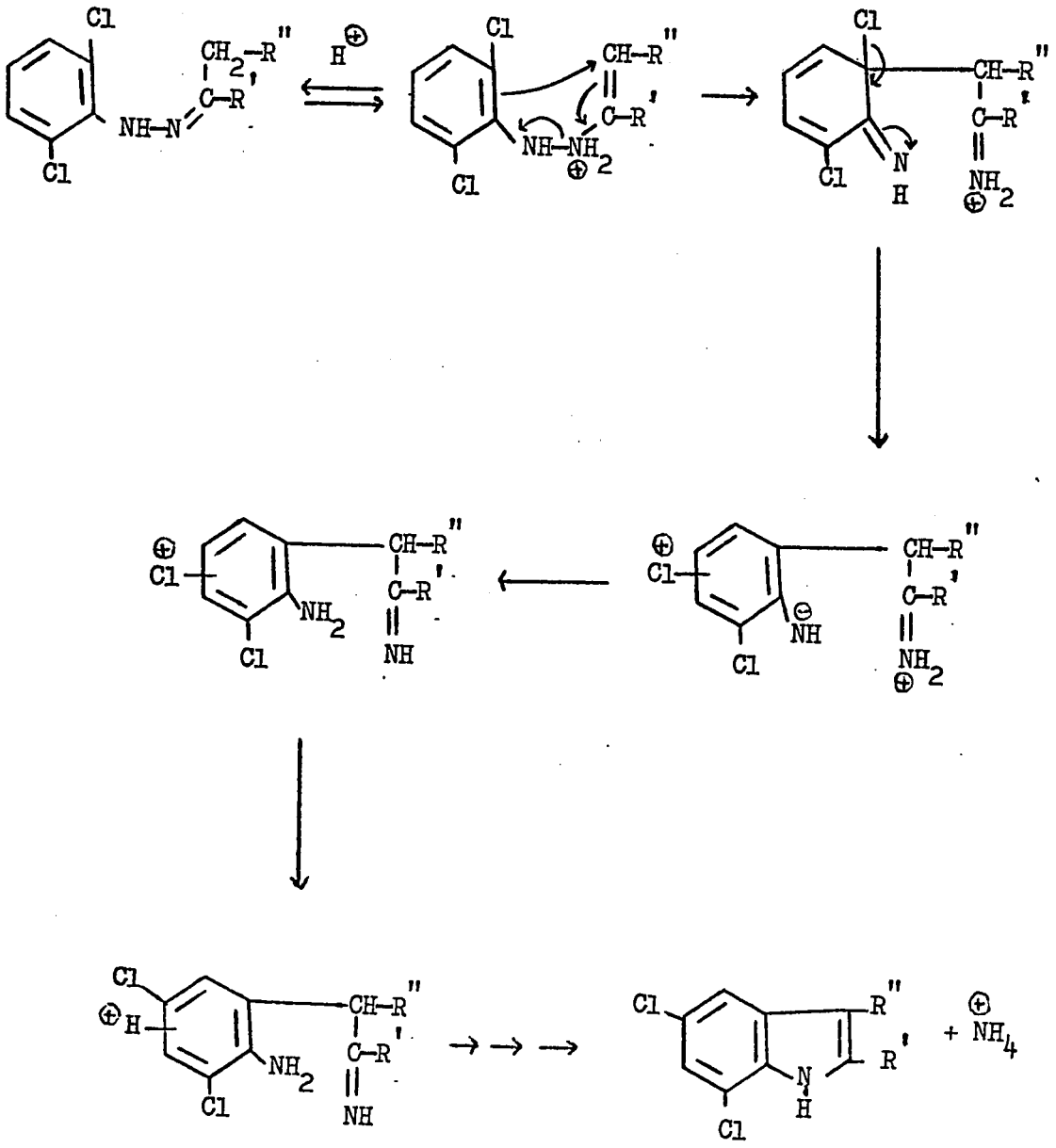
2. Group migrations and rearrangements observed during the Fischer indole synthesis.

(i) Halogen migration

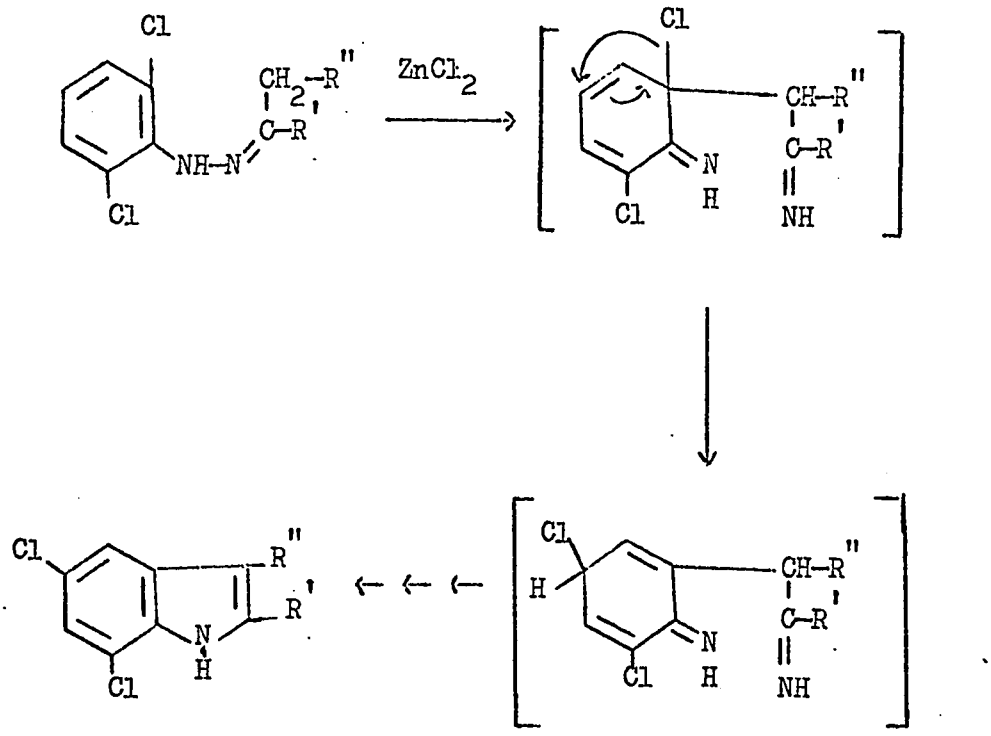
In an attempt to obtain further evidence for the Robinson mechanism, indolization of the 2,6-dihalophenylhydrazones was examined (41). This reaction furnished 5,7-dihaloindole derivatives as illustrated below.



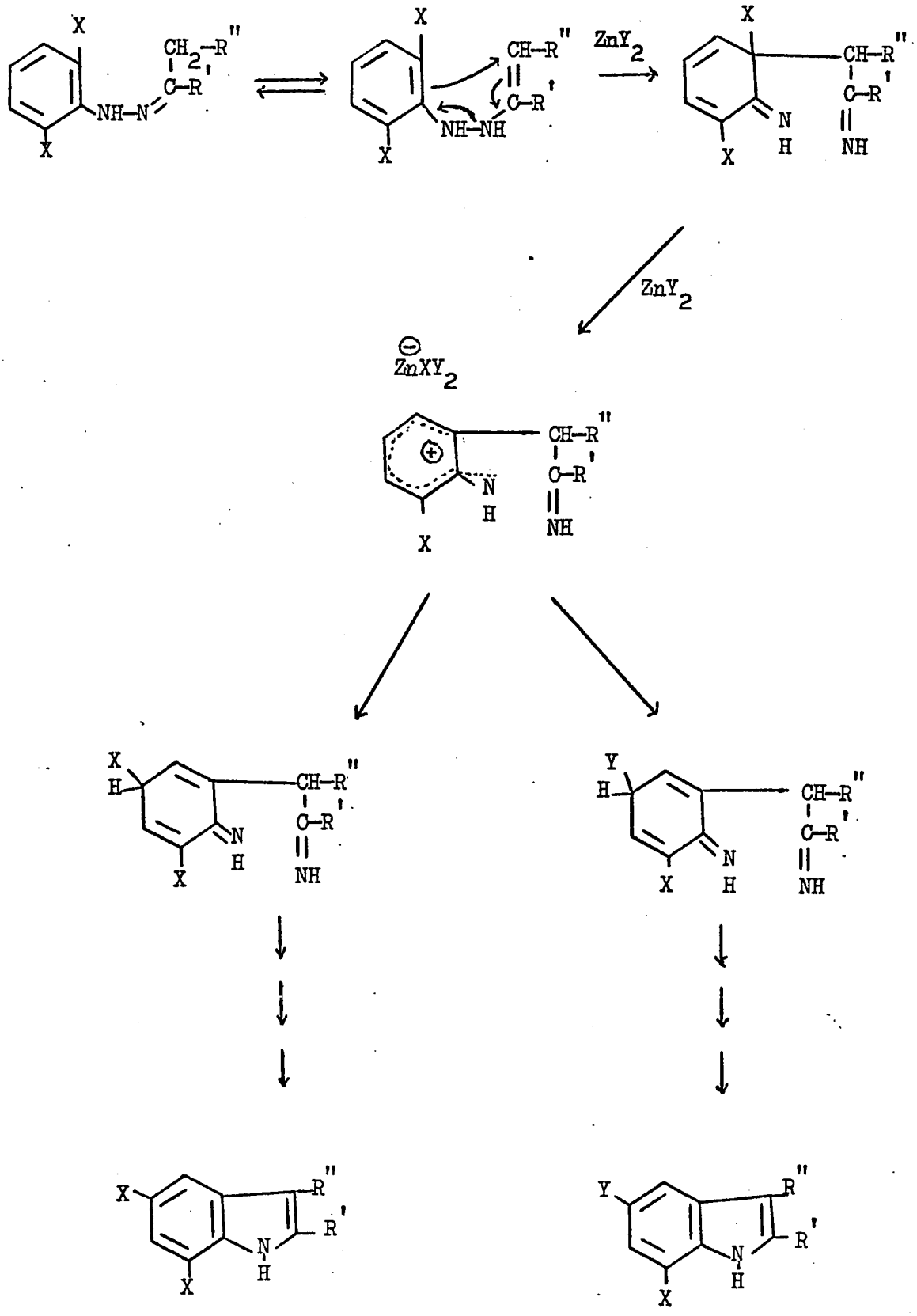
The migration of the chlorine atom (70) was found to take place prior to the formation of the indole ring (41) and was at first considered to occur via a "positive chlorine-π electron complex" (70). Thus the migration of halogen is intramolecular rather than intermolecular (70). The following mechanism was suggested (70) to account for this observation.



However, Southwick (70, footnote) pointed out that the chlorine atom could actually migrate as a negatively charged species as shown in the following scheme.



Later investigations (71) showed that treatment of acetophenone 2,6-dibromophenylhydrazone with anhydrous zinc chloride in refluxing nitrobenzene formed 7-bromo-5-chloro-2-phenylindole and 5,7-dibromo-2-phenylindole. Similarly, indolization of acetophenone 2,6-dichlorophenylhydrazone in the presence of zinc bromide gave a mixture of 5,7-dichloro-2-phenylindole and 5-bromo-7-chloro-2-phenylindole. Thus, there is a migration as well as exchange of the halogen under these indolization conditions. The following interpretation (71) is believed to rationalize the above observations.



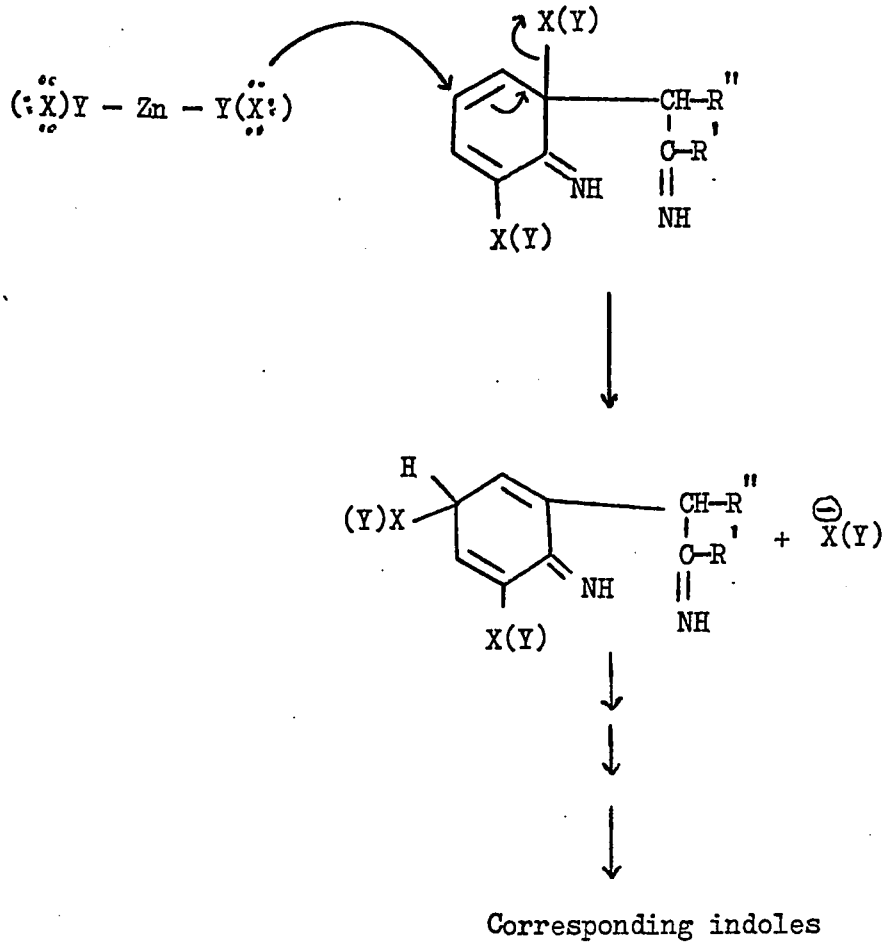
Although the above mechanism accounts fully for all the experimental observations, it does not exclude the following possible reaction paths (72).

(a) SN_1 Mechanism

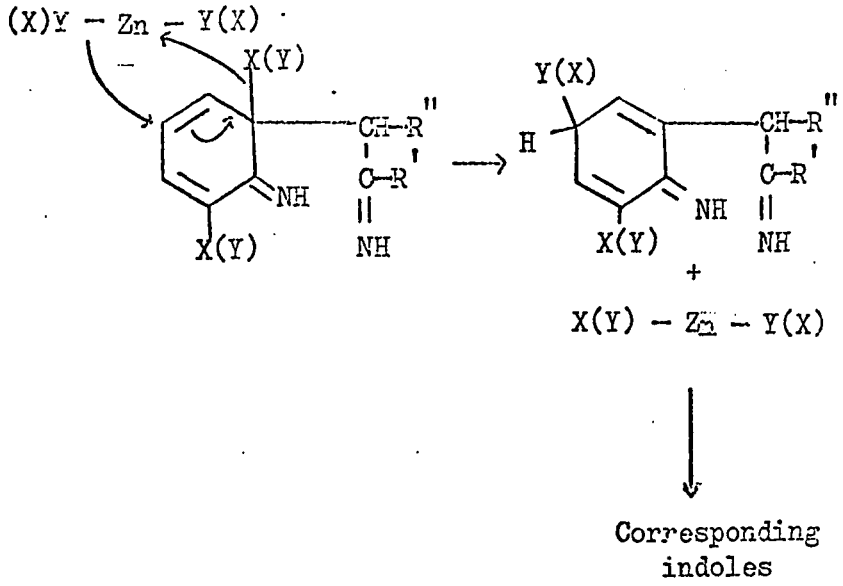
This differs from the above mechanism only in the degree of separation of the migrating halogen from the organic moiety.

(b) SN_2' Mechanism

This is illustrated below.

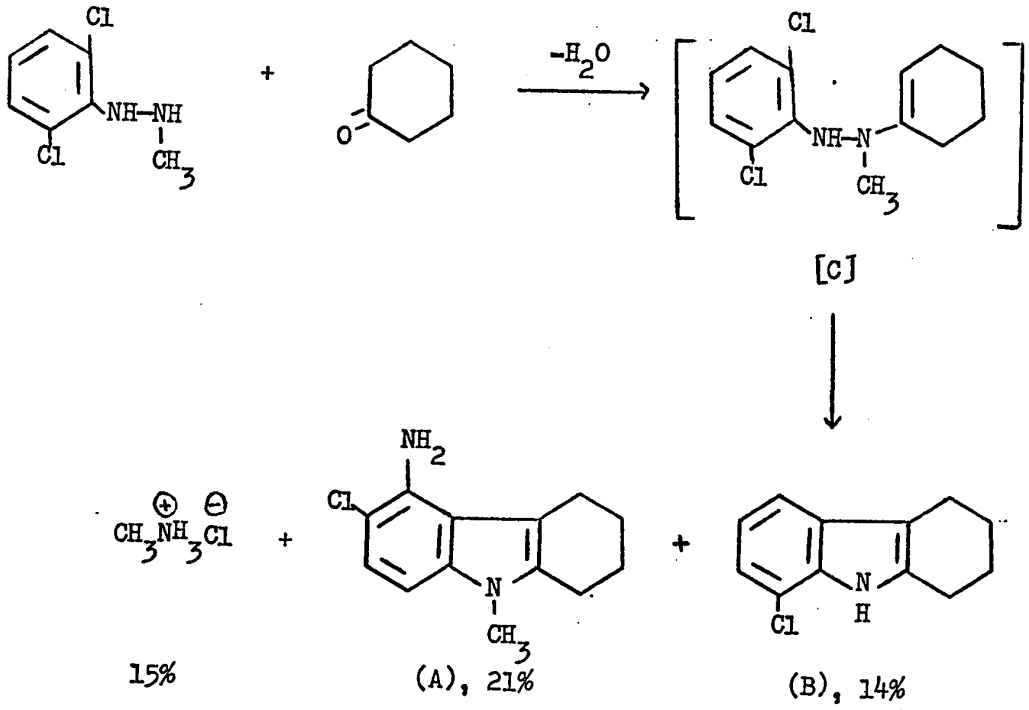


(c) Formation of Six Membered Transition State.

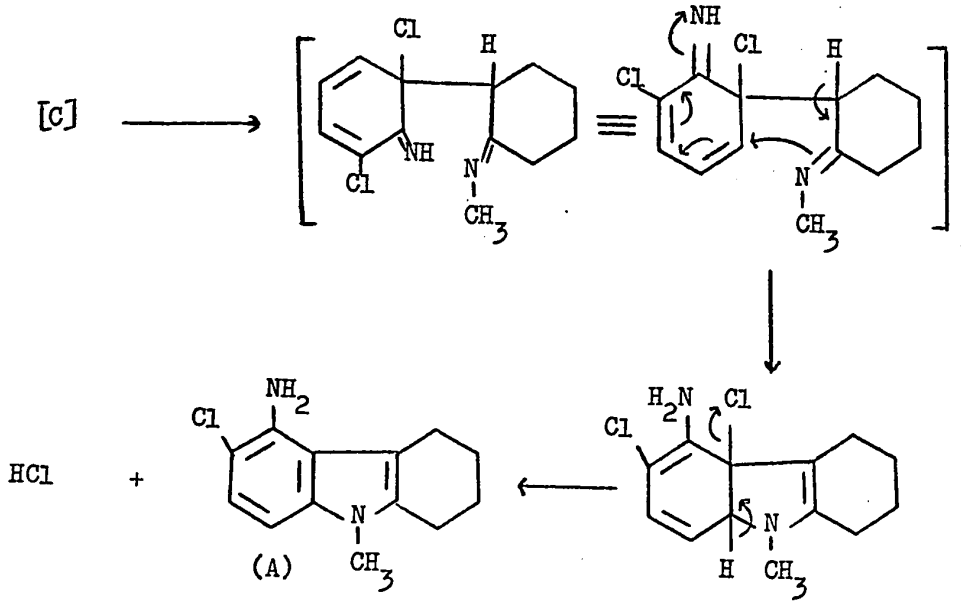


The exact mechanism of halogen migration as observed (71) above will become clear only when the species displacing the halogen is known.

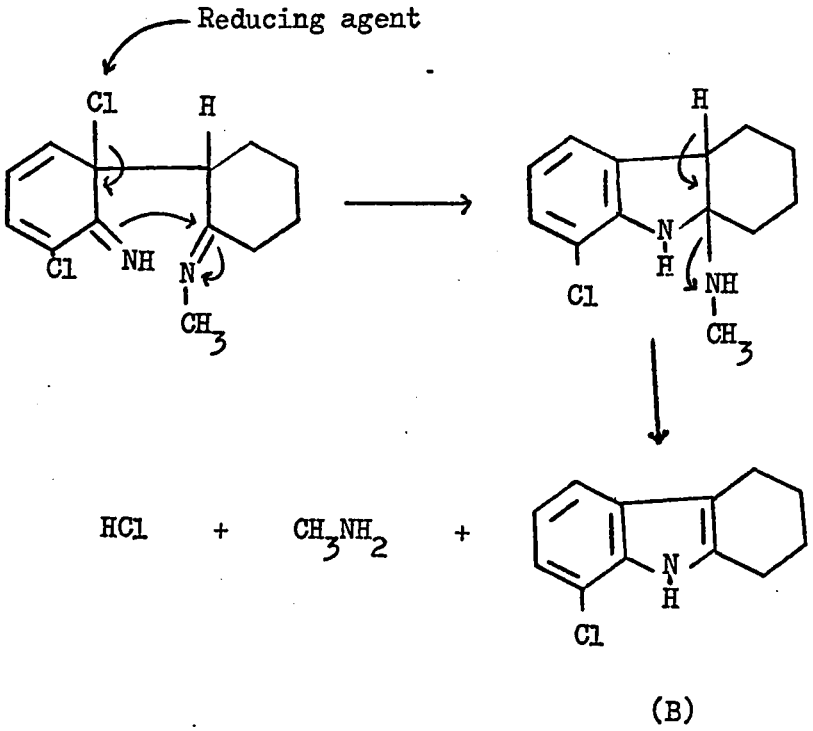
Recent papers on the reaction of N'-methyl-2,6-dichlorophenylhydrazine with cyclohexanone (25) report the elimination of one chlorine atom in the formation of indole products. The reaction was found to proceed under mild conditions without the aid of the catalyst, as shown below.



The formation of the products (A) and (B) could be rationalized by accepting the intermediacy of the dienone-imine structure, illustrated as below.



The formation of (B) can be rationalized (25) by the postulation that the allylic halogen atom in the dienone-imine intermediate can be reductively removed by any readily oxidizable substance present in the reaction mixture. This is illustrated below.



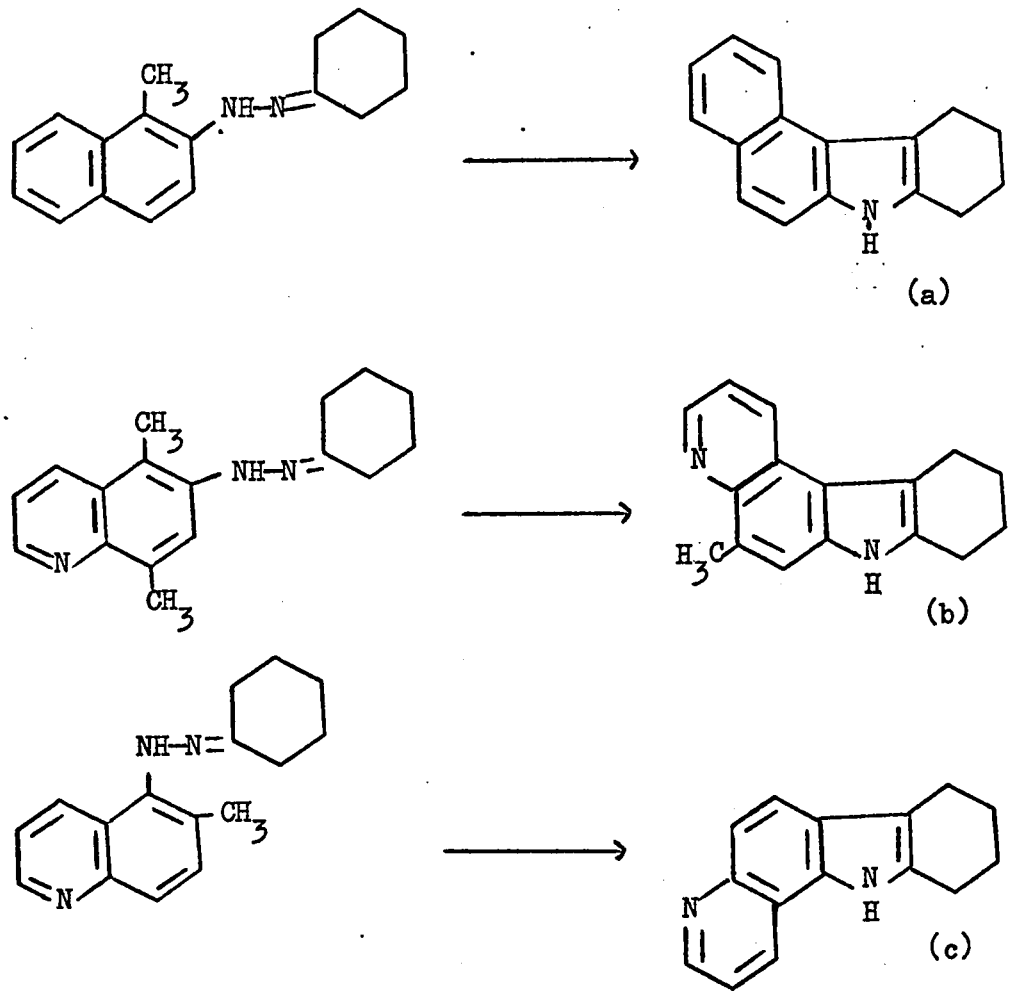
(B)

(ii) Methyl group migration.

A study of the indolization of 2,6-dialkylphenylhydrazones has been undertaken in order to gain further evidence for the Robinson mechanism. It was found that ethyl pyruvate 2,6-dimethylphenylhydrazone formed 2-carbethoxy-4,7-dimethylindole (72). Thus a methyl group had migrated to the 4-position of the indole nucleus.

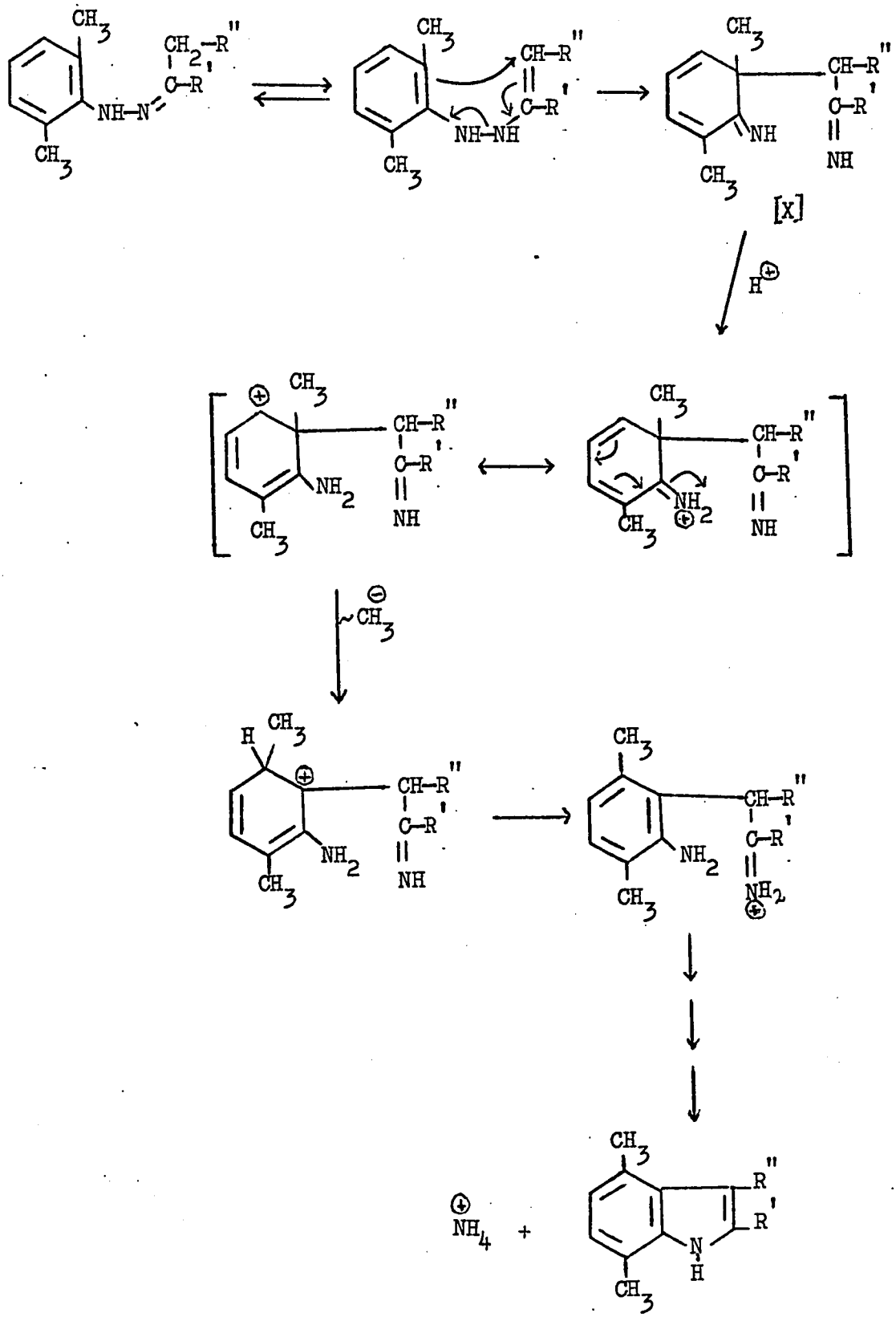
However, in some experiments, elimination (73) of the methyl group was observed such as in the indolization of cyclohexanone 1-methyl-2-naphthylhydrazone, cyclohexanone 5,8-dimethyl-6-quinolylhydrazone and cyclohexanone 6-methyl-5-

quinolylhydrazone. These reactions gave respectively the compounds (a), (b) and (c) shown below.

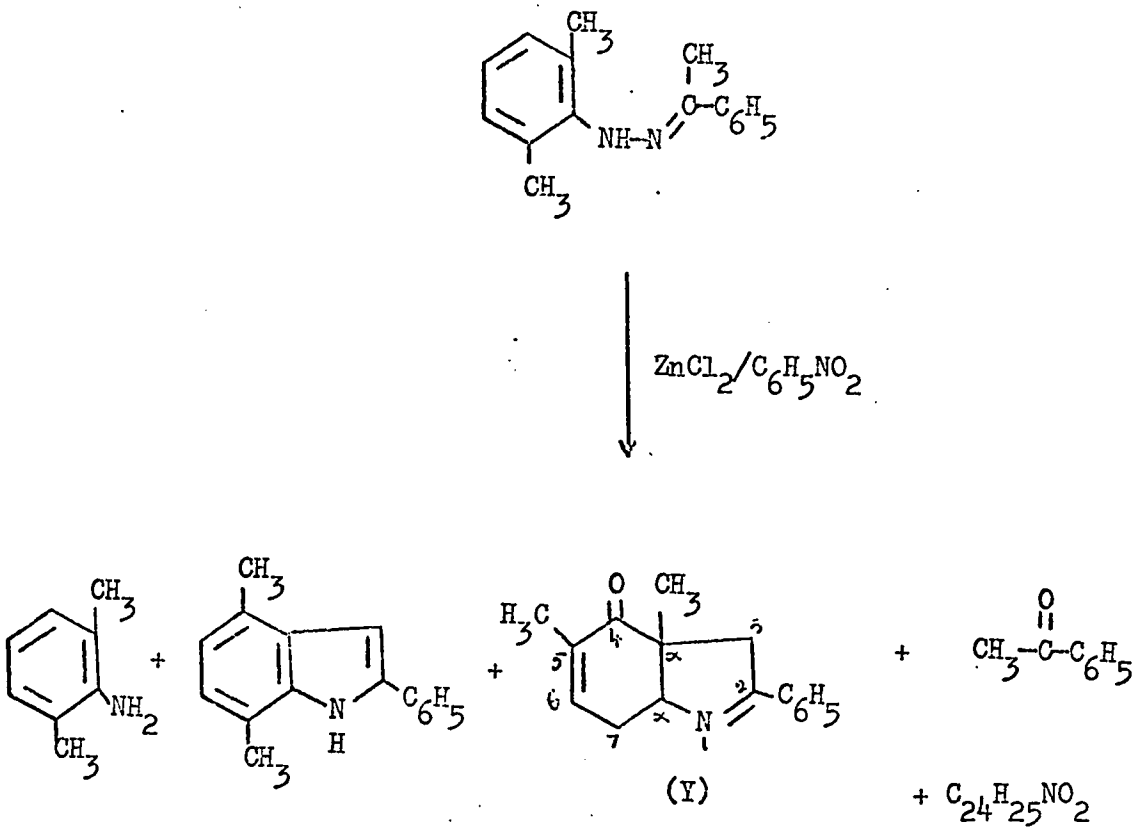


In these three cases, the migration of the methyl group is prohibitive due to the absence of adjacent unsubstituted positions (50).

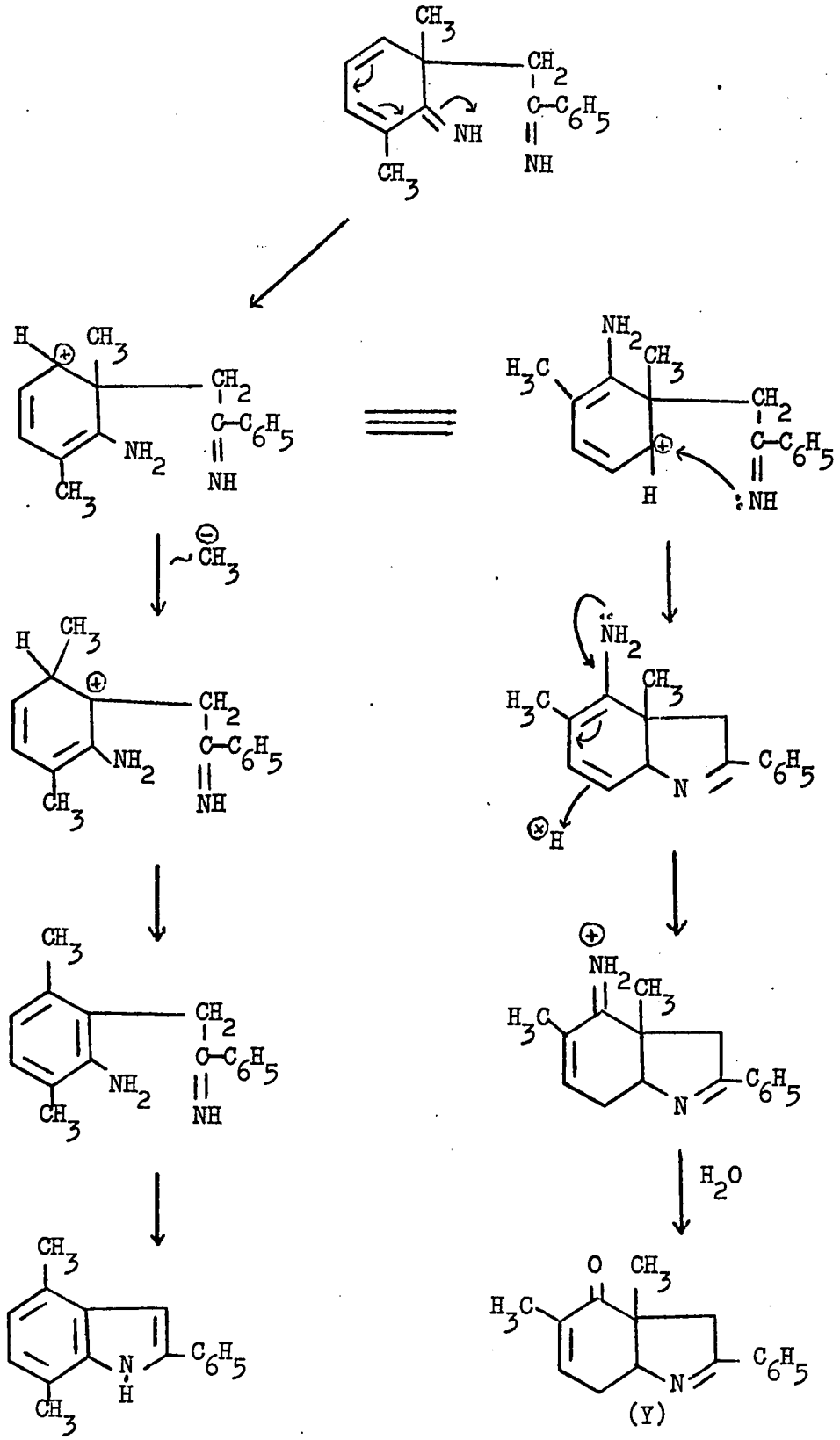
To account for the methyl group migration, Carlin et al (72) proposed the following reaction path which involves a dienone-imine intermediate.



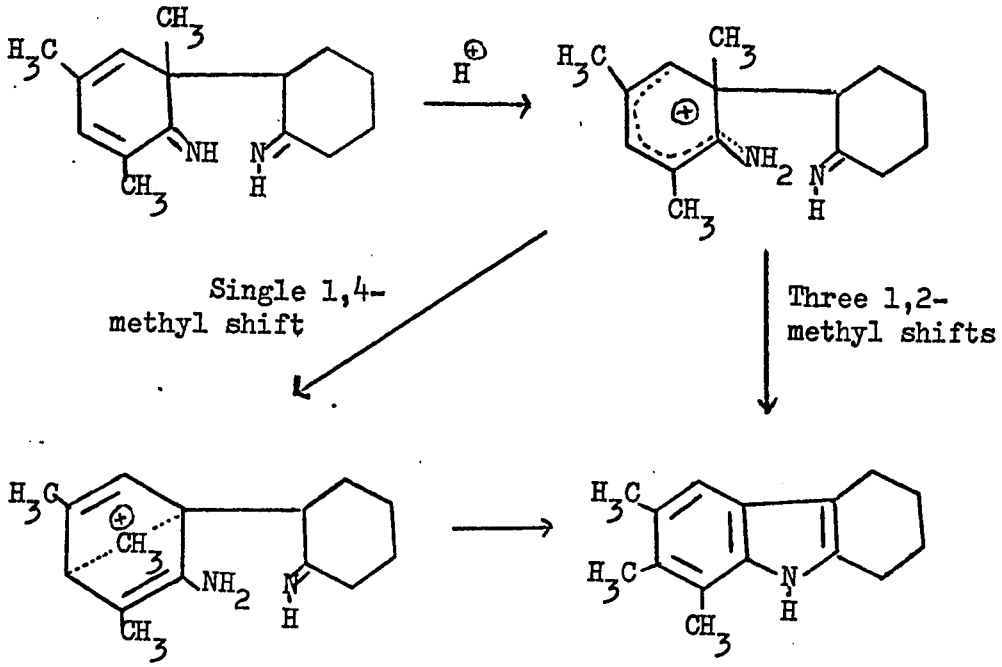
Attempts (72) made to trap the dienone-imine intermediate [X] as a Diels-Alder reaction product were unsuccessful. Subsequent publications (74) reported the isolation of a non-aromatic, high energy intermediate (Y) during the indolization of acetophenone 2,6-dimethylphenylhydrazone. This is illustrated below.



The formation of (Y), i.e., 2-phenyl-3α,5-dimethyl-3α,4,7,7 - tetrahydro[3H] pseudoindolone-4 (formed in 33% yield) as well as the other isolated indole product could also be explained on the basis of a dienone-imine intermediate as illustrated below.

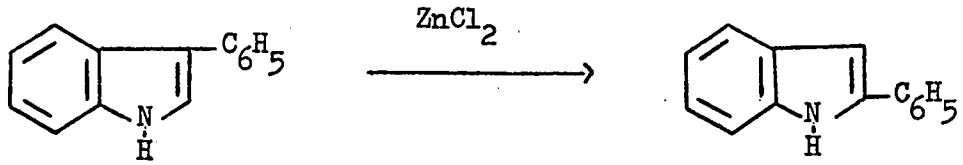

CH3
CH2
C–C6H5
NH
NH
CH3
H
CH3
NH2
CH3
H3C
CH2
C–C6H5
NH
NH
H
:NH
~CH3
NH2
CH3
H3C
C6H5
N
H
NH2
CH3
H3C
C6H5
N
H2O
O
CH3
H3C
C6H5
N
(Y)

In another example illustrating methyl migration, it was found that cyclohexanone mesitylhydrazone (75) provided 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole rather than 1,2,3,4-tetrahydro-6,8,12-trimethylisocarbazole as had been previously claimed (76). The formation of 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole can be rationalized either by three 1,2-methyl shifts or a single 1,4-methyl shift (75)(see below).



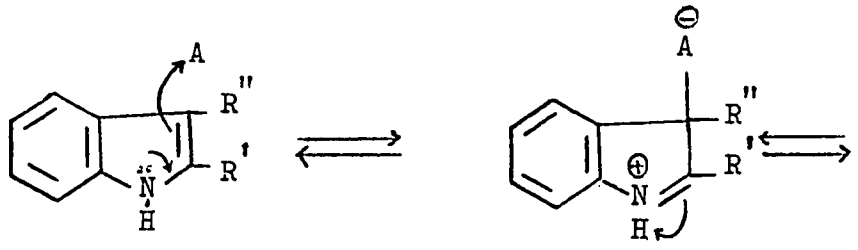
(iii) Twofold Wagner-Meerwein type rearrangement of 2,3-disubstituted indoles.

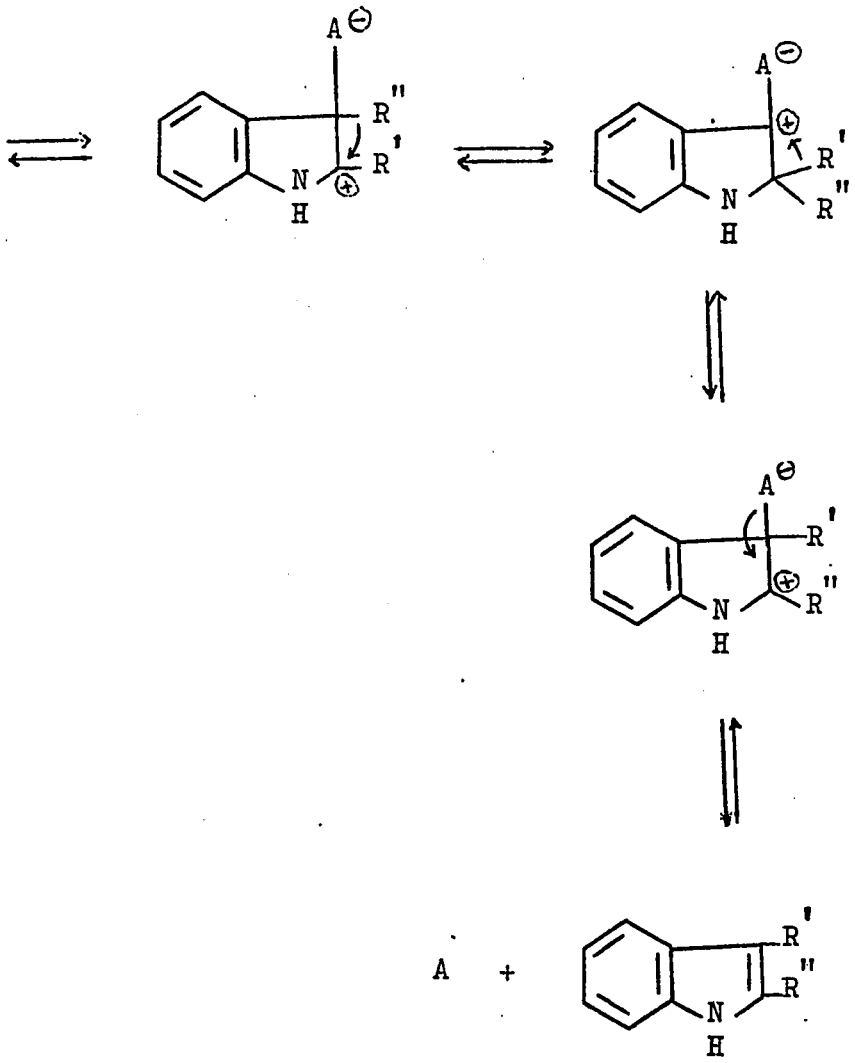
Interesting rearrangements have been reported for some indole derivatives. For example, 3-phenylindole is converted to 2-phenylindole (77) when heated with zinc chloride.



Similar rearrangements of the substituents from C-3 to the C-2 position have been observed when 3-(2-pyridylmethyl) indole, 3-benzylindole and also skatole are treated with aluminum chloride (78).

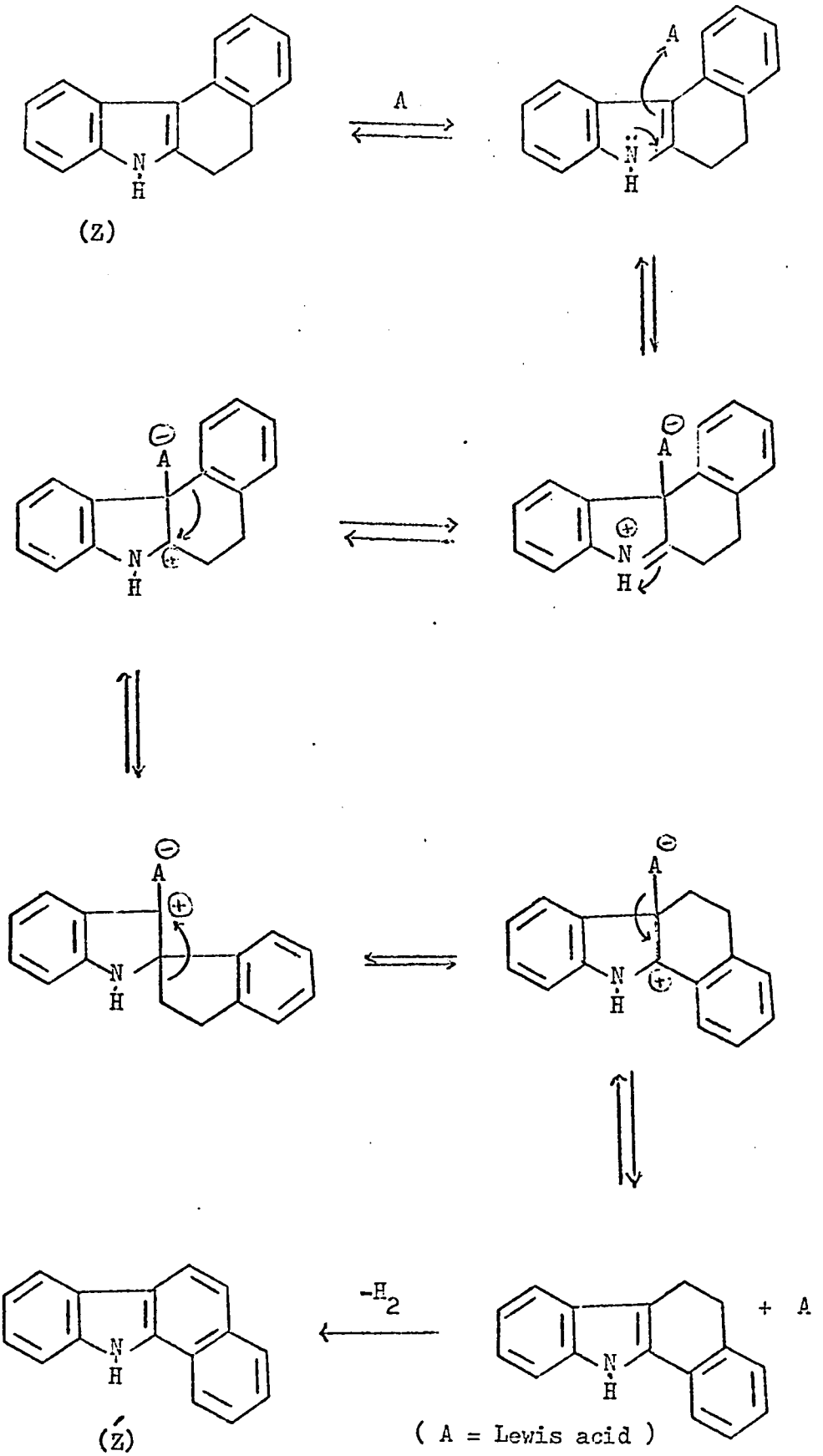
Among the 2,3-disubstituted indole derivatives, 2-methyl-3-phenylindole is converted (79) to 2-phenyl-3-methylindole when it is heated with aluminum chloride at 220-240° for 20 minutes. These rearrangements are analogous (79) to the rearrangments of indolenines (3c, 80) and Plancher's rearrangement (3d, 81) of indolenium compounds, and can be rationalized by the twofold Wagner-Meerwein type rearrangement initiated by the electrophilic attack by the Lewis acid on the 3-position of the indoles (79). An example of this is shown below.





(A = Lewis acid)

Similar transformations of 5,6-dihydro-7-benzo[C]carbazole (or 3,4-benzo-1,2-dihydrocarbazole) (Z) to the 11-benzo[a]carbazole (Ź) (79) under the same reaction conditions would proceed through the formation of a spiro-type intermediate as proposed by Woodward (82) in the dienone-phenol rearrangement (83-86). This can be illustrated as follows.


A
A
N
H
(Z)
A
N
H
A
N
H
A
N
H
A
N
H
A
N
H
-H2
+ A
N
H
(Z)
(A = Lewis acid)

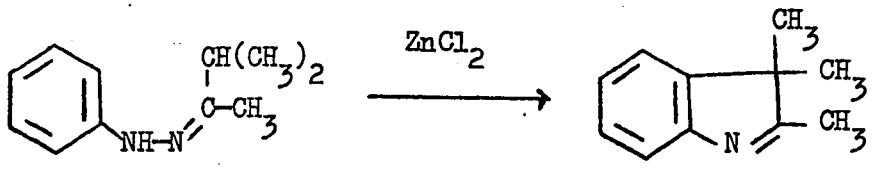
3. Exceptions and limitations to the Fischer indole synthesis.

There are a number of exceptions and limitations which have been observed in attempts to obtain indoles via the Fischer reaction. Typical examples are noted below.

(i) The indolization of acetaldehyde phenylhydrazone (22, 24) has not been achieved as yet. It may be that due to the absence of the terminal alkyl group in the resulting enehydrazine, stage b of the Robinson mechanism is not favoured inductively (52). Or there may be difficulty in the hydrazone-enehydrazine tautomerization e.g., stage a, because in the latter case, enehydrazine will not be stabilized by hyperconjugation.

(ii) Arylhydrazones of 2-keto esters (3a) and 3-keto or 3-aldehydo acids (87-90) undergo cyclization and cyclodehydrations to pyrazolones and pyridazinones respectively rather than form indoles. Thus, 1,3-diketone monoarylhydrazones (91) cyclize to pyrazoles while the indolization of 2-naphthylhydrazones (92, 93) afford the angular isomers exclusively rather than linear isomers. The latter observations show that the formation of the new C-C bond during indolization is an intramolecular electrophilic substitution because this takes place preferentially at the 1- rather than the 2-position of the naphthalene nucleus.

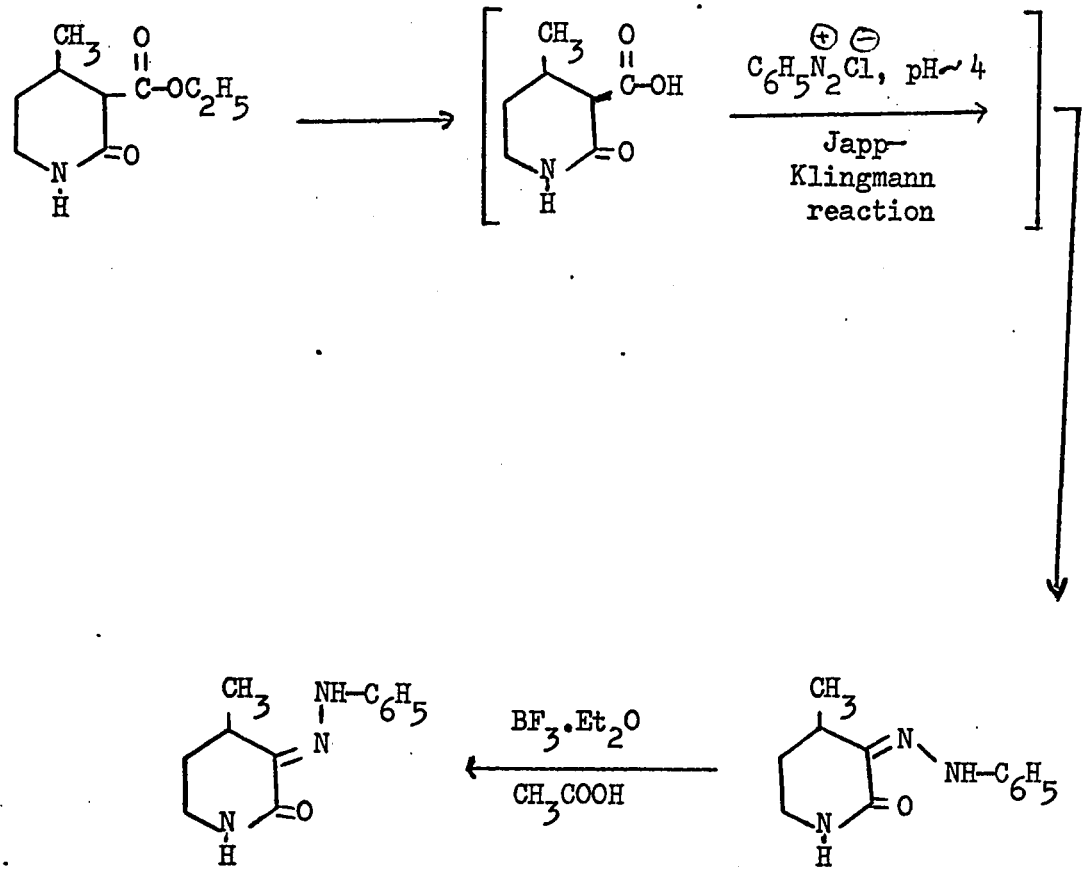
(iii) Phenylhydrazones of unsymmetrical ketones, like methyl isopropyl ketones, form indolenines (e.g. 3H-indoles) on indolization (94) as shown below.



(iv) Indolization of 1,2,3,4-tetrahydro-4-oxoquinoline phenylhydrazone (95) furnishes not the expected indole but the fully aromatized structure. Similar indolizations proceeding with concomitant dehydrogenations have often been reported (96-99).

(v) There are many limitations to the use of dehydrogenating agents employed for the Borsche synthesis (100). Often, the yields are poor or black intractable tars are produced. Elimination of the groups is also recorded during such dehydrogenating conditions. Thus, from 6- and 8-chloro-1,2,3,4-tetrahydrocarbazole using lead oxide (100) and from 7-chloro- and 8-carbethoxy-1,2,3,4-tetrahydrocarbazole using palladised charcoal (101), the only isolable product is carbazole.

(vi) Many other examples are recorded in the literature (21, 102) which did not provide the normal indolization products. For instance, 4-methylpiperidino-2,3-dione-3-phenylhydrazone merely underwent cis-trans isomerization (102) rather than indolization.



anti-configuration

syn-configuration

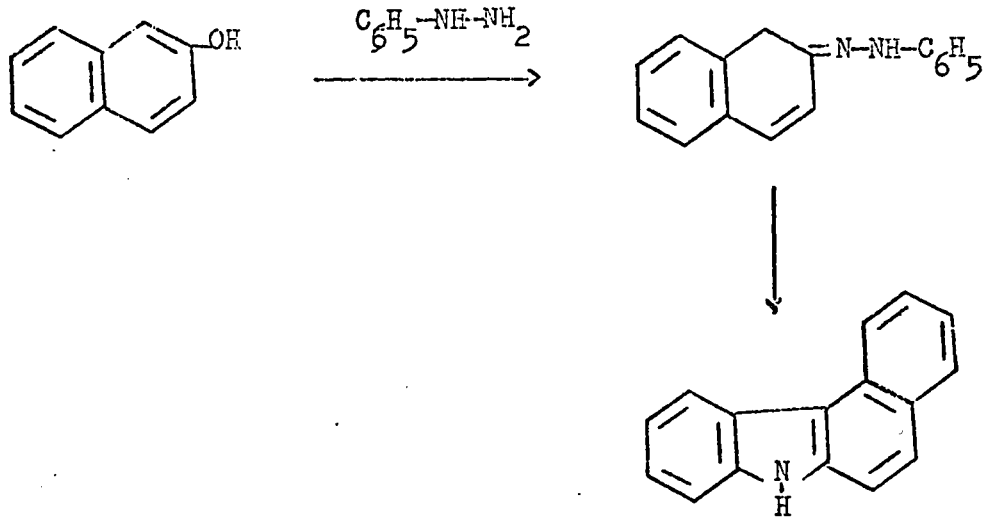
Similarly, ethyl 4-cyano-2-oxobutyrate 2-phenylhydrazone isomerised to a more stable form instead of forming an indole (21), and the latter is probably responsible for the observation of deep red colours during many indolizations. This postulation is fully substantiated by spectroscopic studies (49) e.g., infrared, visible, u.v. and n.m.r. studies of phenylhydrazones, methylphenylhydrazones and benzene azoalkanes as described before (on p. 13). The relative stabilities of the syn and anti isomers have been examined polarographically (46, 47, 103). In addition to this, 2-hydroxycyclohexanone

arylhydrazones produce (104) 1,2,3,4-tetrahydro-1-oxocarbazole. Thus, in this case, indolization proceeds with simultaneous oxidation.

4. Extensions of the Fischer indole synthesis.

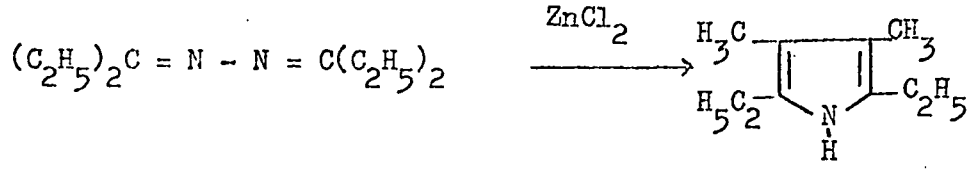
(i) Use of phenols as the carbonyl moieties of arylhydrazones.

Many phenols are known (32c, 105a) which on treatment with arylhydrazines, undergo the normal indolization reaction. For instance, the reaction with β-naphthol, is illustrated below.



(ii) Piloty pyrrole synthesis.

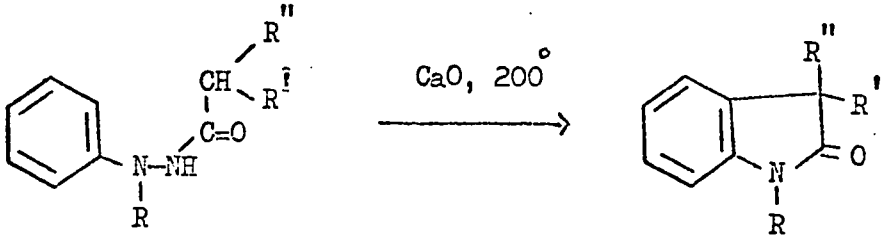
This method involves the conversion of a ketazine or aldazine to the corresponding pyrrole (27a, 106-113).



Robinson and Robinson (27a) proposed an analogous mechanism for this conversion. Although this method is quite general in its utility, there are many exceptions to it. Simpler aliphatic azines have a tendency (27a) to form pyrazolines rather than pyrroles. Thus, acetaldazine and dimethyl ketazine formed pyrazole and pyrazoline rather than pyrrole and dimethylpyrrole respectively.

(iii) The Bruner oxindole synthesis.

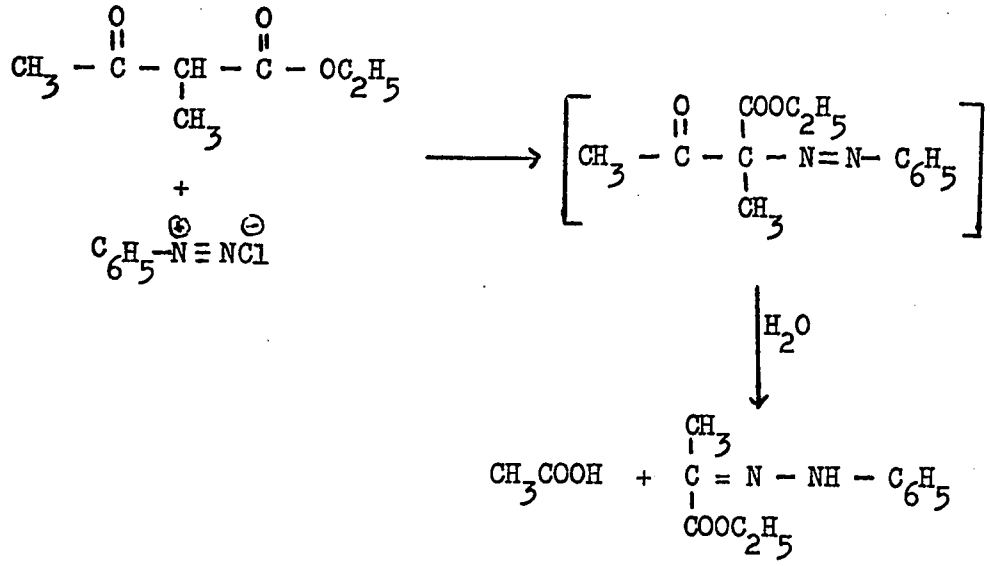
This method comprises the transformation of acylphenylhydrazines to the corresponding oxindoles under the influence of a basic catalyst (3e, 32d).



The mechanism of the reaction (27b) after enolization, is considered to be analogous with that postulated for the Fischer indole synthesis.

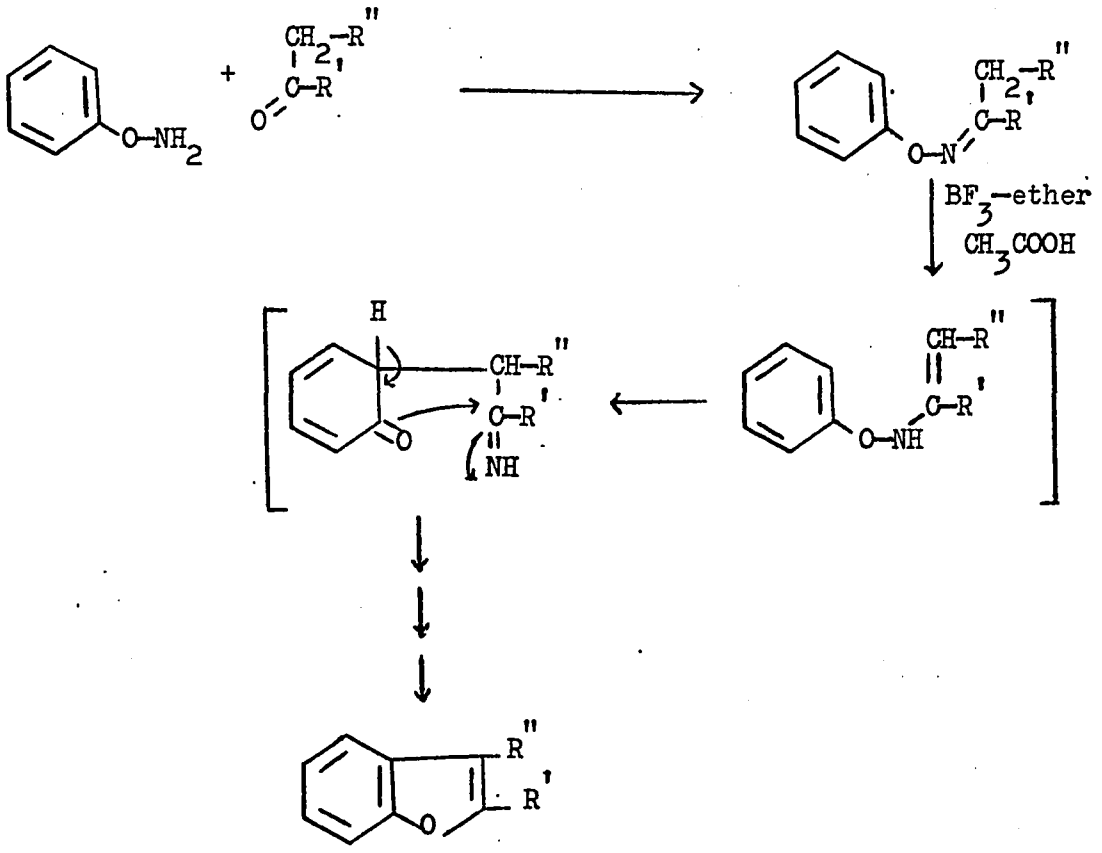
(iv) The Japp-Klingmann Reaction.

This reaction embodies another procedure for the formation of arylhydrazones which is the starting material for the Fischer synthesis. To illustrate, the phenylhydrazone of ethyl pyruvate was obtained by coupling benzene diazonium chloride with ethyl 2-methylacetoacetate (114).

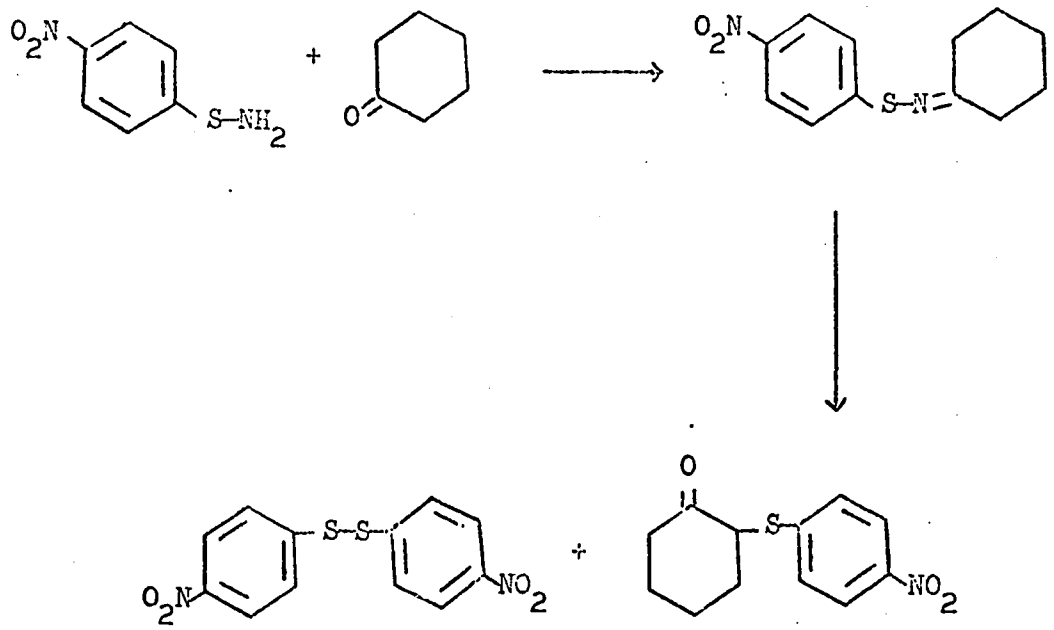


(v) Application of the Fischer indole synthesis to the formation of benzofurans and benzothiophenes.

T. Sheradsky (115) has developed a simple and useful approach to the synthesis of benzofurans which entail yet another extension of the Fischer indole synthesis. According to this method, the O-phenyloximes are cyclized to the corresponding benzofurans under the Fischer indolization conditions. An example is shown below.



Similar cyclizations are reported (116) and are also extended (117) to the attempted formation of benzothiophenes. Thus, (117) N-cyclohexylidene-p-nitrophenylsulfenamide gave 50 - 70% of p-nitrophenyl disulphide and 15-30% of 2-(p-nitrophenylthio)-cyclohexanone.



Although the mechanism of the above reaction (117) is still under investigation., the rearrangment of O-aryloximes to the corresponding benzofurans as depicted before, is visualised to follow a mechanism analogous to that proposed for the Fischer indole synthesis.

From the preceeding discussion, it becomes apparent that the Fischer indole synthesis has captivated the attention of many workers and has a wide applicability in the field of indolization. Mechanistically, it is a many-step reaction and synthetically, it occupies a prominent place among the modern reactions.

RESULTS AND DISCUSSION

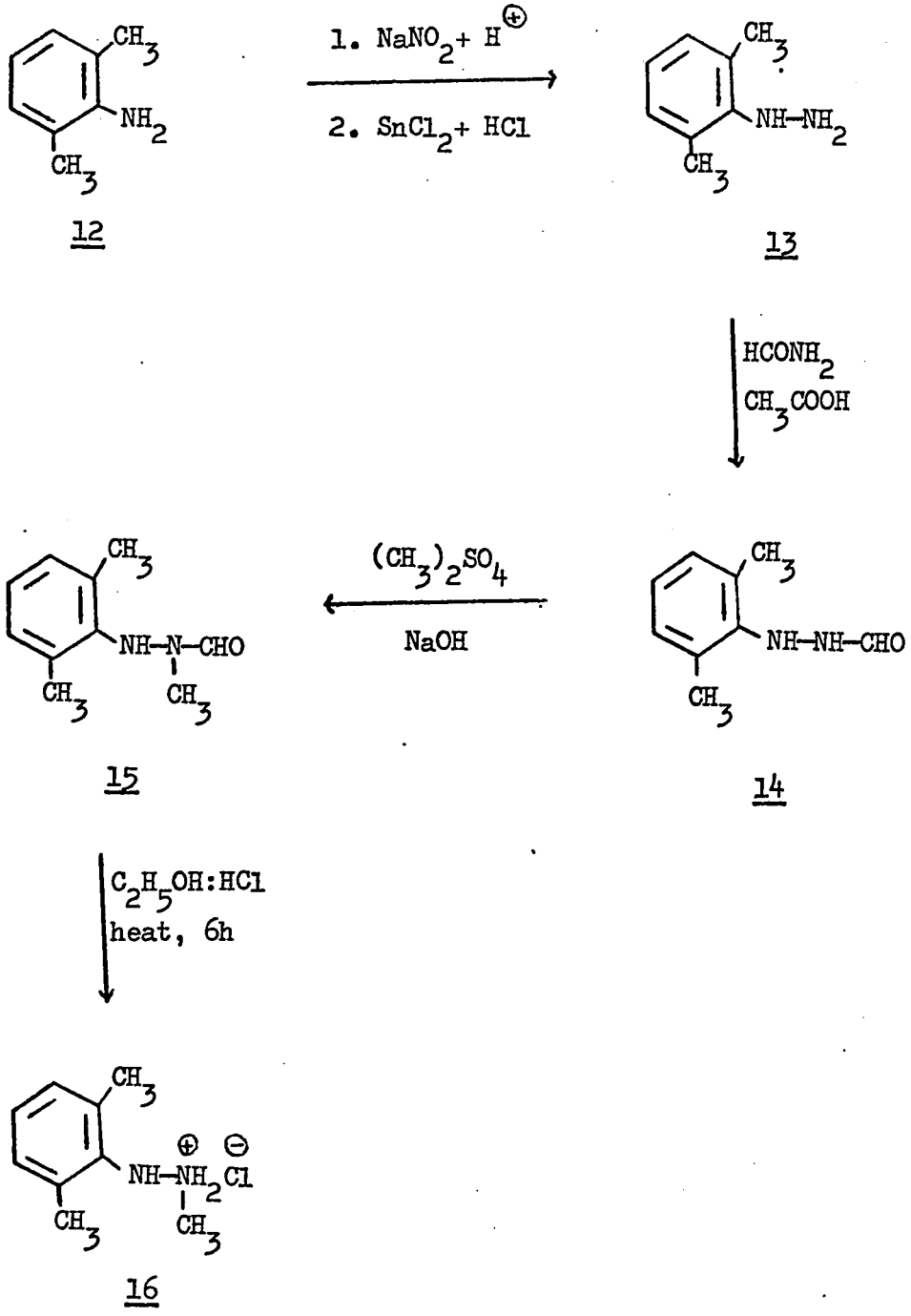
RESULTS AND DISCUSSION

PART I

A. Experiments with N'-methyl-2,6-dimethylphenylhydrazine and cyclohexanone.

For the present studies, it was felt that the most suitable hydrazine would be N'-methyl 2,6-dimethylphenylhydrazine. The presence of a methyl group at the β-nitrogen atom of the hydrazine would assure the formation of the enehydrazine rather than the hydrazone, thus avoiding the first step of the Fischer mechanism — the conversion of the hydrazone to the enehydrazine.

The presence of methyl groups in the 2 and 6 position of the aromatic ring system ensures the absence of enolizeable hydrogens on the dienone-imine structure and thus prevents conversion of the dienone-imine ring system to the fully aromatized structure. This would facilitate the isolation of the dienone-imine or its trapping as a Diels-Alder adduct. The N'-methyl-2,6-dimethylphenylhydrazine was obtained by the following Scheme II. The diazonium salt of 2,6-dimethylaniline was reduced with stannous chloride in hydrochloric acid to the corresponding hydrazine 13 in 70% yield as previously described (74). As had been found by Carlin (74), this hydrazine was unstable in the presence of light and air and started decomposing within half an hour of its preparation. However, it could be preserved in the form of its hydrazine hydrochloride.



12 13 14 15 16

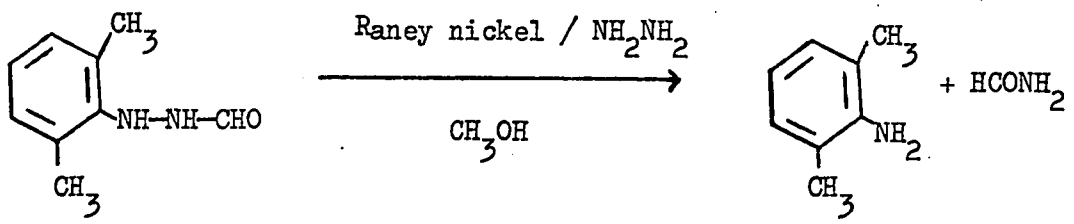
Scheme II

The 2,6-dimethylphenylhydrazine was formylated with formamide in acetic acid (25) to give N'-formyl-2,6-dimethylphenylhydrazine 14 in 73% yield. The formylated product melted at 139-140° and gave the elemental analysis expected for this compound.

The infrared spectrum in Nujol of this product showed bands at 3240 cm^{-1} and 3295 cm^{-1} (two different NH) and a strong band at 1670 cm^{-1} (C=O).

The nuclear magnetic resonance (n.m.r.) spectrum in $CDCl_3$ showed two sharp signals at τ 7.62 and τ 7.72 for the protons of two methyl groups attached to the aromatic ring. These two methyl groups are in the area ratio of 28:11 respectively. In pyridine-d_5, the 100 MHz spectrum (Fig. 1a) showed them to be in the area ratio of 2:1. They collapsed to a singlet at 100° (Fig. 1b) but reappeared when the temperature was decreased below 90°. This indicates that the N'-formyl-2,6-dimethylphenylhydrazine exists in two conformations at temperatures below 90°.

The exact position of the formyl group in this hydrazine was confirmed by Raney nickel reduction (119) of the hydrazine to 2,6-dimethylaniline and formamide, as illustrated below.



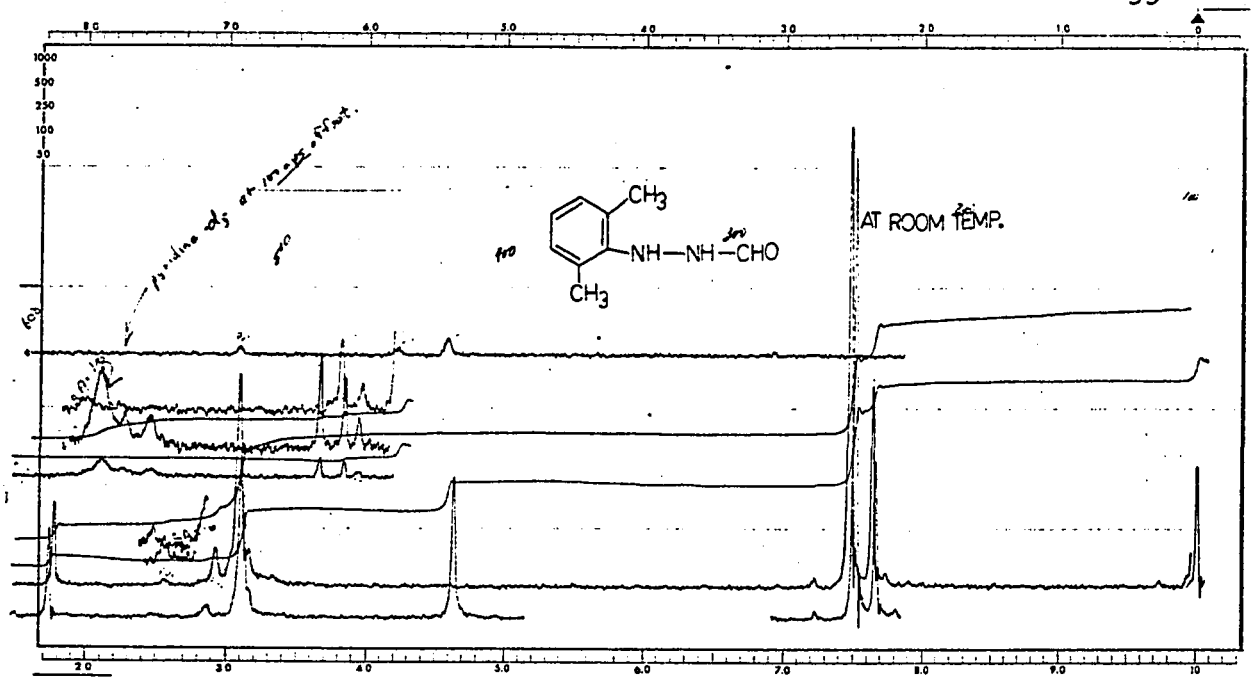


Fig. 1a. N.m.r. spectrum (60 MHz) of Ń-formyl-2,6-dimethylphenylhydrazine at room temperature in pyridine-$\underline{d}_5$. Reference, tetramethylsilane.

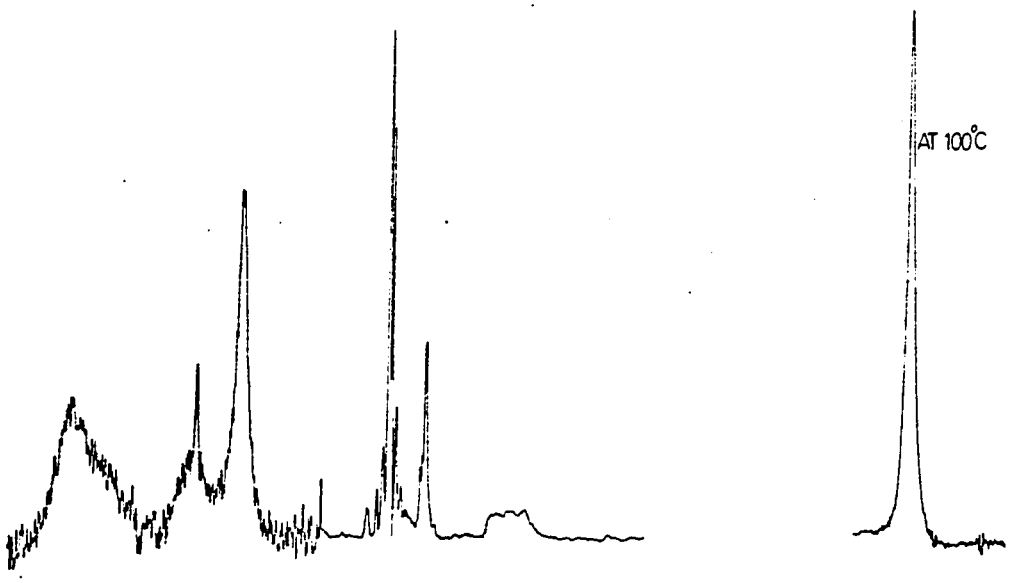


Fig. 1b. N.m.r. spectrum (100 MHz) of Ń-formyl-2,6-dimethylphenylhydrazine at 100° in pyridine-$\underline{d}_5$. Reference, tetramethylsilane.

The isolation of 2,6-dimethylaniline and formamide confirmed that the formyl group is on the nitrogen atom remote from the phenyl group. No evidence could be obtained for the formylation on the nitrogen atom adjacent to the ring or for diformylation.

Formylation of the 2,6-dimethylphenylhydrazine was also carried out with two equivalents of formamide in acetic acid. It also furnished the N'-formyl-2,6-dimethylhydrazine. The reformylation of the latter gave back the unchanged starting material, showing that certainly under our conditions, it is very difficult, if not impossible, to introduce a second formyl group. This is attributed to the steric interference which resists entrance of a formyl group on the nitrogen atom adjacent to this phenyl group. The inability of N-2 to accommodate the second formyl group could most likely be associated with its decreased nucleophilicity caused by the presence of a previous formyl group on it. From the evidence given above, there is no doubt that we have the required N'-formyl-2,6-dimethylphenylhydrazine 14.

Following the published procedure (25), the methylation of the N'-formyl-2,6-dimethylphenylhydrazine was effected with equimolar amounts of dimethyl sulfate and sodium hydroxide in dimethyl sulfoxide for 3 h at room temperature. Dilution with water and subsequent work up of this reaction mixture, afforded a yellow oil in 87% yield. This oil was difficult to purify and showed signs of decomposition at room temperature in the presence of air and light. The presence of a carbonyl peak at 1690 cm^{-1} in the infrared spectrum of the oil and the appearance of more than one

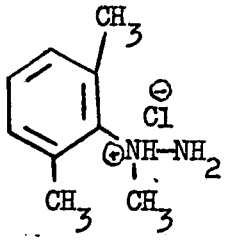
N-CH_3 group signal in the region of τ 6.6-7.21 in the n.m.r. spectrum indicated that it was a mixture but that it contained a substantial amount of N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine (the presence of the latter in this mixture was indicated by the N-CH_3 signal at τ 7.21). The N-CH_3 signal in the n.m.r. spectrum (Fig. 3) of an authentic sample of N-formyl-N-methyl-2,6-dimethylphenylhydrazine appears at τ 7.21.

It is interesting to note that the hydrogenolysis of N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine by following the recommended directions (119) was unsuccessful. Similar results are reported by Hinman (120) on the hydrogenolysis of 1,2-diacetyl-1,2-dimethylhydrazine. This may be attributed to the greater electron density at the two nitrogen atoms of this hydrazine due to the inductive effect of the N-methyl group, thus making acceptance of the electrons from the reducing agent more difficult. Alternatively, this inability for the nitrogen-nitrogen bond cleavage, may be associated with the steric factors (120). Since the reductive cleavage reaction occurs at the surface of the catalyst, the bulky groups hinder access by the nitrogen-nitrogen bond to the surface of the catalyst (120).

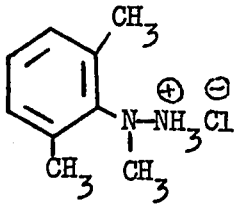
Thus, this study could not establish the exact position of the methyl group on the two nitrogen atoms of the hydrazine. However, by analogy with the formylation as discussed before, it is assumed that the methylation has taken place at the nitrogen atom remote from the aryl group of this hydrazine. This conclusion is fully corroborated by the product obtained from the hydrolysis of the crude N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine with

refluxing alcoholic hydrogen chloride. The resulting N'-methyl-2,6-dimethylphenylhydrazine showed a strong tendency to decompose rapidly and, therefore, had to be preserved as its hydrochloride. The elemental analysis of the hydrochloride agreed with the postulated structure. The n.m.r. spectrum (Fig. 2) of this hydrazine hydrochloride showed a singlet for the N-CH_3 group at τ6.98.

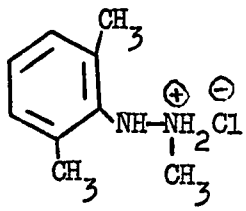
The i.r. spectrum (in Fluorolube) did make a clear distinction between the three possible structures (A, B or C) for this hydrazine hydrochloride.



A



B



C

It showed one band at 3240 cm^{-1} showing the presence of >N-H absorption and another at 2700 cm^{-1} for $\overset{\oplus}{N}H_2$. This evidence discards both structures B and A because the former would not show any such band as at 3240 cm^{-1} while the latter would show two bands at 3500-3300 cm^{-1} (121a) rather than one at 3240 cm^{-1}.

From the above evidence, it is obvious that we have the required compound, N'-methyl-2,6-dimethylphenylhydrazine hydrochloride 16. This compound could be formylated to give the pure N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine 15 in good

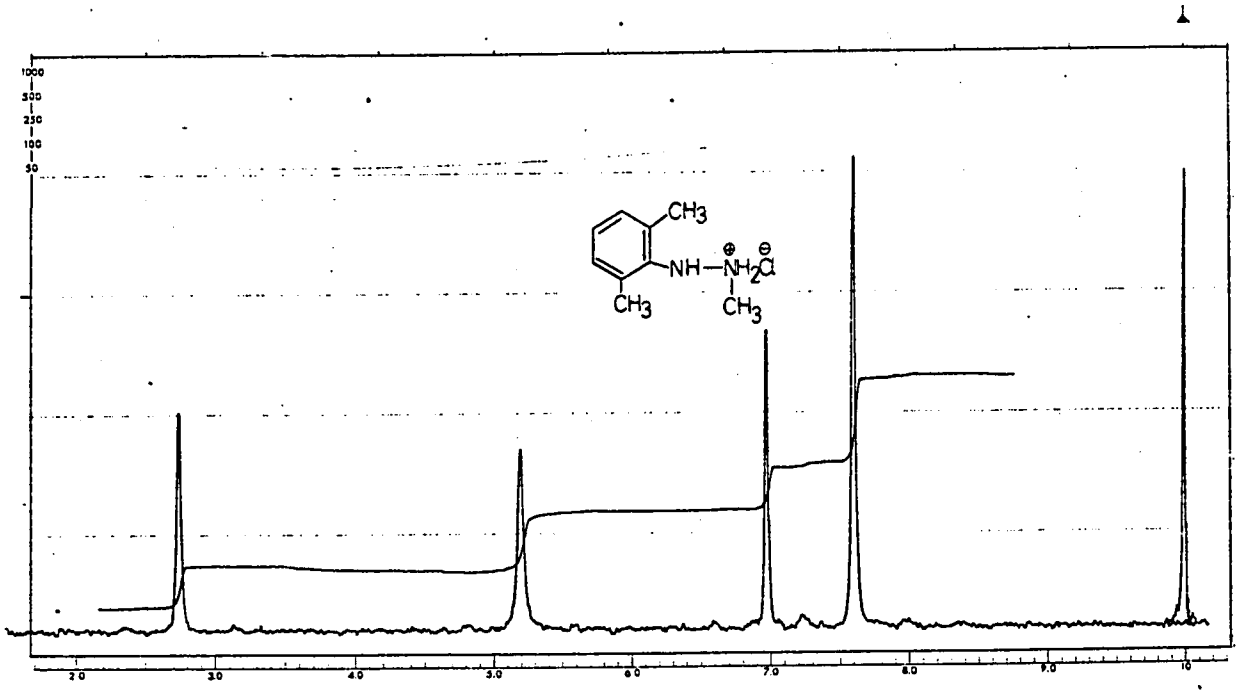


Fig. 2. N.m.r. spectrum (60 MHz) of N´-methyl-2,6-dimethylphenylhydrazine hydrochloride in D_2O. Reference, tetramethylsilane.

yield. The n.m.r. spectrum of this formylated compound is in Fig. 3.

It is of interest to point out here that when the methylation of the Ń-formyl-2,6-dimethylphenylhydrazine was carried out with a two molar proportion of both dimethyl sulfate and sodium hydroxide to one of the hydrazine, the resulting crude Ń-formyl-Ń-methyl-2,6-dimethylphenylhydrazine on hydrolysis furnished a substantial yield of Ń,Ń-dimethyl-2,6-dimethylphenylhydrazine hydrochloride along with the Ń-methyl-2,6-dimethylphenylhydrazine hydrochloride.

The structure of the dimethylated product is supported by its elemental analysis as well as by its i.r. and n.m.r. spectra. The i.r. spectrum in Fluorolube showed absorptions at 3228 cm^{-1} (NH), 2940 cm^{-1} (CH_3), 2700 cm^{-1} (NH) and 1578 cm^{-1} (aromatic C=C).

The n.m.r. spectrum (Fig. 4) of this dimethylated compound in D_2O showed signals at τ 2.90 (3H, aromatic), τ 5.27 (DOH, broad singlet, w/2 $\approx$ 4 Hz), τ 6.96 (3H) and τ 7.12 (3H) sharp singlets for the two N-CH_3 groups and at τ 7.68 (6H, singlet for two CH_3 groups attached to the aromatic ring). The appearance of two N-CH_3 groups as two sharp singlets at τ 6.96 and τ 7.12, suggests that this hydrazine hydrochloride exists in two conformations. However, in view of the difficulty in finding a suitable solvent, high temperature studies (above 90°) on its n.m.r. analysis could not be carried out to confirm this.

Apparently, dimethylation had occurred as a result of hydrolysis of the Ń-formyl-Ń-methyl-2,6-dimethylphenylhydrazine or Ń-formyl-2,6-dimethylphenylhydrazine under these reaction

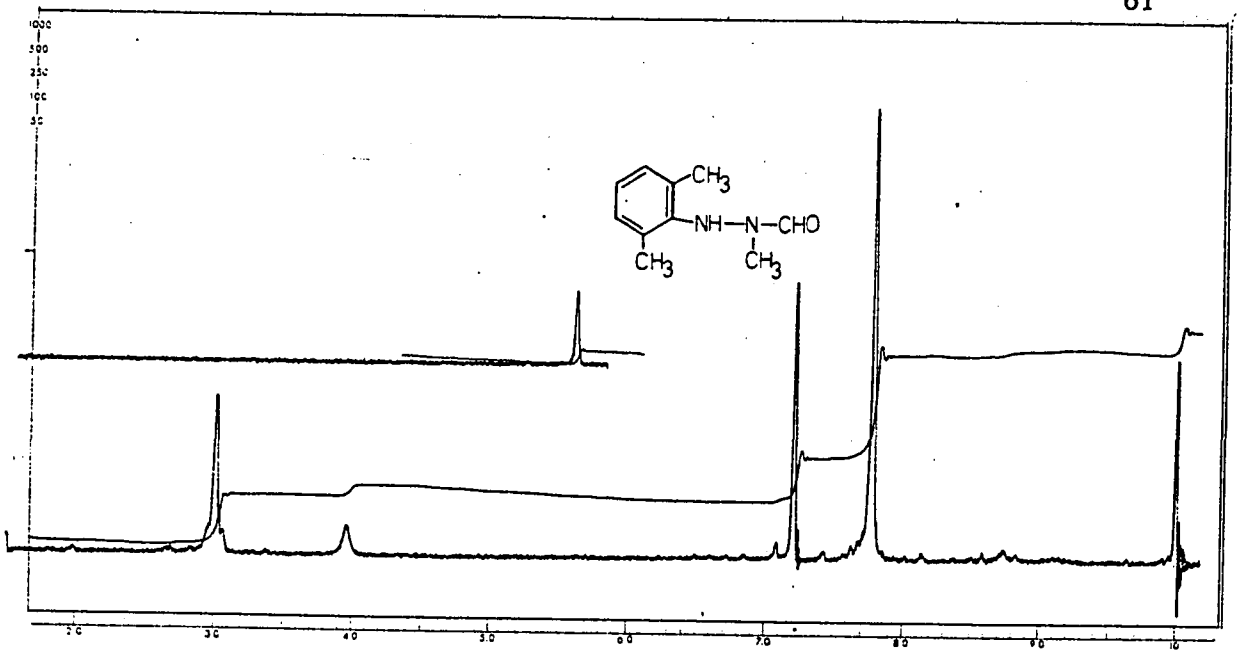


Fig. 3. N.m.r. spectrum (60 MHz) of pure N´-formyl-N´-methyl-2,6-dimethylphenylhydrazine in $CDCl_3$. Reference, tetramethylsilane.

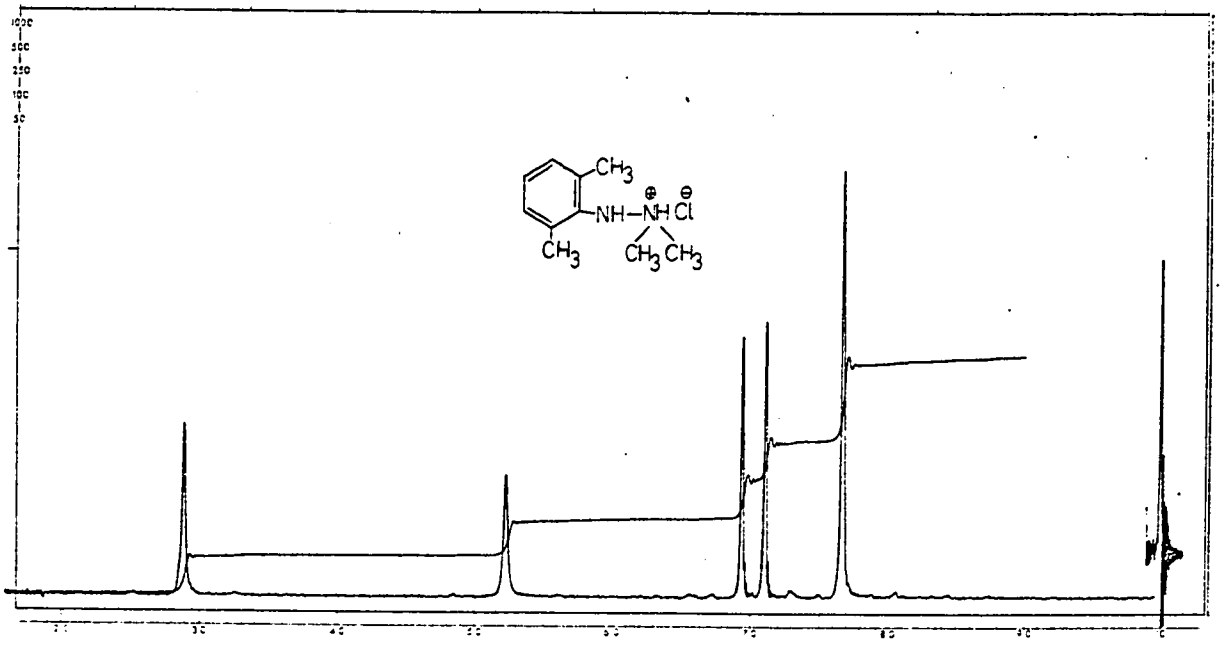


Fig. 4. N.m.r. spectrum (60 MHz) of N´,N´-dimethyl-2,6-dimethylphenylhydrazine hydrochloride in D_2O. Reference, tetramethylsilane.

conditions.

Cyclohexanone was chosen as the appropriate ketone for condensation with N-methyl-2,6-dimethylphenylhydrazine. Its hydrazone is known to form the indole structure very readily. Also, it was thought that the product(s) obtained would be solids.

Thus, N-methyl-2,6-dimethylphenylhydrazine was condensed with an equimolar amount of cyclohexanone in refluxing benzene for 1/2 to 4 h using a Dean-Stark apparatus (122a). Water was collected in the Dean-Stark apparatus showing that the reaction had proceeded at least to the enehydrazine stage.

All the gases evolved during this reaction were led through dry ether, saturated with dry hydrogen chloride. A precipitate was obtained which was found to be ammonium chloride contaminated with a small amount of methylamine hydrochloride.

From the benzene solution, there was obtained a 22% yield of a solid melting at 152-153°. It analyzed for $C_{14}H_{17}N$ and had the following characteristics.

The i.r. spectrum of this compound in CCl_4 showed absorptions at 3020 cm^{-1}(=C-H), 1600 cm^{-1} (aromatic C=C).

The n.m.r. spectrum in $CDCl_3$ (Fig. 5) showed signals at τ 2.5-3.3 (3H, aromatic, multiplet), τ 6.18 (3H, for N-CH_3; singlet), τ 7.27 (3H, aromatic methyl, singlet), two characteristic closely spaced multiplets centered at τ 7.35 and τ 8.12 for the 8H of the tetrahydro ring.

The u.v. absorption spectrum in cyclohexane is shown in

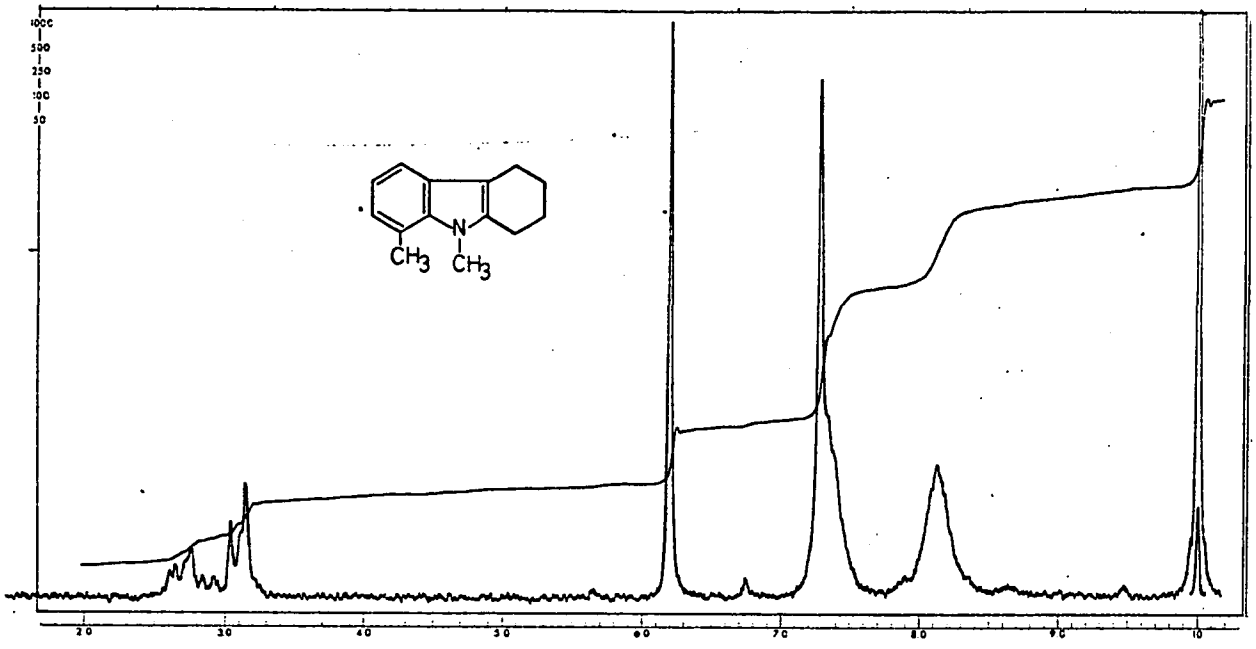
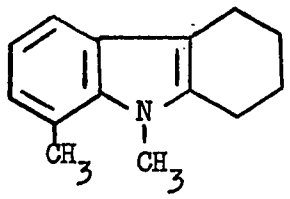


Fig. 5. N.m.r. spectrum (60 MHz) of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole (reaction product) in $CDCl_3$. Reference, tetramethylsilane.

Fig. 6; λ_{max}, 234 mμ (ε, 38000), 287 mμ(ε, 3700).

From the above evidence, the reaction product (m.p. 152-153°) of this condensation was assigned the structure, 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole.



The structure was corroborated by its independent synthesis, by the following Scheme III. The precursor, 8-methyl-1,2,3,4-tetrahydrocarbazole 17, is known in the literature (18, 122b) and was obtained by following the published directions (18). It could not be methylated with dimethyl sulphate and sodium hydroxide or sodium hydroxide and methyl iodide since in all attempts, only the starting material was recovered quantitatively. This can be ascribed to the steric interaction offered by the methyl group present at position 8 of the tetrahydrocarbazole system.

However, when BaO and $Ba(OH)_2$ was used as a base with dimethyl sulphate as a methylating agent in a 1:1 (by volume) solution of N,N-dimethylformamide and dimethyl sulfoxide, methylation could be effected, but only in poor yield. The methylation under the reaction conditions, can afford three products, 18, 19, 20 as illustrated in Scheme III.

The formation of methylated products 19 and 20 under these reaction conditions is ruled out by the following evidence.

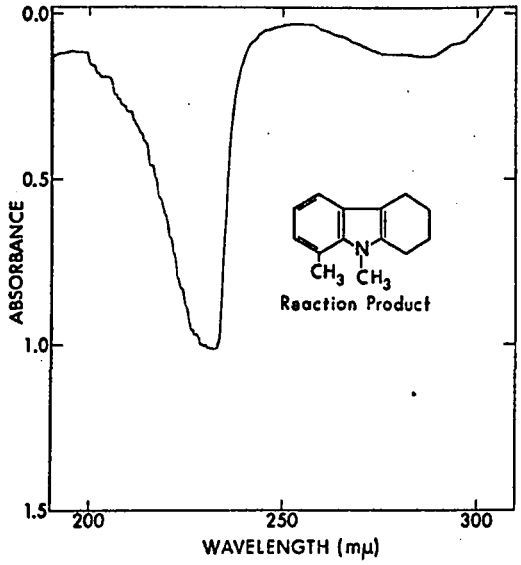


Fig. 6. U.v. spectrum of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole (reaction product) in cyclohexane.

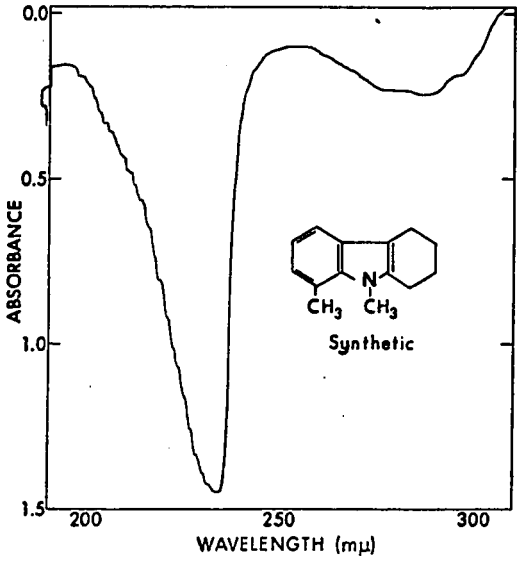
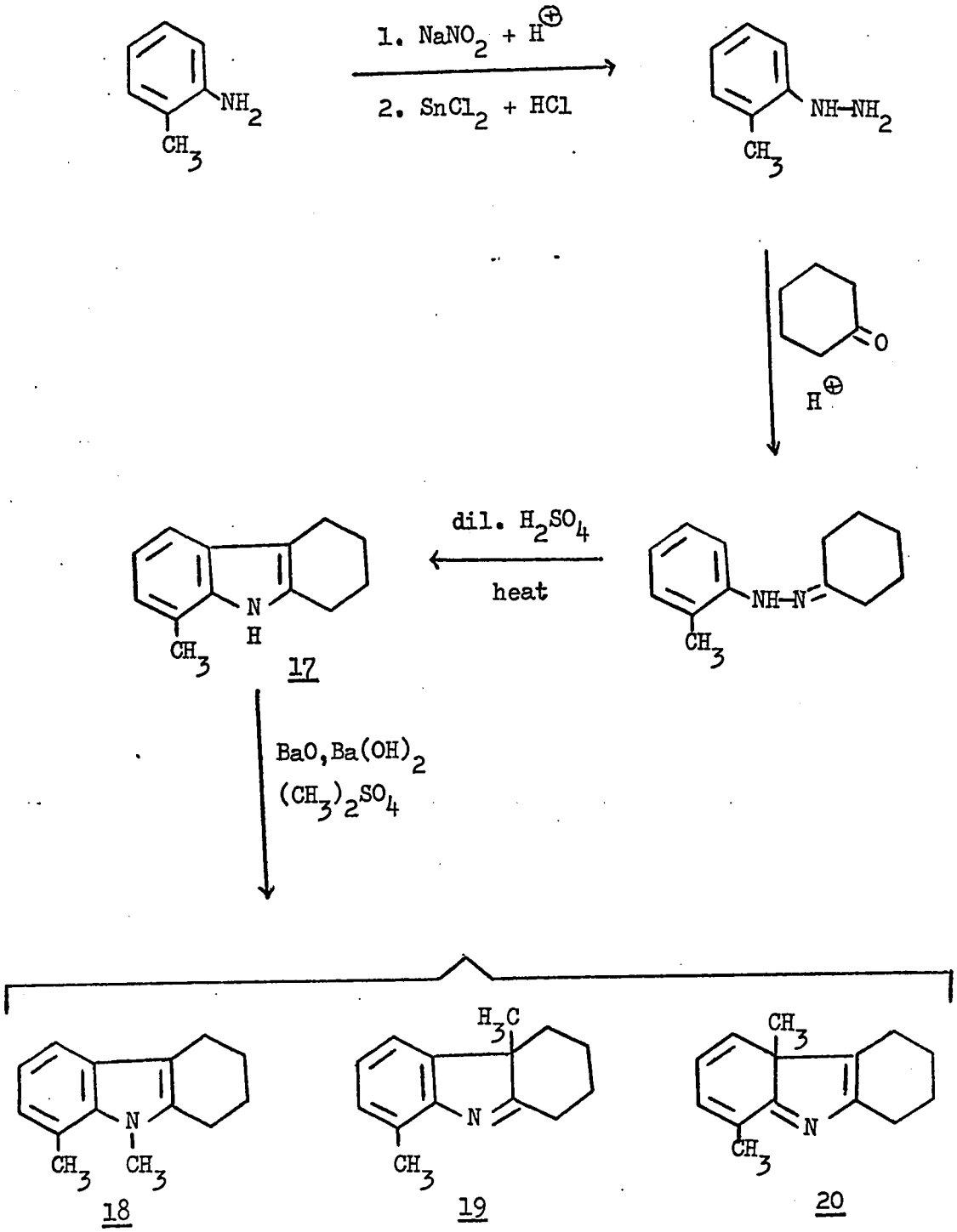


Fig. 7. U.v. spectrum of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole (synthetic product) in cyclohexane.


1. NaNO2 + H⊕
2. SnCl2 + HCl
NH2
CH3
NH–NH2
O
H⊕
NH–N
dil. H2SO4
heat
N
H
17
BaO, Ba(OH)2
(CH3)2SO4
H3C
18
19
20

Scheme III

(1) There is no C=N absorption in the region 1630-1690 cm^{-1} in the i.r. spectrum.

(2) The u.v. spectrum of the synthesised 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole differs markedly from that of 2,3,3-trimethylindolenine but closely resembles that for 8-methyl-1,2,3,4-tetrahydrocarbazole 17. This is illustrated in Figs. 7, 8 and 9.

(3) The n.m.r. spectrum shows signals at τ 7.27 and τ 6.20 in the region expected respectively for the methyl groups attached to the carbon of an aromatic system and nitrogen atom of an amine. In structures 19 and 20, there is no N-CH_3 group. As well, both 19 and 20 contain an aliphatic C-CH_3 group whose resonance signals are expected to occur in the region τ 8 to τ 9. No signals appear at such high field. Therefore, the n.m.r. spectrum supports structure 18 and excludes the possibility of structures 19 and 20. Thus, from the foregoing evidence, the methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole gives N-methylation and not C-methylation.

The i.r., n.m.r. and u.v. spectra of the methylated compound, 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole were superimposeable on the corresponding spectra of the reaction product obtained by the direct condensation of N'-methyl-2,6-dimethylphenylhydrazine and cyclohexanone. Furthermore, the melting points of these products are the same and show no depression on admixture.

It was now considered worthwhile to postulate a mechanism for the formation of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole from the

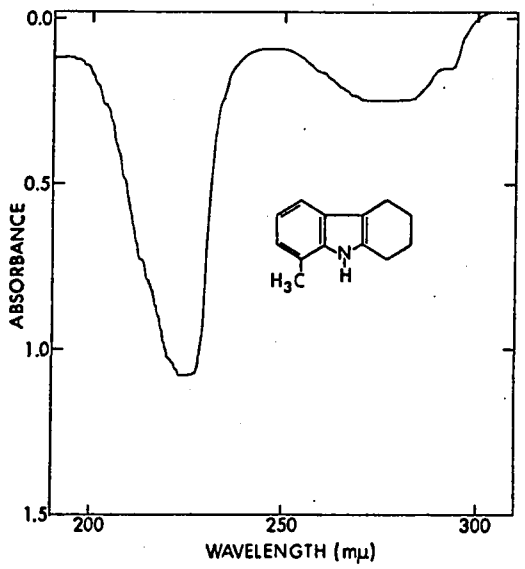


Fig. 8. U.v. spectrum of 8-methyl-1,2,3,4-tetrahydrocarbazole in cyclohexane.

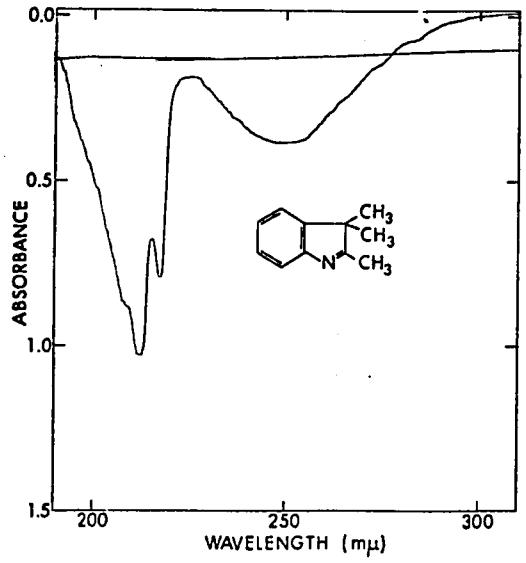


Fig. 9. U.v. spectrum of 2,3,3-trimethylindolenine in cyclohexane.

Fischer reaction of N-methyl-2,6-dimethylphenylhydrazine with cyclohexanone. For such a study, it was felt that the amount of methylamine and ammonia formed in this condensation, should be known. Under the present conditions, methylamine was formed in such a small amount that quantitative measurement was difficult. Hence attempts were made to improve the yield of the 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole and to obtain a quantitative measure of the methylamine and ammonia formed in this reaction.

The hydrochloride of N-methyl-2,6-dimethylphenylhydrazine is quite stable as compared to the free hydrazine itself. It was thought that the stability of the hydrazine hydrochloride might cut down the amount of decomposition which occurs with the free hydrazine and thus improve the yield of the 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole. The hydrogen chloride (attached to the hydrazine as hydrochloride) would tie up the methylamine and ammonia liberated in situ in the form of their insoluble hydrochlorides in a solvent such as benzene. Thus, this method should also improve the determination of methylamine and ammonia formed in this reaction.

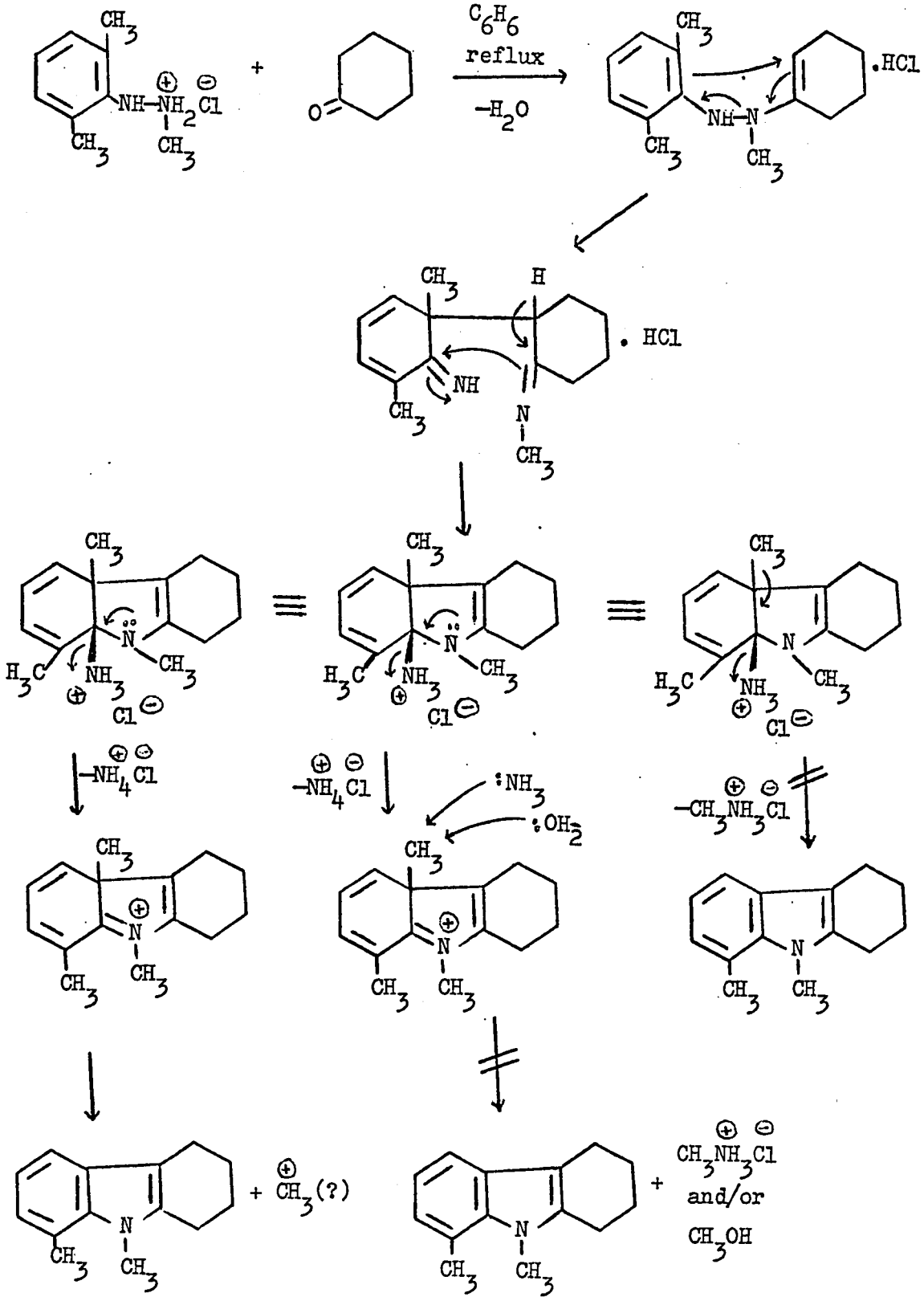
When the hydrochloride of N-methyl-2,6-dimethylphenylhydrazine was condensed with cyclohexanone, it was found that the yield of the 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole increased to 42% (reaction with free hydrazine gave only 22% yield). The insoluble precipitate of the ammonium chloride (formed in $\sim$ 33% yield) was contaminated with $\sim$ 6% of methylamine hydrochloride. The gases evolved during this reaction were passed through ether

saturated with dry hydrogen chloride. On the evaporation of this ether solution, no precipitate could be isolated showing that the methylamine and ammonia were retained in the benzene solution as their hydrochlorides. Also, a blank experiment, in which N'-methyl-2,6-dimethylphenylhydrazine hydrochloride was refluxed in benzene for 10 h, showed no evidence for the formation of ammonia and/or methylamine indicating that the latter were formed only as a result of the reaction of this hydrazine hydrochloride with cyclohexanone.

The evidence given above leads to the following Scheme IV, involving a dienone-imine intermediate, which explains the formation of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole from the reaction of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride with cyclohexanone.

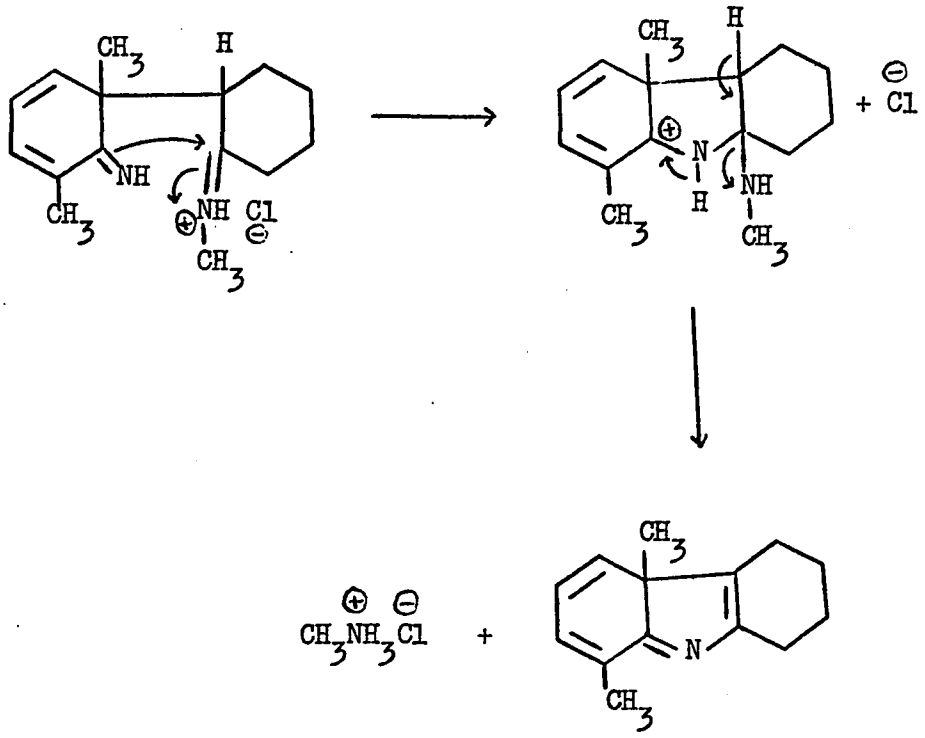
It is clear that one of the methyl groups of the aromatic ring is lost. The evolved gases absorbed in ether or in benzene showed no evidence (by mass spectrometry) for the presence of methane, which might arise by a reductive process such as that suggested (25) for the liberation of halogens as halide ion. Failure to detect or isolate methyl alcohol or methylamine (except for the small amount of the latter, $\sim$ 6%, detected when the hydrochloride was used) indicates that the liberated water or ammonia do not provide the chief nucleophile which attacks the labile methyl group. Similar loss of methyl groups have previously been reported (73), the fate of which (as in the present case) is as yet unknown.

The small amount of methylamine formed during this reaction,



Scheme IV

could have its origin in an alternate reaction such as shown below (Scheme V). That such alternate reactions do occur has already been shown by Carlin (74).



Scheme V

B. Experiments with Ń-ethyl-2,6-dimethylphenylhydrazine.

In order to obtain more information concerning the reaction discussed in section A, a study of the condensation of Ń-ethyl-2,6-dimethylphenylhydrazine with cyclohexanone was undertaken.

The Ń-ethyl-2,6-dimethylphenylhydrazine was made by the same procedure (Scheme II) as employed for the formation of Ń-methyl-2,6-dimethylphenylhydrazine.

Ń-Formyl-2,6-dimethylphenylhydrazine (14, Scheme II) was ethylated with diethyl sulfate and sodium hydroxide to give Ń-ethyl-Ń-formyl-2,6-dimethylphenylhydrazine in 85% yield.

The i.r. spectrum (film) showed two bands in the N-H region at 3330 cm^{-1} and 3220 cm^{-1} (two different NH) and a strong band at 1685 cm^{-1} (C=O).

The n.m.r. spectrum (Fig. 10) in $CDCl_3$ showed signals at τ 2.95-3.2 (aromatic), two overlapping quartets for the methylene protons of the ethyl group centered at τ 6.81 and τ 6.72 and one at τ 5.92, J=7 Hz; at least two overlapping triplets for the methyl moiety of the ethyl group, between τ 8.5 and τ 9.1, J= 7 Hz; two prominent singlets at τ 7.63 and τ 7.76 for methyl groups attached to the aromatic nucleus. These data indicate the presence of more than one N-ethylated species. This oily material had a strong tendency to decompose and hence could not be purified and analyzed.

However, by analogy with our previous observations on the methylation of Ń-formyl-2,6-dimethylphenylhydrazine, it is presumed that ethylation has occurred on the nitrogen atom remote from the

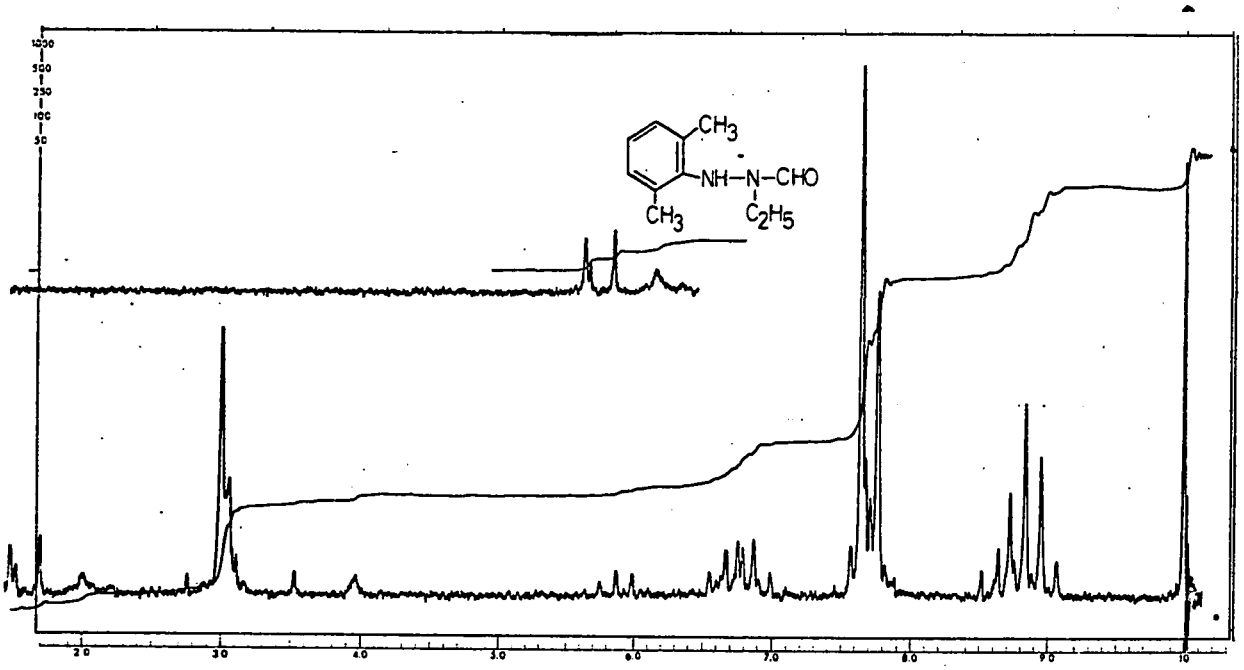


Fig. 10. N.m.r. spectrum (60 MHz) of N'-ethyl-N'-formyl-2,6-dimethylphenylhydrazine (crude) in $CDCl_3$. Reference, tetramethylsilane.

phenyl group.

The crude N-ethyl-N-formyl-2,6-dimethylphenylhydrazine was hydrolyzed by refluxing with alcoholic hydrogen chloride and gave N-ethyl-2,6-dimethylphenylhydrazine hydrochloride. The latter analyzed correctly for $C_{10}H_{17}N_2Cl$.

The i.r. spectrum of this hydrazine hydrochloride (in Fluorolube) showed absorptions at 3245 cm^{-1} (NH) and at 2700 cm^{-1} ($\overset{\oplus}{N}H_2$).

The n.m.r. spectrum (Fig. 11) in D_2O showed signals at τ 2.80 (3H, aromatic, singlet), τ 5.3 (DOH), τ 6.57 (2H, one quartet for N-$\underline{CH_2}$-CH_3, J=7 Hz), τ 8.61 (3H, one triplet for N-CH_2-$\underline{CH_3}$, J=7 Hz), τ 7.59 (6H, one singlet for two aromatic methyl groups).

When 1 g quantitites of this hydrazine were freed from hydrochloric acid and then condensed with cyclohexanone in refluxing benzene for various lengths of time and with or without various acid catalysts, none of the expected product could be isolated following the usual work-up of the reaction mixture. The reaction mixture darkened and decomposed even under an atomosphere of nitrogen and absence of light. Similarly, refluxing in toluene, p-xylene, mesitylene (to conduct the reaction at high temperature) with or without various acid catalysts, did not improve the results.

However, when N-ethyl-2,6-dimethylphenylhydrazine hydrochloride was condensed with cyclohexanone in refluxing benzene for 3 h, better results were obtained. A solid which precipitated from the reaction mixture (benzene solvent), was removed and found by its n.m.r. spectrum to consist of ammonium chloride contaminated with ethylamine hydrochloride. The residual benzene solution, after

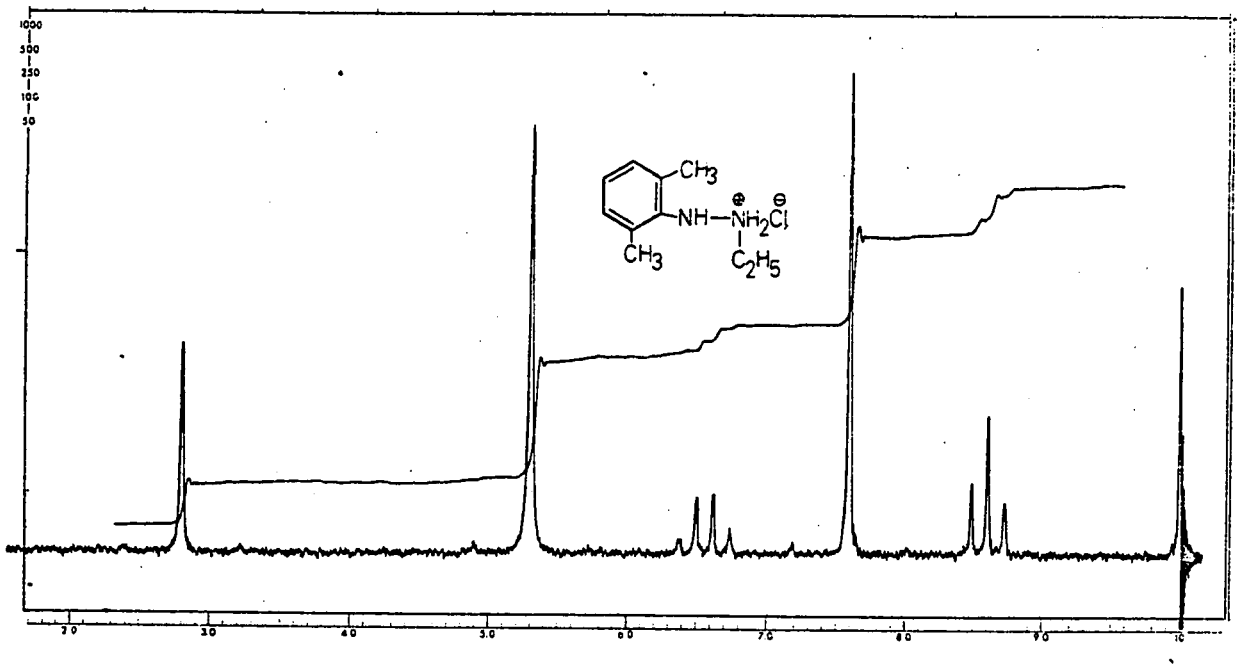


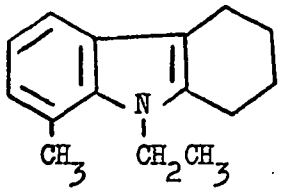
Fig. 11. N.m.r. spectrum (60 MHz) of N'-ethyl-2,6-dimethylphenylhydrazine hydrochloride in D_2O. Reference, tetramethylsilane.

the removal of the above salts, when freed from solvent afforded a solid. This solid was crystallized from 95% ethanol to give a 13% yield of a single solid material, m.p. 55-57° and analyzed for $C_{15}H_{19}N$.

Its u.v. spectrum (Fig. 12) showed bands at λ_{max}, 232 mμ (ϵ, 36000) and at 286 mμ(ϵ, 7100). This spectrum is closely similar to that for 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole (shown in Figs. 6 and 7).

The i.r. spectrum showed no N-H absorption. The n.m.r. spectrum (Fig. 13) in $CDCl_3$ showed signals at τ 2.6-3.3 (3H, aromatic, multiplet), τ 5.82 (2H, quartet for N-$\underline{CH_2}$-CH_3, J=7 Hz), τ 8.77 (3H, triplet for $\underline{CH_3}$-CH_2N, J=7 Hz), τ 7.33 (3H, singlet for aromatic CH_3), and two multiplets centered at τ 7.37 and 8.16 for the 8H characteristic of the tetrahydro ring.

From the above evidence, the structure under consideration is 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole, as shown below.



To corroborate the above structure, 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole, an attempt was made to prepare an authentic sample of this compound by an independent synthesis. Thus, N-ethylation of 8-methyl-1,2,3,4-tetrahydrocarbazole $\underline{17}$ was attempted by the same procedure as employed for the N-methylation

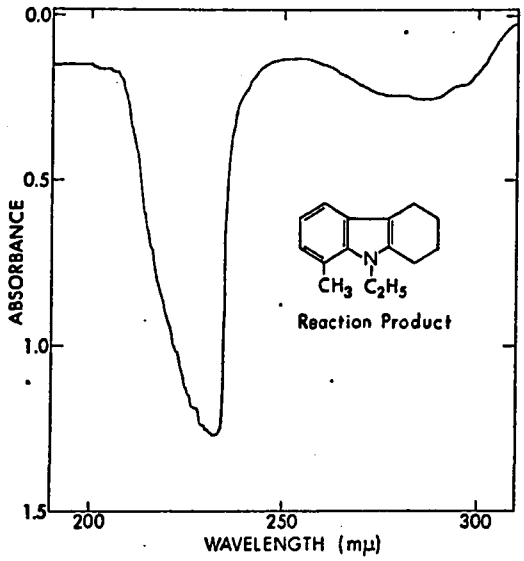


Fig. 12. U.v. spectrum of 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole in cyclohexane.

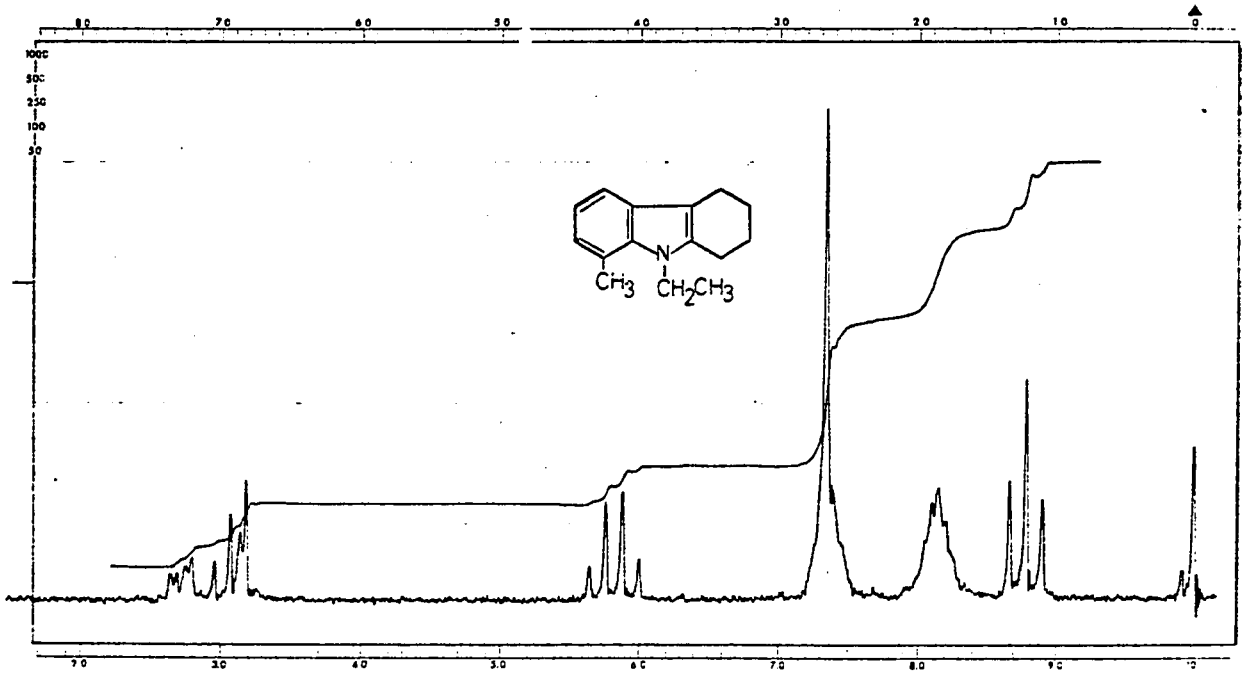
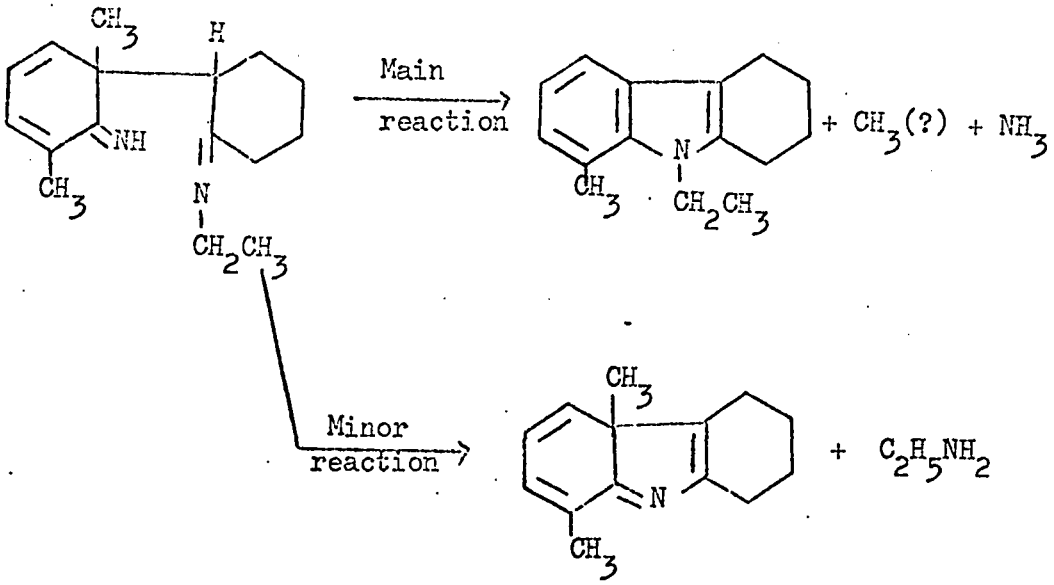


Fig. 13. N.m.r. spectrum (60 MHz) of 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole in $CDCl_3$. Reference, tetramethylsilane.

in Scheme III. However, no product corresponding to the 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole could be isolated by following the usual work-up of the reaction mixture. In all attempts, only the starting material was recovered in good yield. This is probably due to the greater steric hindrance to the N-ethylation of the tetrahydrocarbazoles when substituents are present at position 8 of this ring system. Such steric interaction is evident in the methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole. In the latter case, a yield of only 7% (~20% when based on the tetrahydrocarbazole consumed) was obtained as compared to the one of at least 45% when 1,2,3,4-tetrahydrocarbazole was methylated under identical conditions.

The formation of 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole and ethylamine is rationalized by pathways similar to those illustrated in Schemes IV and V respectively. For the sake of convenience, it is illustrated in Scheme VI.

This study clarifies several points about the previous study dealing with the condensation of N'-methyl-2,6-dimethylphenylhydrazine with cyclohexanone (section A). Thus, the major reaction proceeds by the loss of an alkyl group from the aromatic ring. This supports the reaction pathway illustrated in Scheme IV. The minor reaction is one which leads to this formation of an alkylamine. The latter comes from the elimination of the N'-alkyl group of the phenylhydrazine rather than by the elimination of the aromatic alkyl group because, in the experiments



Scheme VI

just described, only ethylamine was obtained and no methylamine was detected. This supports Scheme V which was advanced to explain the formation of the alkylamine during these reactions.

It may be noted that this N-ethylhydrazine shows a strong tendency to decompose when present either as a free base or its hydrochloride. Accordingly, no 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole could be crystallized from the reaction mixture when free hydrazine was condensed with cyclohexanone. However, a 13% yield of the above tetrahydrocarbazole could be

isolated from the reaction mixture when hydrazine hydrochloride was used rather than free hydrazine. This is attributed to the greater stability of the hydrazine hydrochloride as compared to that of the free hydrazine.

C. Experiments with N'-methyl-2,6-diethylphenylhydrazine.

The previous reaction of N'-ethyl-2,6-dimethylphenylhydrazine with cyclohexanone (in section B) furnished a clue to the origin of the amine formed in this reaction. This lent support to the reaction pathway suggested for the formation of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole in Scheme IV.

However, it was made clear that the reaction of N'-ethyl-2,6-dimethylphenylhydrazine with cyclohexanone was accompanied by a considerable amount of decomposition. Accordingly, neither the yield of 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole was improved nor the ethylamine formed in this reaction could be assessed with accuracy. In view of these considerations, it was thought that the reaction of N'-methyl-2,6-diethylphenylhydrazine with cyclohexanone might prove more suitable for the present investigations.

N'-methyl-2,6-diethylphenylhydrazine was obtained by the procedure illustrated for the formation of N'-methyl-2,6-dimethylphenylhydrazine in Scheme II. A brief account of this is given below.

The 2,6-diethylphenylhydrazine obtained by the reduction of the diazonium salt of 2,6-diethylaniline, was formylated in the presence of formamide and acetic acid in 68% yield. The resulting N'-formyl-2,6-diethylphenylhydrazine analyzed correctly for $C_{11}H_{16}N_2O$. Its i.r. spectrum (CCl_4) showed absorptions at 3430 cm^{-1} and 3358 cm^{-1} (medium, for two N-H groups) and a strong band at 1700 cm^{-1} (C=O).

The n.m.r. spectrum (Fig. 14) in $CDCl_3$ showed signals at τ2.06 (1H, broad, singlet for C<u>H</u>=O), τ 2.25 and τ 4.33 (broad singlets, 2H, for two NH, located by deuterium exchange), τ 8.78 (6H, one triplet for two <u>CH_3</u>-CH_2- groups, J=7.5 Hz) and two overlapping quartets centered at τ 7.23 and τ 7.37 (4H, for two CH_3-<u>CH_2</u>- groups, J=7.5 Hz).

In pyridine, the 100 MHz spectrum showed two overlapping triplets centered at τ 8.82 and τ 8.85 (J=7.5 Hz) roughly in the ratio 2:1 respectively (methyl protons of the ethyl group). The methylene protons of the ethyl group gave two overlapping quartets centered at τ 7.02 and τ 7.22 (J=7.5 Hz). The former collapsed to one triplet while the two methylene proton quartets merged into one quartet at temperatures above 80°, thus indicating that at room temperature in pyridine, N'-formyl-2,6-diethylphenylhydrazine exists in two conformers roughly in the ratio of 2:1.

The methylation of N'-formyl-2,6-diethylphenylhydrazine was carried out with dimethyl sulphate and sodium hydroxide, and gave N'-formyl-N'-methyl-2,6-diethylphenylhydrazine in 62% yield. In the n.m.r. spectrum (in $CDCl_3$) of this product, the appearance of two singlets, at τ 7.18 and τ 7.22, indicated that N-methylation had occurred. It also indicated that the reaction mixture contained more than one methylated material. In view of the difficulty in purifying this yellow oily material, it was hydrolyzed without purification.

The hydrolysis of N'-formyl-N'-methyl-2,6-diethylphenylhydrazine (crude) was carried out by heating it in alcoholic hydrogen chloride for six hours under reflux. It afforded N'-methyl-2,6-

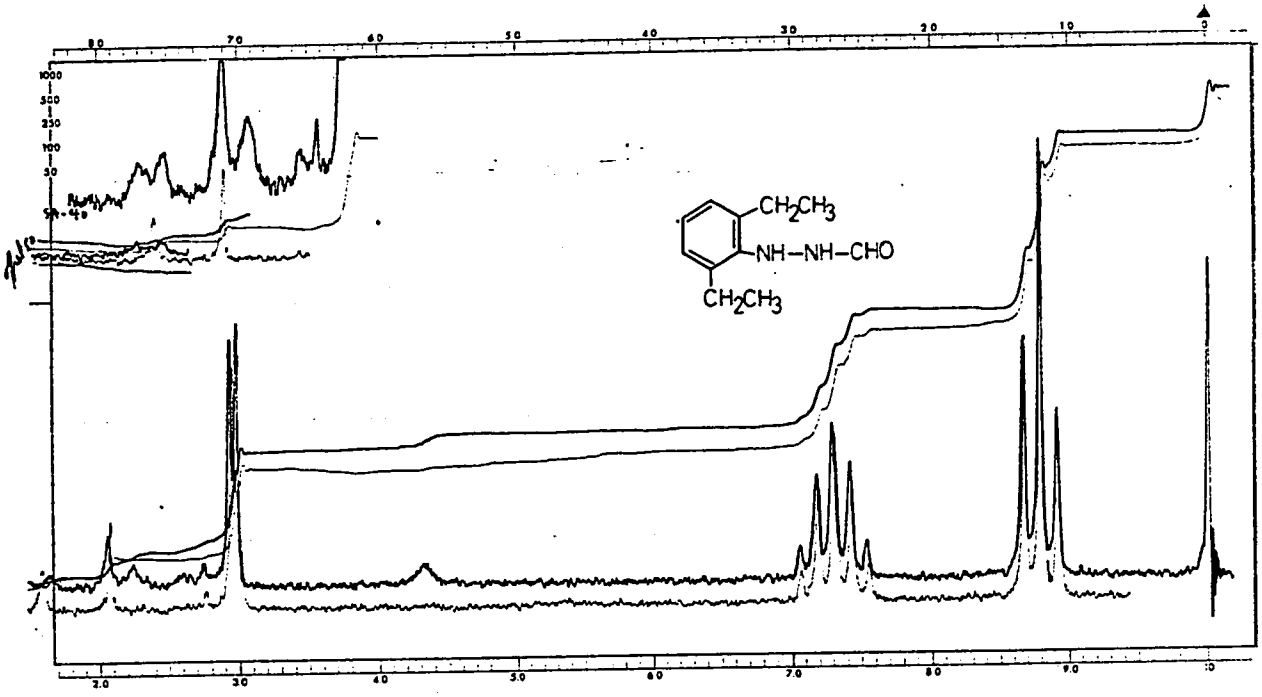


Fig. 14. N.m.r. spectrum (60 MHz) of N'-formyl-2,6-diethylphenylhydrazine in $CDCl_3$. Reference, tetramethylsilane.

diethylphenylhydrazine hydrochloride in 20% yield. The latter analyzed correctly for $C_{11}H_{19}N_2Cl$.

Its i.r. spectrum in Fluorolube showed a sharp band at 3240 cm^{-1} (NH) and a medium strength band at 2690 cm^{-1} ($\overset{\oplus}{N}H_2$).

The n.m.r. spectrum (Fig. 15) in D_2O agreed with the structure and showed signals at τ 2.74 (3H, narrow multiplet, aromatic), τ 5.28 (DOH), τ 7.0 (3H for N-CH_3, singlet), τ 7.25 (4H for two CH_3-$\underline{CH_2}$ groups, one quartet, J=7.5 Hz) and τ 8.82 (6H for two $\underline{CH_3}$-CH_2- groups, one triplet, J=7.5 Hz).

The N-methyl-2,6-diethylphenylhydrazine was condensed with cyclohexanone in refluxing benzene for four hours using acetic acid as the catalyst. Then the benzene was removed and the yellow oil deposited 4% of a pure material, m.p. 58-59°. It analyzed correctly for $C_{15}H_{19}N$, and on the following evidence, was assigned the structure of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole.

The u.v. spectrum (Fig. 16) in cyclohexane supported the above structure and showed absorptions at λ_{max}, 233 mμ (ϵ, 32000), 286 mμ (ϵ, 5900). This u.v. spectrum is closely similar to the u.v. spectrum of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole illustrated in Figs. 6 and 7.

The i.r. spectrum in CCl_4 showed no N-H absorption at 3500-3300 cm^{-1} and no C=N absorption at 1630-1690 cm^{-1} (121b). It showed a strong band at 3025 cm^{-1} (aromatic =$\underline{C-H}$) and a medium band at 1605 cm^{-1} (aromatic C=C).

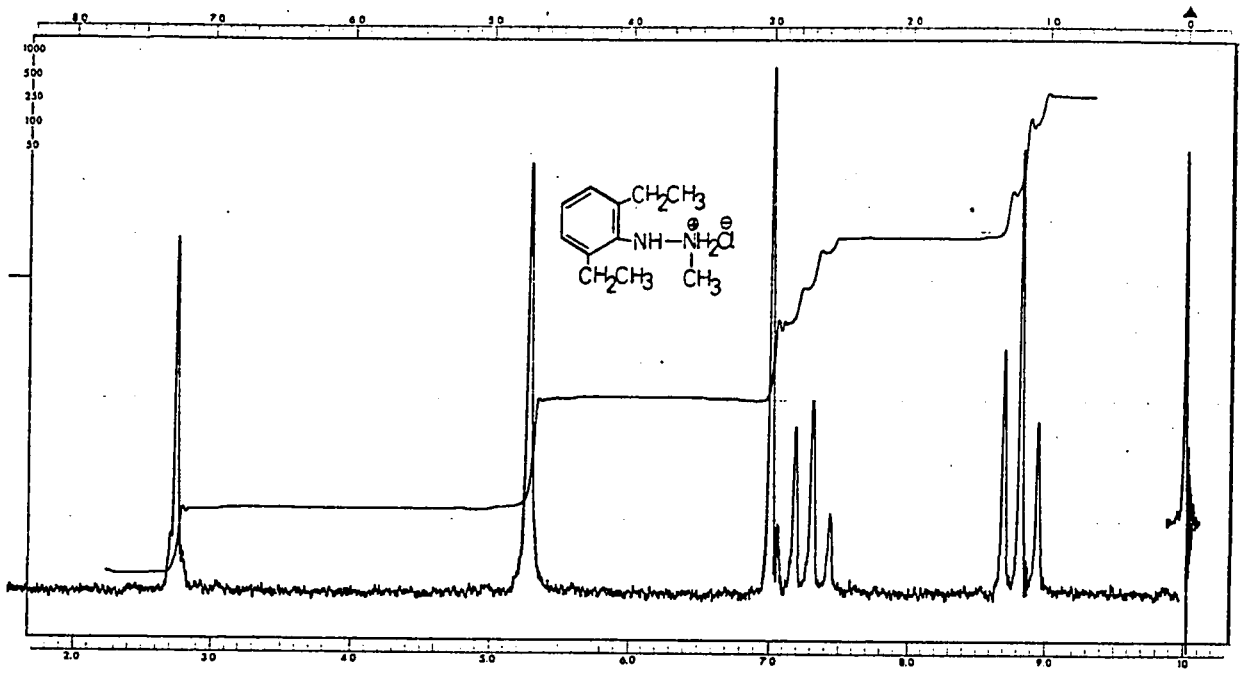


Fig. 15. N.m.r. spectrum (60 MHz) of N'-methyl-2,6-diethylphenylhydrazine hydrochloride in D_2O. Reference, tetramethylsilane.

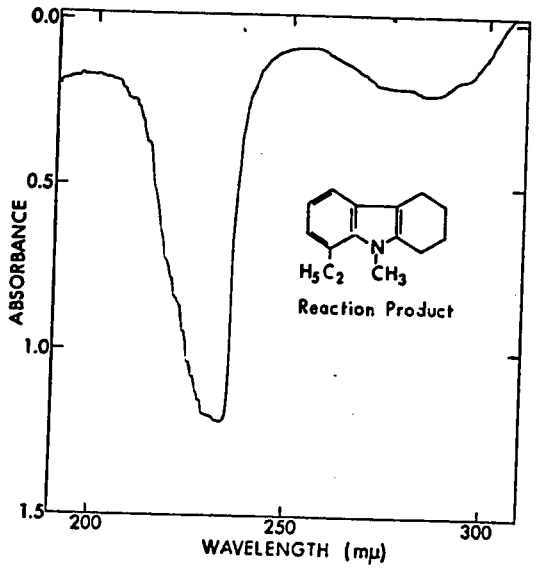


Fig. 16. U.v. spectrum of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole in cyclohexane.

The n.m.r. spectrum (Fig. 17) in $CDCl_3$ showed signals at τ 2.5-3.2 (3H, aromatic, multiplet), τ 6.26 (3H, singlet for N-CH_3), τ 6.94 (2H, quartet for -$\underline{CH_2}$-CH_3 attached to the benzene ring, J=7.5 Hz), τ 8.70 (3H, triplet for -CH_2-$\underline{CH_3}$, J=7.5 Hz) and two multiplets at τ 7.35 and τ 8.13 (8H, characteristic of the tetrahydro ring).

An attempt was made to corroborate the structure of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole by its synthesis following the same procedure as illustrated for the N-methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole 17 in Scheme III. A brief account of it is given below.

Cyclohexanone o-ethylphenylhydrazone, obtained by the reaction of o-ethylphenylhydrazine with cyclohexanone, had a strong tendency to decompose rapidly and therefore, could not be analyzed. However, its i.r. and n.m.r. spectra supported the structure completely (see experimental section, 6b).

The above hydrazone was cyclized with 3N aqueous sulphuric acid to give 8-ethyl-1,2,3,4-tetrahydrocarbazole in 61% yield. It analyzed correctly for $C_{14}H_{17}N$ and was supported by its dehydrogenation to the known 1-ethylcarbazole (123).

Its u.v. spectrum in cyclohexane (Fig. 18) showed absorptions at λ_{max}, 227 mμ(ϵ, 27,000), 277 mμ (ϵ,6,200). This u.v. spectrum is closely similar to the u.v. spectrum of 8-methyl-1,2,3,4-tetrahydrocarbazole shown in Fig. 8.

The i.r. spectrum in CCl_4 showed a sharp strong band at 3480 cm^{-1} (N-H).

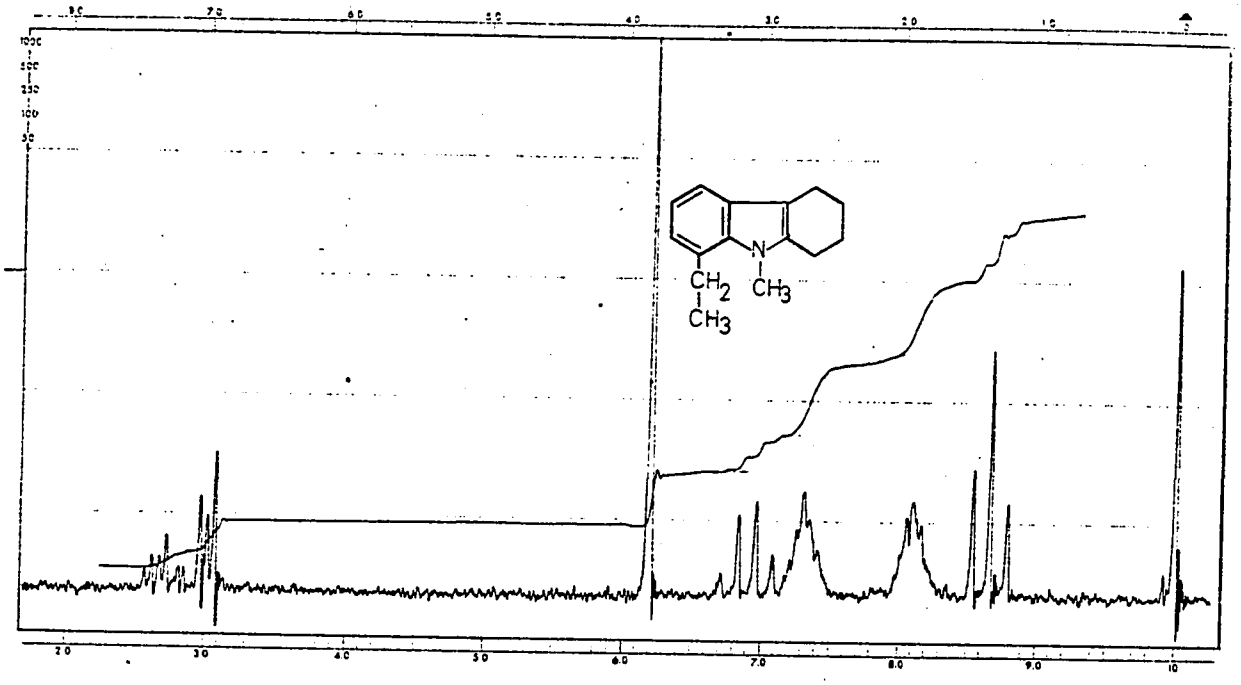


Fig. 17. N.m.r. spectrum (60 MHz) of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole in $CDCl_3$. Reference, tetramethylsilane.

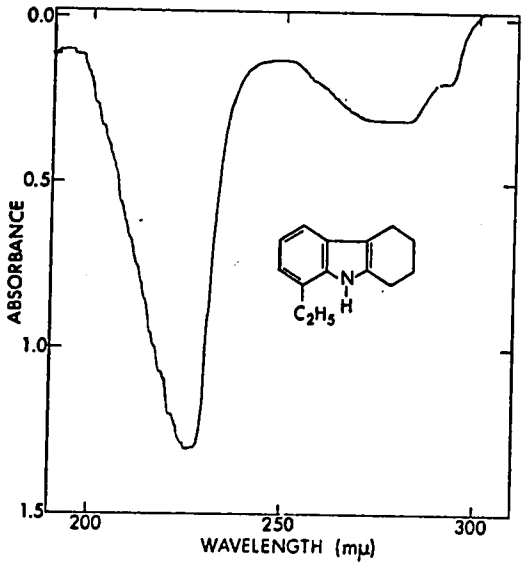


Fig. 18. U.v. spectrum of 8-ethyl-1,2,3,4-tetrhydrocarbazole in cyclohexane.

The n.m.r. spectrum (Fig. 19) in $CDCl_3$ supported the structure. It showed signals at τ 2.6-3.2 (3H, aromatic, multiplet), τ 2.4-3.2 (1H, for NH, broad, identified by deuterium exchange), τ 7.26 (quartet, 2H for methylene group of this ethyl moiety, J=7.5 Hz), two multiplets at τ 7.0-7.5 and τ 7.9-8.4 (8H for the tetrahydro ring), τ 8.70 (3H, triplet for $\underline{CH_3}$-CH_2-, J=7.5 Hz).

The methylation of this 8-ethyl-1,2,3,4-tetrahydrocarbazole could not be effected, and in all attempts the starting material was recovered in good yield. This is attributed, as discussed in section B, to the steric hindrance offered by the ethyl group present at position 8 of the tetrahydrocarbazole.

N-Methyl-2,6-diethylphenylhydrazine hydrochloride was condensed with cyclohexanone in refluxing benzene for 4 hours. A white solid was isolated which was filtered off and shown by its n.m.r. spectrum to be mainly ammonium chloride contaminated with a small amount of methylamine hydrochloride.

The filtrate after separation of the above solid, was freed from solvent to furnish a 38% yield of the pure 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole.

The formation of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole is rationalized by the pathway (Scheme IV) similar to that proposed for the formation of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole. The formation of methylamine in this condensation is explained by the pathway similar to that as illustrated in Scheme V.

These results support the observations recorded in the

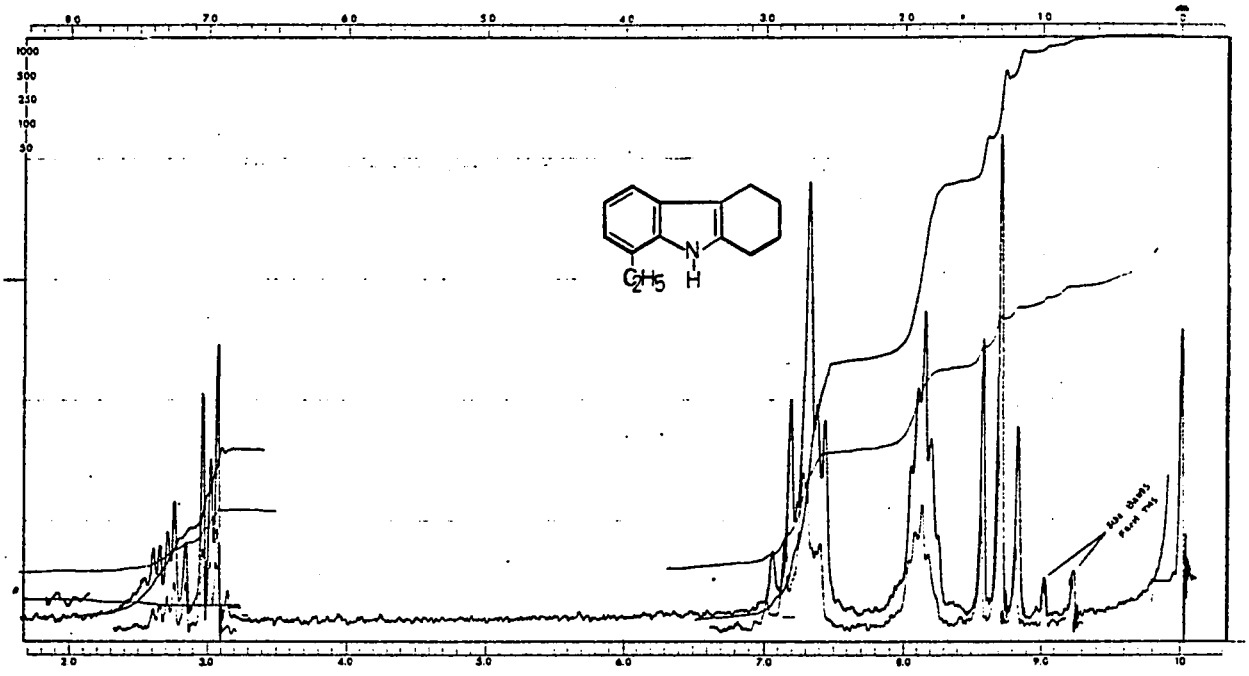
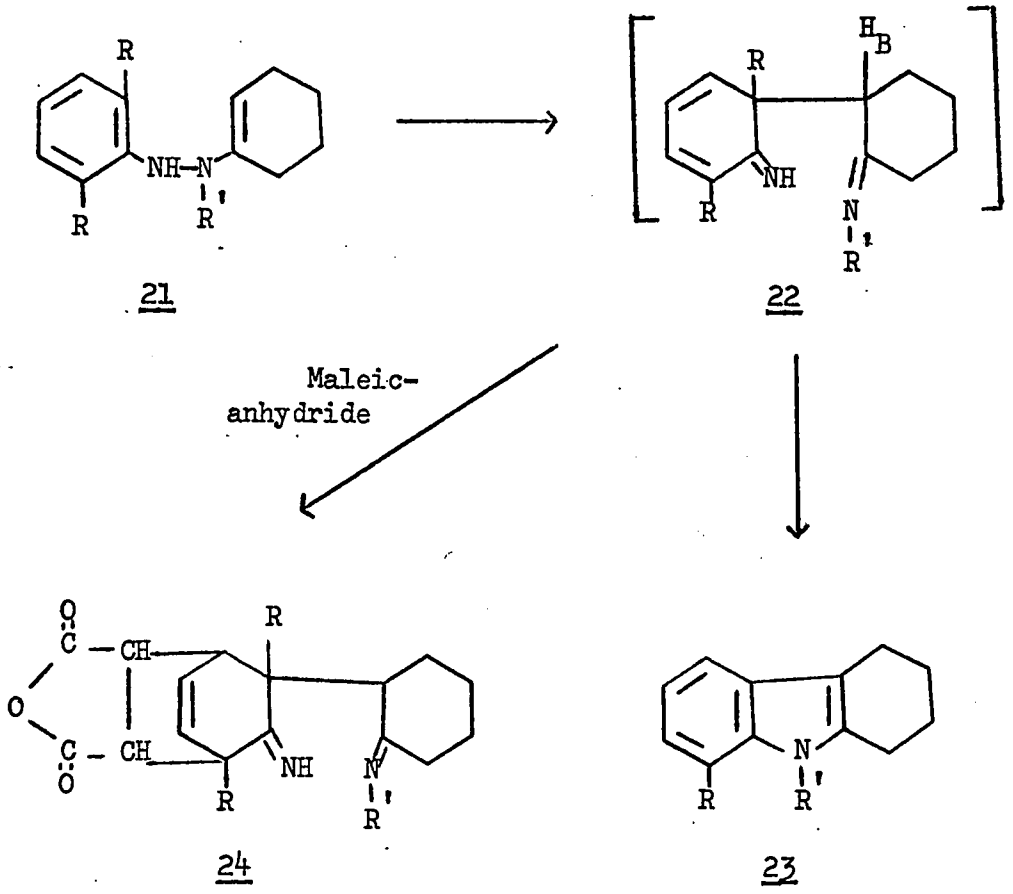


Fig. 19. N.m.r. spectrum (60 MHz) of 8-ethyl-1,2,3,4-tetrahydrocarbazole in $CDCl_3$. Reference, tetramethylsilane.

previous sections dealing with the condensation of cyclohexanone with N′-methyl-2,6-dimethylphenylhydrazine (section A) and with N′-ethyl-2,6-dimethylphenylhydrazine (section B).

D(i). Experiments at room temperature and reduced pressure.

In sections A, B, C, N-alkyl-2,6-dialkylphenylhydrazine was condensed with cyclohexanone in refluxing benzene and water was removed azeotropically in the Dean-Stark apparatus (122a). It was thought that these reaction conditions, previously advocated for the formation of enamines (124), would also lead to the isolation of the corresponding enehydrazine 21, Scheme VII.



Scheme VII

However, no compound corresponding to the enehydrazine 21 could be isolated under these enamine formation conditions. This is perhaps due to the vigorous reaction conditions employed as well as due to the inductive effect of the N'-alkyl group which would facilitate the cleavage of the N-N bond to cause the enehydrazine to rearrange to the further structures as shown in Scheme VII. It was thought that it might be possible to isolate the enehydrazine if the above reactants were condensed at room temperature and water removed under vacuum. Thus, N'-methyl-2,6-dimethylphenylhydrazine was condensed with cyclohexanone by following this procedure. A yellow oil was obtained which showed a strong tendency to decompose and therefore, could not be analyzed. Its i.r. spectrum (film) showed two new absorption bands at 1630 cm^{-1} and 1660 cm^{-1}. These two bands could be ascribed to the carbon-carbon double bond (non-conjugated, (121h)) expected in the enehydrazine 21 (R = R' = CH_3). However, no vinyl proton was discernible in the n.m.r. spectrum (in $CDCl_3$) between τ 4.0-5.4. The vinyl proton in the 1-morpholinocyclohexene-1 appears at τ 5.4 and its infrared spectrum (film) shows C=C abosrption at 1645 cm^{-1}. The lack of the vinyl proton signals could be due to the low concentration of the enehydrazine in the reaction mixture. Further, all attempts either to isolate the pure sample of the enehydrazine or concentrate the latter in the reaction mixture by column chromatography, were unsuccessful. The oil showed no evidence for the presence of dienone-imine 22 (R = R' = CH_3) in it (indicated by the absence of signals for the olefinic protons between τ 4-4.8 in the n.m.r. spectrum).

D(ii). Use of maleic anhydride to trap the dienone-imine intermediate.

It is apparent from sections A, B, C that dienone-imine intermediate 22, Scheme VII, could not be isolated. It was thought that it might be possible to trap it as its Diels-Alder adduct with maleic anhydride. Thus, maleic anhydride was added to the yellow oil obtained above in D(i) and the reaction mixture (in benzene) warmed gently to 40-50°. At this temperature, the reaction mixture started becoming dark and showed signs of decomposition. The solvent was removed completely at 50° and the remaining dark oil chromatographed on neutral alumina. By this procedure, ~10% of the pure 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole 23 ($R=R'=CH_3$) could be isolated. No other product corresponding to the Diels-Alder adduct 24 ($R=R'=CH_3$), could be crystallized out or separated by chromatography from the remaining dark oil. Similar results were reported by Carlin et al (72) when ethyl pyruvate 2,6-dimethylphenylhydrazone was treated with maleic anhydride.

Thus all attempts to isolate the dienone-imine intermediate 22 or its Diels-Alder adduct 24 ($R=R'=CH_3$), were unsuccessful. This is probably due to the presence of an enolizeable hydrogen H_B in 22 which makes it less stable. It is quite possible that this enolizeable hydrogen H_B provides a 'driving force' for 22 to decompose to the aromatic reaction product 23 rather than to stay as such in the reaction mixture or form the Diels-Alder adduct 24 ($R=R'=CH_3$).

PART II

From Part I, it is clear that although the dienone-imine intermediate 22 could not be isolated, the products, i.e. 23, of the reaction could only be explained through its intermediacy (Schemes IV and V) and by the loss of an alkyl group by an unknown route. The preference for the route (Scheme IV) which gives only ammonia is due to the easily removable H (also discussed in Section D(ii) of Part I) on the carbon atom, α- to the imino carbon of the former cyclohexanone ring. If that proton were replaced by a CH_3 which is less readily lost as compared to H, then we might slow down the reaction sufficiently to be able to isolate the dienone-imine intermediate. This would require 2,6-dimethylcyclohexanone. Since this compound was not readily available, a substitute, isobutyraldehyde was used in its place.

The above reactants, e.g. isobutyraldehyde and N-methyl-2,6-dimethylphenylhydrazine hydrochloride were condensed in refluxing benzene for 10-14 hours using a Dean-Stark water trap. The amount of water which was collected showed that 90% of the reaction had gone at least to the enehydrazine formation stage. The insoluble precipitate, which resulted from this condensation, was filtered off and crystallized from 95% ethanol in 40% yield, m.p. 186°. This hydrochloride analyzed correctly for $C_{13}H_{21}N_2Cl$ and was neutralized with 1% $NaHCO_3$ to give a free base. The latter analyzed correctly for $C_{13}H_{20}N_2$.

The formation of this hydrochloride and free base, is

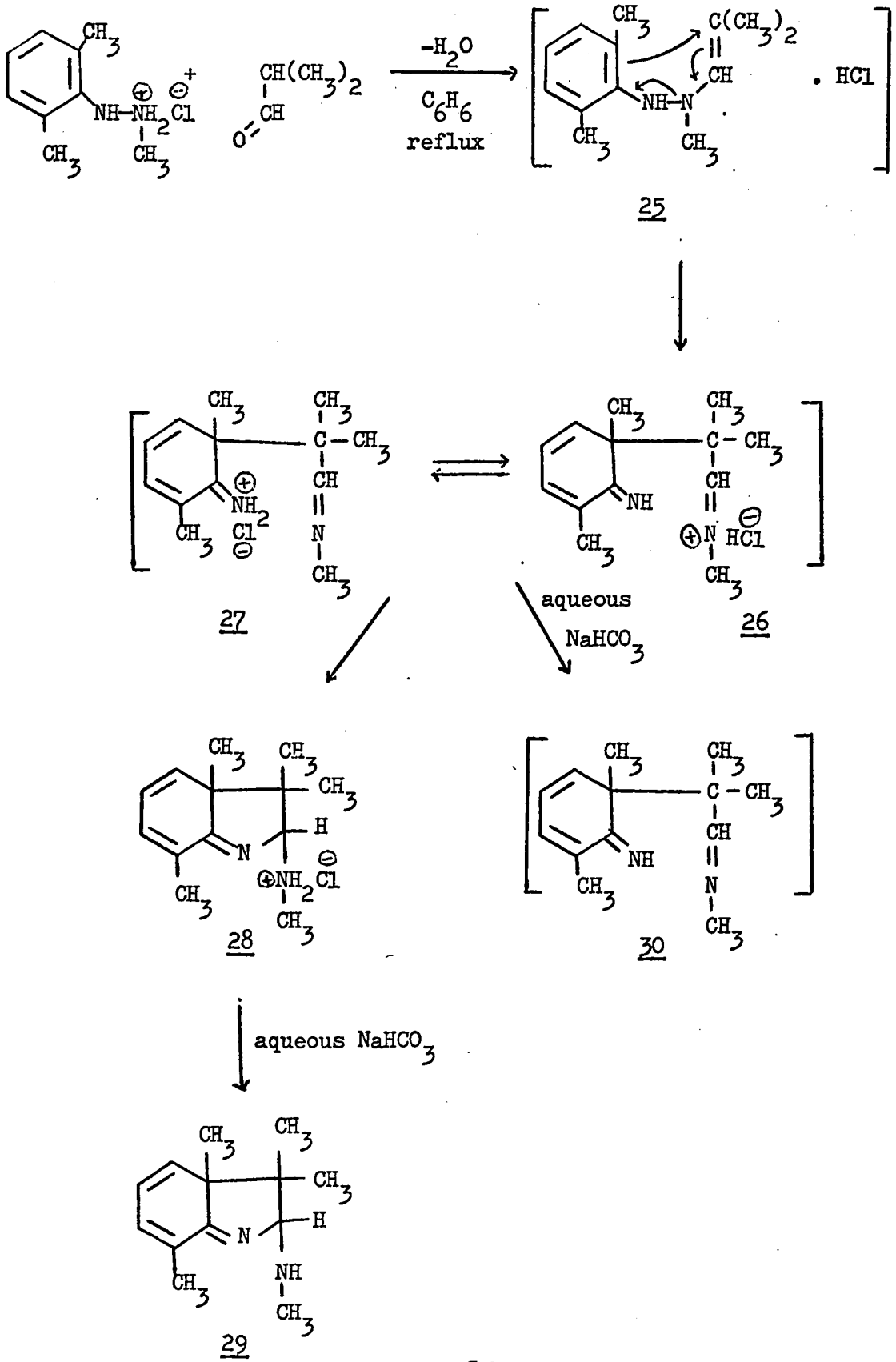
illustrated in Scheme VIII. Again, it involves the intervention of a dienone-imine (the free base 30 or the hydrochloride 26 or 27). In this case there is no methine proton, which prevents the imine 30 from re-arranging to an enamine so that the resulting amino group can add to the imino unit and thus produce an indole structure.

The above scheme predicts two possibilities. The reaction may give the dienone-imine hydrochloride 26 or 27 (which will give the dienone-imine 30 on neutralization with aqueous $NaHCO_3$). This is the usually accepted structure of the intermediate dienone-imine (cf. 4, Scheme I) of the Fischer indole synthesis. However, as Scheme VIII suggests, it may proceed further to the formation of the hydrochloride 28 (which will give structure 29 on neutralization with aqueous $NaHCO_3$). These structures, 28 and 29, represent another dienone-imine which may be obtained.

The following spectroscopic evidence (i.r. and u.v.) and the chemical analysis support either structures 26, 27, or 28 (30 or 29 as the free base).

1. As stated before, the dienone-imine hydrochloride analyzed correctly for $C_{13}H_{21}N_2Cl$ and the free dienone-imine for $C_{13}H_{20}N_2$.
2. The infrared spectrum (in Nujol) for the hydrochloride showed a strong band at 1575 cm^{-1} (conjugated C=C and C=N stretching (121c)). A weak though sharp band at 2240 cm^{-1} and a broad band at 2700-2790 cm^{-1} indicated $\overset{\oplus}{N}H$ (121i). Faint absorption in a broad band at 3400 cm^{-1} supported NH (bonded).

The infrared spectrum of the free imine in Nujol showed a sharp weak band at 3330 cm^{-1} (NH) and a sharp medium band at


-H2O
C6H6
reflux
• HCl
25
27
26
aqueous
NaHCO3
28
30
aqueous NaHCO3
29

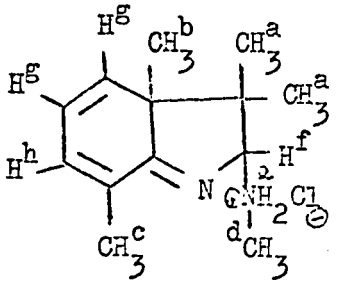
Scheme VIII

1630 cm^{-1} (C=N) and a strong band at 1585 cm^{-1} (conjugated C=C or C=N).

3. The ultraviolet absorption spectrum (Fig. 20) of the hydrochloride in 95% ethanol, showed a narrow band at λ_{max} 205* mμ (ε, 15,390) and a broad band at λ_{max} 320 mμ (ε, 5290).

The ultraviolet spectrum (Fig. 21) of the free base in 95% ethanol showed a narrow band at λ_{max} 204* mμ (ε, 6490) and a broad band, λ_{max} 310 mμ (ε, 3155).

4. However, the 100 MHz n.m.r. spectrum (Fig. 22) of the hydrochloride and that of the free imine (Fig. 23) clearly showed that the compounds under consideration possessed the structure 28 (for the hydrochloride) and 29 (for the free dienone-imine), and not the respective structures 26 or (27) and 30. This is shown in the following analysis of the spectra (Figs. 22 and 23). For convenience, the structures 28 and 29 are labelled as below.



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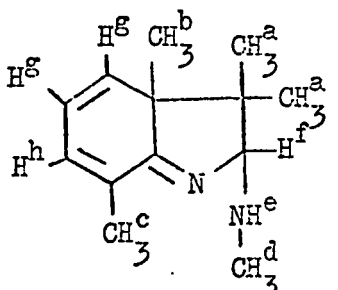


29

* strong end absorptions due to the limitations of our instrument.

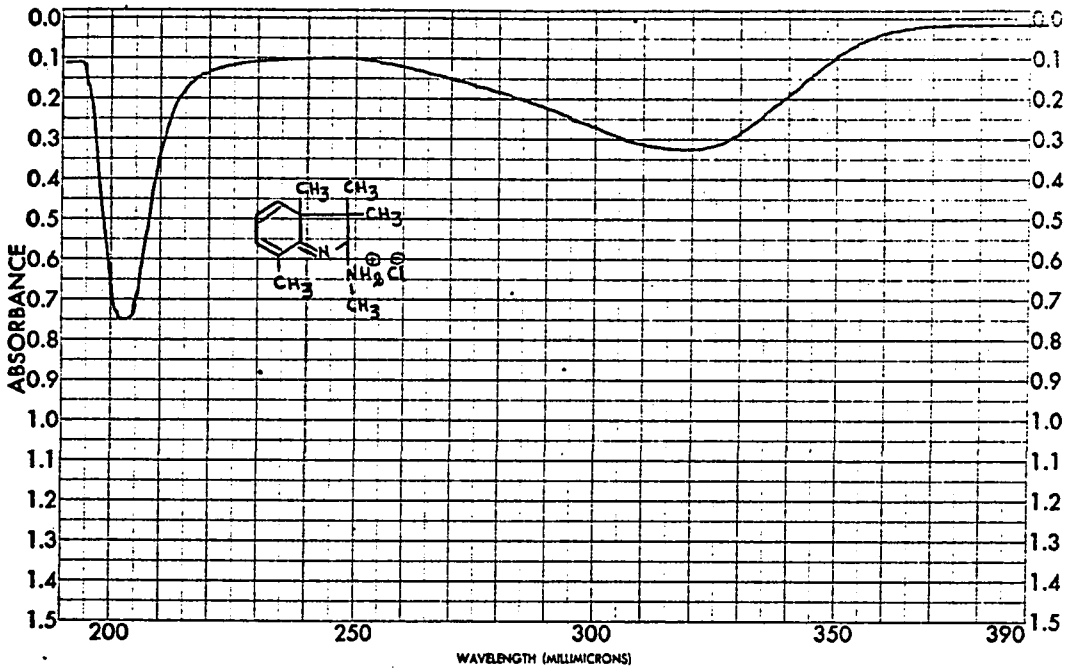


Fig. 20. U.v. spectrum taken in 95% ethanol.

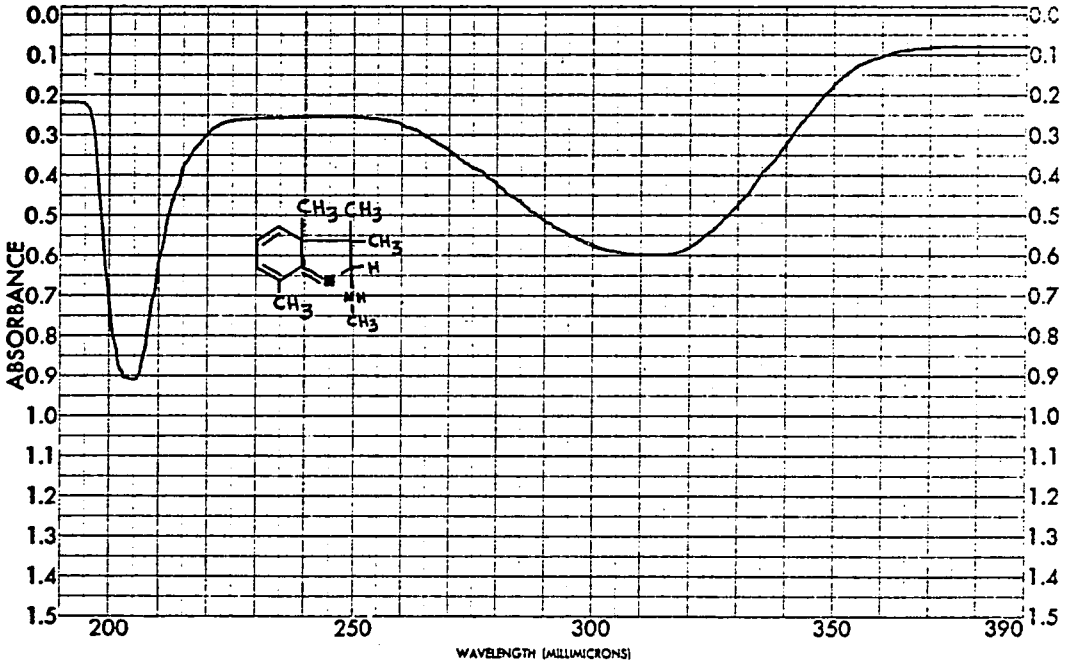


Fig. 21. U.v. spectrum taken in 95% ethanol.

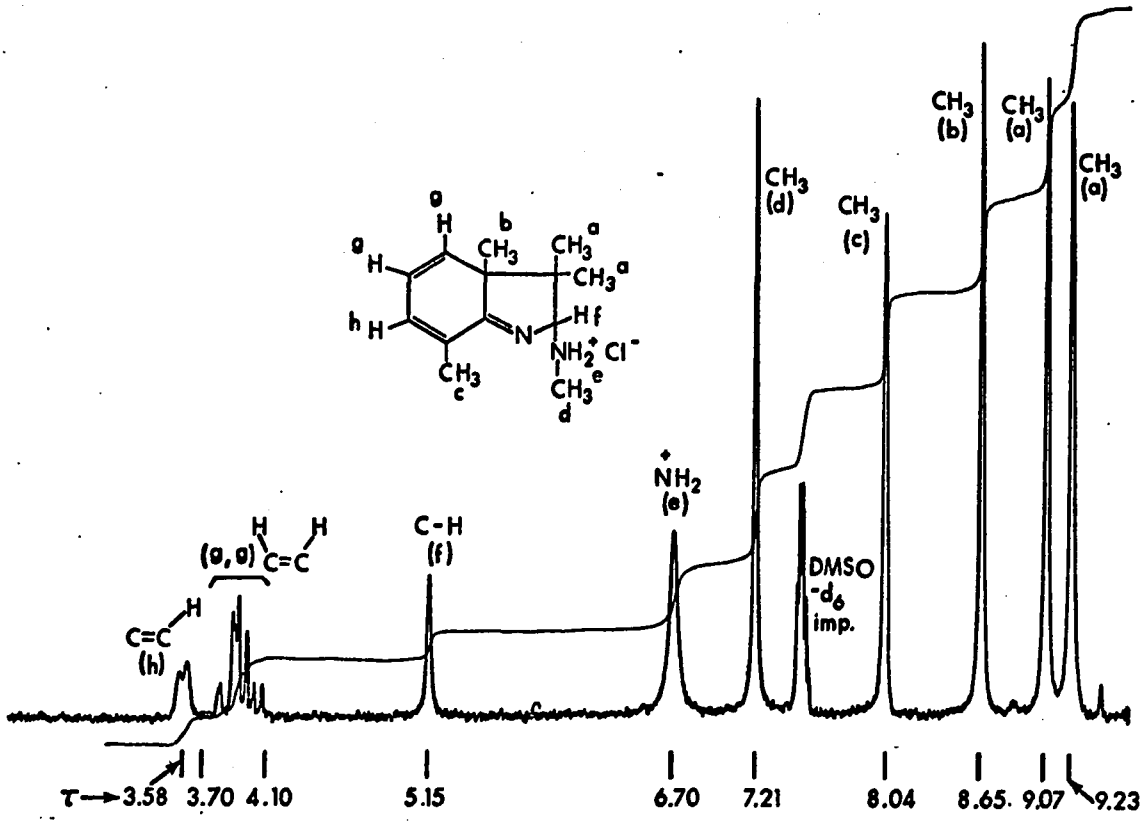


Fig. 22. N.m.r. spectrum (100 MHz) taken in dimethylsulfoxide-d_6. Reference, tetramethylsilane.

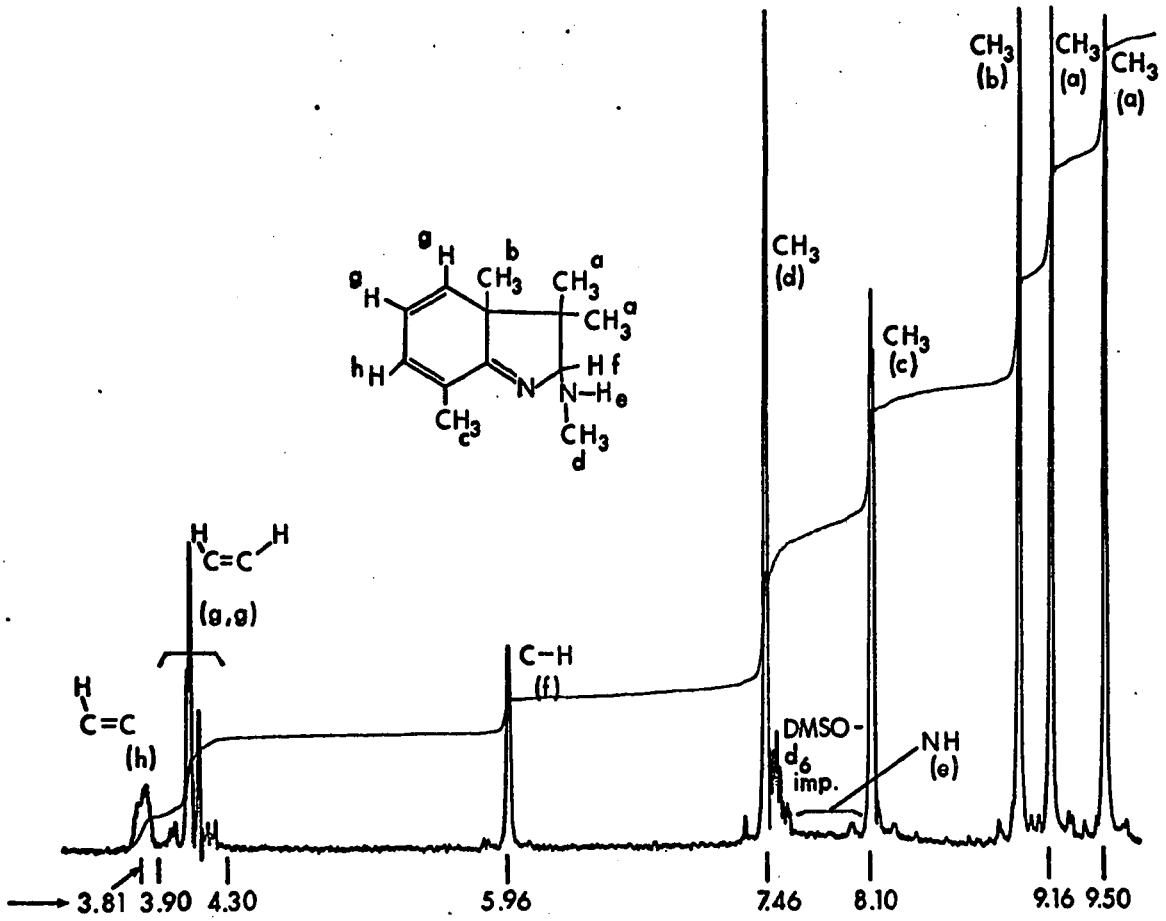


Fig. 23. N.m.r. spectrum (100 MHz) taken in dimethylsulfoxide-d_6. Reference, tetramethylsilane.

(i) The three high field singlets (τ 8.6-9.6), each representing three protons, were assigned to the three aliphatic methyl groups a, a, b. The protons of the two methyl groups a,a, because of their different environment should have different chemical shifts, as was observed. These are time averaged because of the rotatory oscillation (limited) of this gem-dimethyl group. A sufficient decrease in the rate of this oscillation should cause a broadening of each of the signals, with eventual formation of a doublet because of an adjacent asymmetric center for each. When an ethanol-d_6 solution of either the amine or the hydrochloride was cooled to $< -40^{\circ}$, the two highest field singlets (a,a) did broaden increasingly until a temperature of -90° was obtained. The signals for the protons of the methyl group b broadened only very slightly under these conditions. At this temperature, precipitation from the solution occurred, thus imposing a limit to this resolution. The observed broadening, however, did support the assignment of the two highest field signals to the methyl groups labelled a,a (Figs. 22 and 23). The remaining high field signal, b, must then be due to the protons of the methyl group attached to the sp^3 hybridized carbon of what was formerly the aromatic ring.

(ii) The signal (3H) lying between τ 8.04-8.10 (Figs. 22 and 23) was assigned to the protons of the methyl group c since this is the region expected for the signals of protons of a methyl group attached to carbon-carbon double bond.

(iii) The singlet, d, (3H) in the region τ 7.0-7.4 was assigned to the N-CH_3 group.

(iv) The narrow multiplet (1H) centered at τ 3.58 (Fig. 22) and 3.81 (Fig. 23) was assigned to proton h. Support for this was obtained from the finding that the proton irradiation at τ 3.81 (Fig. 23) caused a collapse of a narrow doublet at τ 8.10 to a singlet with loss of coupling of 1.7 Hz. In turn, irradiation at τ 8.10 clearly simplified the multiplet at τ 3.81 but had little effect on the multiplet at τ 3.95-4.3 assigned to the protons g,g. It is expected that stronger coupling would occur between the protons of the methyl group c and proton h than between c and protons g,g.

(v) The singlet (2H at τ 6.70, Fig. 22) was assigned to the NH proton and the proton of the hydrogen chloride since this signal disappeared when deuterium oxide was added. This proton in the free amine (Fig. 23) gives a broad low signal over a range τ 7.4-8.2 which is eliminated on deuteration. The spectrum of the free amine in $CDCl_3$ showed the N-H proton as a broad singlet, $w/2 \sim 3.5$ Hz at τ 8.65.

(vi) The signal (1H) at τ 5.15 (Fig. 22) and at τ 5.96 (Fig. 23) was due to the former aldehyde proton f. This proton f is coupled with h ($J=0.7$ Hz). However, no coupling could be detected between protons f and e and apparently, this is due to the rapid exchange involving the N-H proton.

The following features of the n.m.r. spectrum (as discussed above) clearly show that 28 (or 29 for the free amine) is the structure of the isolated compound.

(a) The signal for the protons of N-H and hydrogen chloride (Fig. 22) is a singlet (integration, 2H) at τ 6.70 (see 'v' above). This indicates that these two protons (i.e., N-H and HCl) are in the same electronic

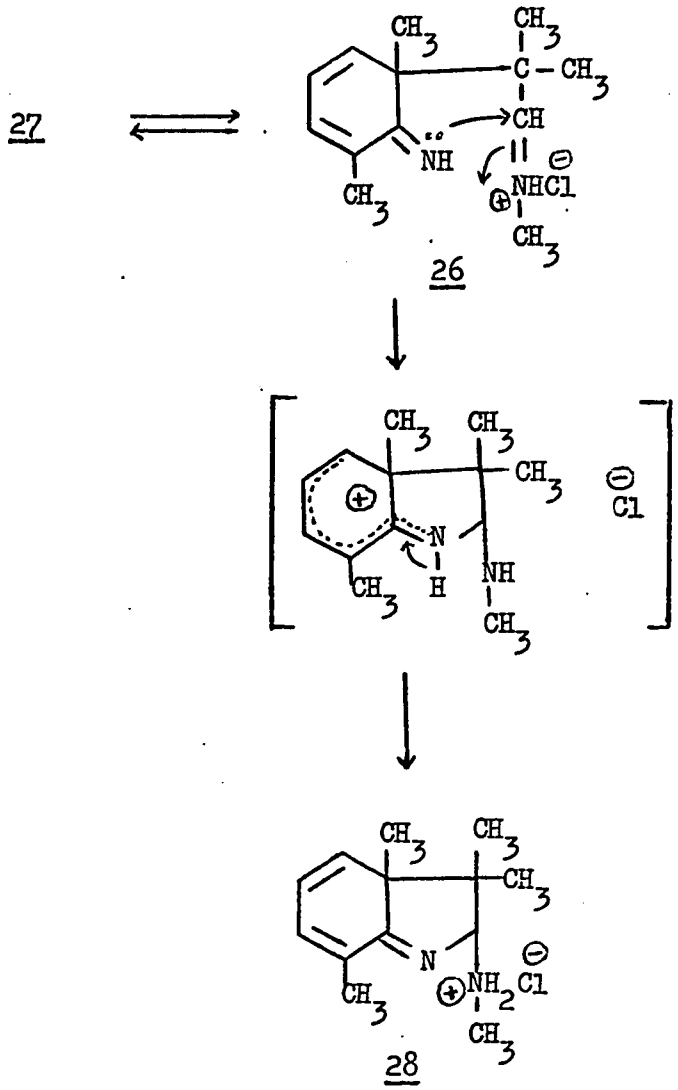
environment. This observation is explained only if the structure 27 or 28 is assigned to the hydrochloride. Structure 26 would be expected to show these two protons at different chemical shifts because they are in different electronic environments.

(b) The signal (1H) for the former aldehydic proton (see 'vi' above) appears at τ 5.15 for the hydrochloride (Fig. 22) and at τ 5.96 for the free amine (Fig. 23). This signal position is at much too high a field strength to be due to the aldehydic proton represented by the aldimine structures in the hydrochloride 26, 27 or the free dienone-imine 30. The signals for such protons are found at low field — in the region τ 0.7-1.8 (125). However, if the structure 28 for the hydrochloride and 29 for the dienone-imine free base is accepted, the chemical shift of this methine proton in the region τ 5-6 is explicable. Since in structures 28 and 29, this proton is very much like the anomeric protons in the glucosides or the acetals (-O-CH-O-), it is expected to produce a signal in a part of the n.m.r. spectrum ($\sim\tau$ 5-7) where such anomeric protons are found to absorb (126a, 126b).

(c) The long-range coupling (of 0.7 Hz) through six bonds (see 'vi' above) between protons f and h can be rationalized by structures 28 and 29 and not by structures 26, 27 and 30.

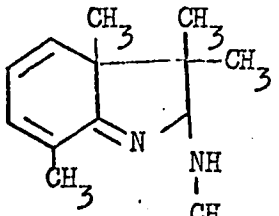
From the foregoing evidence, it is clear that the condensation of N-methyl-2,6-dimethylphenylhydrazine hydrochloride with isobutyraldehyde, leads to the formation of a dienone-imine hydrochloride of structure 28 which on neutralization with aqueous $NaHCO_3$, furnishes the dienone-imine of structure 29 (Scheme VIII).

That the dienone-imine 28 (or 29) was obtained rather than the expected dienone-imine 26, 27 (or 30) is probably due to the fact that in the presence of HCl, the methylimino group is protonated. This catalyses attack by the =N-H group, with subsequent migration of the proton to the methylamino group, as shown below.



PART III

From Part II, a dienone-imine 29 had been isolated from the reaction of N-methyl-2,6-dimethylphenylhydrazine hydrochloride with isobutyraldehyde.

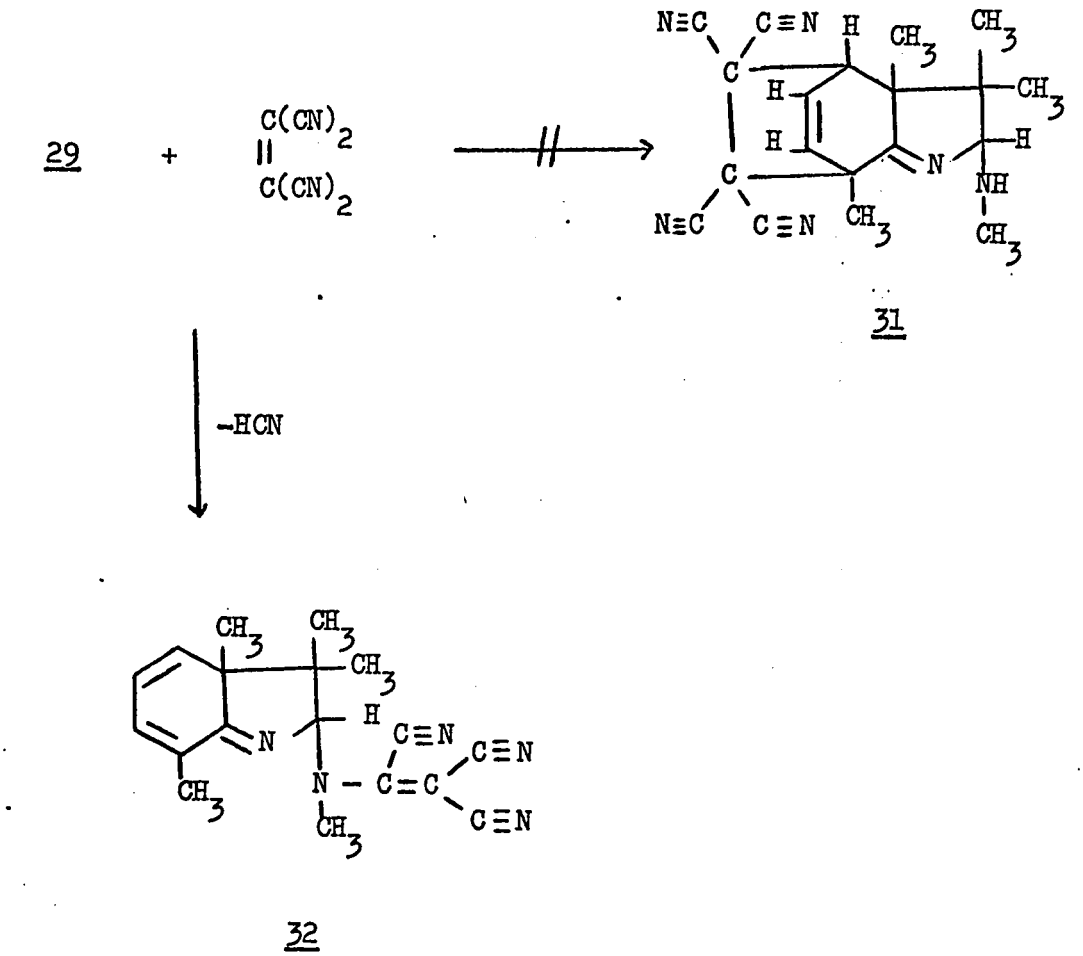


29

The work in this part deals with its chemical properties. Of the number of reactions attempted, only those which have produced isolable compounds will be described.

A. Reaction with tetracyanoethylene.

Dienone-imine 29 has a conjugated triene system. In addition, it possesses a secondary amino group. It was thought that because tetracyanoethylene has been reported as a good dienophile for the conjugated dienes (126c), its reaction with 29 would lead to the formation of Diels-Alder adduct 31, Scheme IX. When dienone-imine 29 was treated with tetracyanoethylene, it gave a Michael-type condensation product 32 (after elimination of HCN) rather than the Diels-Alder adduct 31, as shown in Scheme IX. This behaviour of tetracyanoethylene is similar to its reactions reported (127) with primary and some secondary amines.



Scheme IX

The product gave the correct elemental analysis for $C_{18}H_{19}N_5$ (structure 32) and showed the following spectroscopic properties.

Its infrared spectrum in Nujol showed absorption bands at 2220 cm^{-1} (-C≡N, strong) (121e), a sharp band of medium strength at 1630 cm^{-1} (C=N) and a strong broad band at 1565 cm^{-1} (conjugated C=C or C=N).

Its u.v. spectrum in 95% ethanol showed a narrow band at

λ_{max}, 207 mμ(ε, 11300) and a broad band at λ_{max}, 335 mμ(ε, 15250).

The n.m.r. spectrum (Fig. 24) of this product 32 showed signals at τ 3.35-3.5 (1H, broad multiplet) and at τ 3.78-3.98 (2H, multiplet) for the three olefinic protons; τ 4.04 (1H, singlet, former aldehydic proton), τ 6.55 (3H, N-$\underline{CH_3}$, singlet), τ 7.88 (3H, C=C-$\underline{CH_3}$, doublet), τ 8.63 (3H, C=C-C-$\underline{CH_3}$, singlet), and at τ 8.95 (3H, singlet), τ 9.28 (3H, singlet) for the protons of two aliphatic methyl groups.

The salient features of the above spectral analysis, which supported structure 32 and excluded 31 are listed below.

1. The infrared spectrum showed the absence of N-H absorptions, which supports structure 32 rather than 31. The latter, if it were formed, should have shown the N-H absorption at 3300-3500 cm^{-1} (121a) in the infrared spectrum.

2. The electronic environment of the olefinic protons in the starting material 29 is the same as that in product 32 but different from that in the Diels-Alder adduct 31. Thus, if product 31 were formed, it should show a different chemical shift for the olefinic protons as well as for the bridgehead proton from the corresponding chemical shifts of the olefinic protons in the starting material.

The fact that the n.m.r. spectrum of the condensation product has a pattern of signals as well as chemical shifts of the olefinic protons closely comparable with that of the starting material (compare Figs. 23 and 24), supports structure 32 and discards the possibility of 31.

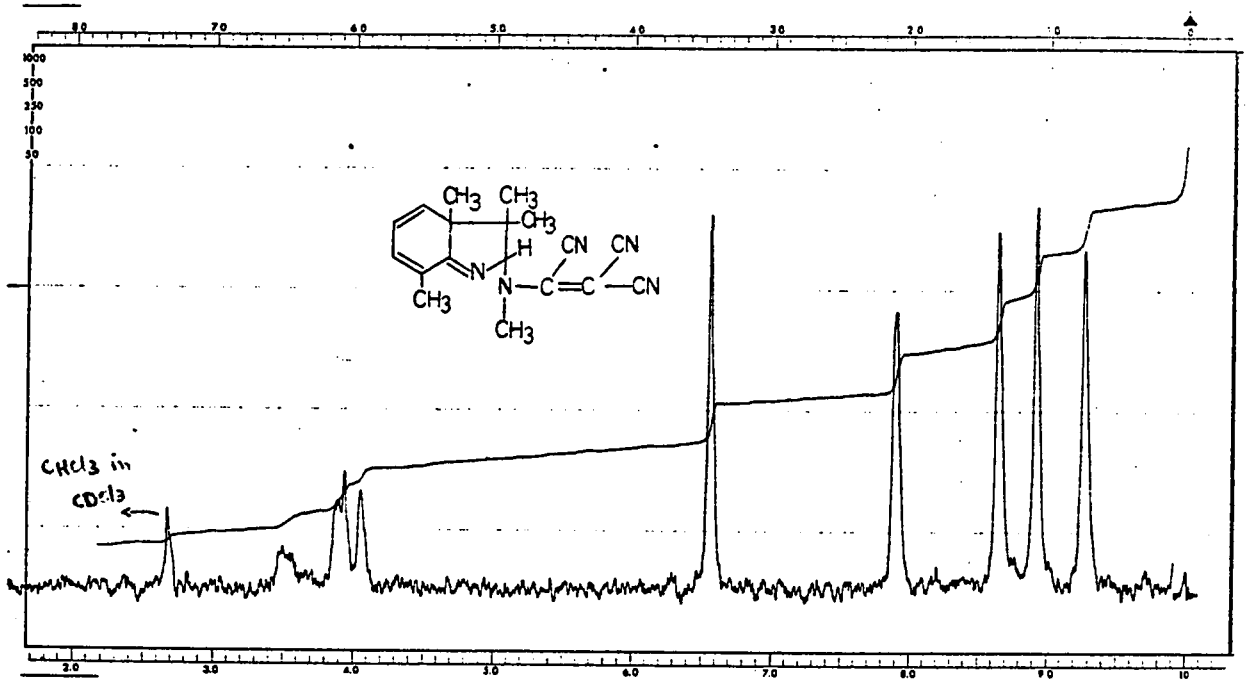


Fig. 24. N.m.r. spectrum (60 MHz) taken in $CDCl_3$. Reference, tetramethylsilane.

3. The tetracyanoethane group in 31 would not effect the chemical shift of the former aldehydic proton whereas in product 32, the tricyanoethylene group could exert a significant effect on the chemical shift of this proton. The fact that the signal of this former aldehydic proton goes from the position τ 5.96 to τ 4.04 (compare Figs. 23 and 24), supports product 32 and rules out the possibility of 31.

4. Product 31 has an exchangeable proton (i.e., $\rangle$N-H) whereas product 32 does not possess such a proton. The n.m.r. spectrum showed the absence of any exchangeable proton (demonstrated by the addition of D_2O) and thus supported structure 32.

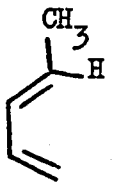
5. The u.v. spectrum of the reaction product (as discussed above) is quite similar to the u.v. spectrum of the starting material 29. This supports structure 32.

From the foregoing evidence, it is confirmed that we have the Michael condensation product 32 and not the Diels-Alder adduct 31. This shows that Michael condensation proceeds in preference to the Diels-Alder reaction.

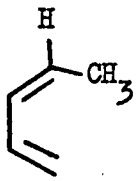
When the reaction was conducted with a two molar equivalent of tetracyanoethylene (one mole would give the Michael condensation and the other would form the Diels-Alder adduct), a lot of tar-formation occurred. Similar results were obtained when product 32 was treated with equivalent amount of tetracyanoethylene. Hence further attempts in this direction were abandoned.

It is interesting that the Diels-Alder adduct 31 could not be obtained under these reaction conditions. The two methyl groups adjacent to the conjugated triene should have activated (128) the triene

system but at the same time could create steric problems (129a, 129b) also. It is known that if a methyl group projects in the direction of approach of the diene to the dienophile, then it opposes (129a) normal condensation. For example, trans-piperylene undergoes while the cis-isomer does not undergo normal diene condensation (129b).



trans-piperylene



cis-piperylene

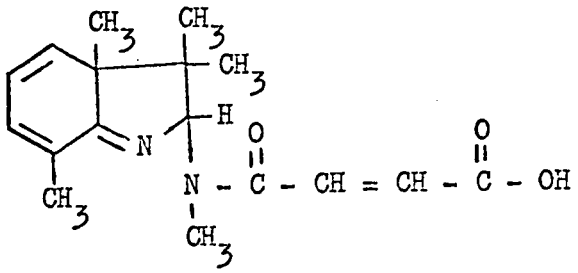
Similarly, the diene-condensation (129a) with 4-methyl-1,3-pentadiene fails and results in the formation of a copolymer.

B. Reaction with maleic anhydride.

Treatment of maleic anhydride with this dienone-imine 29 gave a product which was gelatinous, dark yellow and showed tendencies of decomposition. This product showed a strong tendency to decompose. Accordingly, no satisfactory analysis could be possible on this product.

The infrared spectrum of this product in Nujol showed absorptions at 3400-3500 cm^{-1} (broad, OH), 2600 cm^{-1} (broad, OH stretching) (121f), 1715 cm^{-1} (strong, α,β-unsaturated C=O) (121f).

The n.m.r. spectrum of this product in $CDCl_3$ showed it to be a mixture of many components. However, the appearance of an additional doublet at τ4.05 (CH=CH-$\overset{O}{\overset{\|}{C}}$-), an exchangeable proton at τ0.3 (in another run at τ -1.2) in the n.m.r. spectrum and the absence of N-H absorption in the i.r. spectrum of this product indicated that a compound of structure 33 might be present in the mixture.



33

C. Reaction with acetyl chloride.

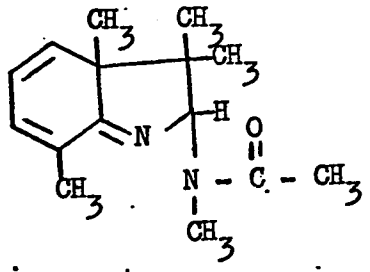
The acetylation of this dienone-imine 29 was also carried out. The yellow oil obtained was crystallized from methanol-water mixture to give a poor yield (~ 5%) of a solid, melting at 71-74°.

The infrared spectrum in CCl_4 showed the absence of N-H absorption but did show a strong absorption at 1650 cm^{-1} (amide) (121g).

The n.m.r. spectrum of this crude material in $CDCl_3$ showed signals at τ 3.7 (2H, one olefinic proton and one methine (aldehydic) proton, broad singlet, w/2 ~ 5 Hz), τ 3.98-4.05 (2H, olefinic protons, broad doublet, J=4 Hz), τ 7.05 (3H, N-$\underline{CH_3}$, singlet), τ 7.85 (3H, -N-C(=O)-$\underline{CH_3}$, singlet), τ 7.95 (3H, C=C-$\underline{CH_3}$; narrow doublet), τ 8.8 (3H, the protons of the allylic methyl group, singlet), and at τ 8.98 and 9.35 (each for 3H, singlets, for the protons of the two aliphatic methyl groups). No exchangeable proton could be discernible in the n.m.r. spectrum (demonstrated by D_2O).

The presence as well of signals at τ 9.33 (singlet), τ 7.77 (singlet), τ 7.13 (singlet) in the above n.m.r. spectrum as well as the elemental analysis of this solid (m.p. 71-74) indicated that the product obtained from the acetylation of 29, contained ~ 2% of impurities in it.

However, from the above evidence, it is concluded that N-acetylation has occurred to give a main product which is believed to possess structure 34.



34

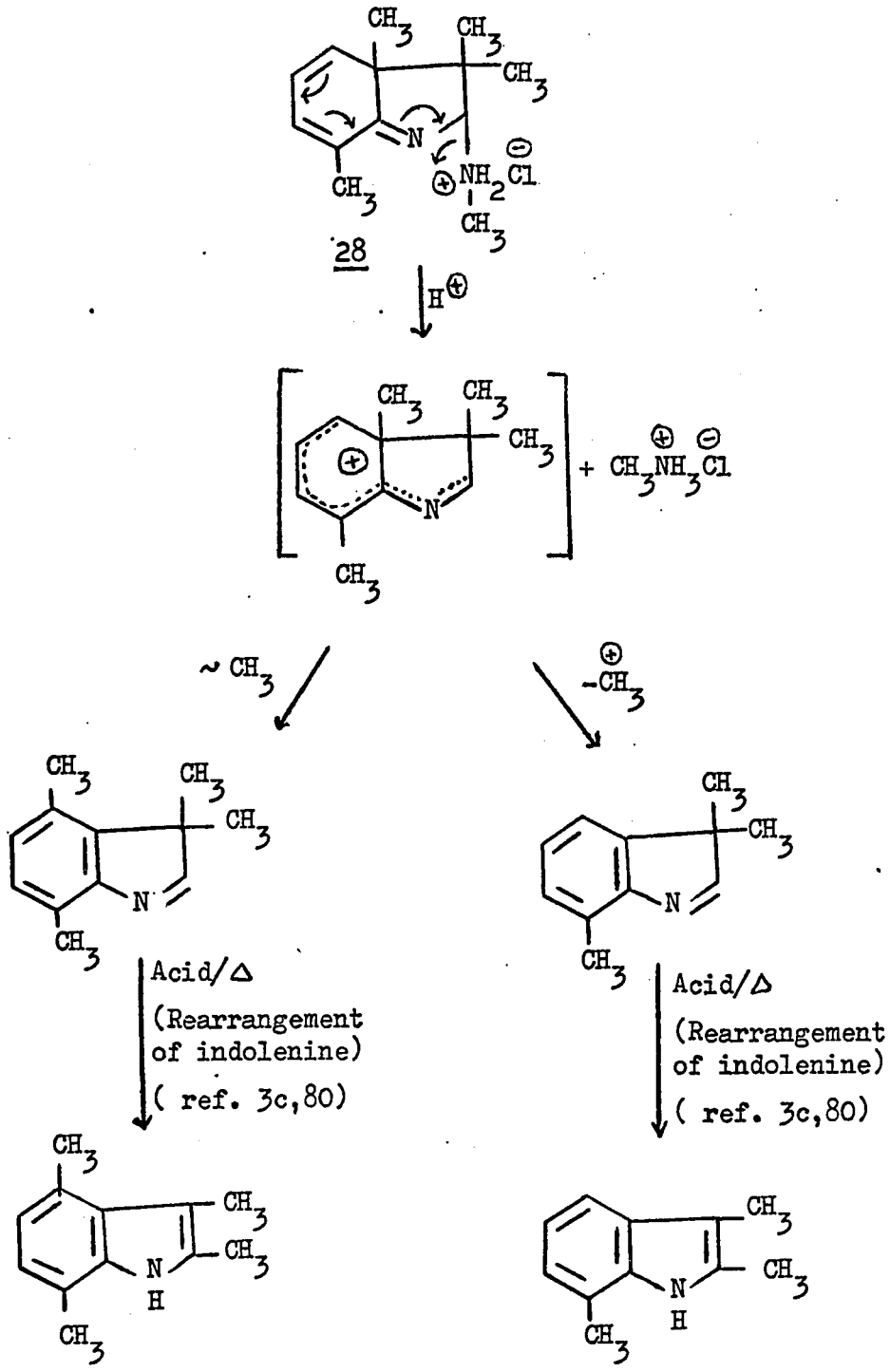
These reactions, thus illustrate the chemical behaviour of this dienone-imine 29 for the three reactions investigated.

PART IV

From Part II, it is evident that the dienone-imine intermediate has been isolated. However, the conversion of this dienone-imine to the final indole molecule was not accomplished. Such a conversion would constitute final proof that this dienone-imine was indeed an intermediate. Accordingly, the isolation of a dienone-imine and its conversion to the corresponding indole constituted the objectives of this part of the research.

The dienone-imine 29 isolated in Part II was subjected to the thermal conditions with $ZnCl_2$ in nitrobenzene(74b) and with hydrogen chloride in benzene (80) to discover whether the following type of rearrangement (Scheme X) to the corresponding indoles might be possible. However, under both these reaction conditions, decomposition of the dienone-imine took place and no product corresponding to the indoles shown in Scheme X could be isolated after the work-up of the reaction mixture. This showed that it was difficult to convert this dienone-imine 28 to the corresponding indoles. Hence attempts were made to find another dienone-imine which could be converted to the corresponding indoles under relatively mild conditions.

A. In the first attempt to obtain such a useful dienone-imine intermediate, it was thought that the condensation of cyclohexanone with N-methyl- 2,6-dimethylphenylhydrazine hydrochloride for a shorter period of time, would lead to the isolation of the dienone-imine intermediate which could be converted to the final indole molecule. When the above reactants were heated in refluxing benzene


28
Acid/Δ
(Rearrangement of indolenine)
(ref. 3c,80)
Acid/Δ
(Rearrangement of indolenine)
(ref. 3c,80)

Scheme X

for 10-12 minutes using the Dean-Stark water collection apparatus, 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole was obtained ~ 40% yield. This showed that under these conditions, it was difficult to obtain a dienone-imine intermediate and if the latter actually was formed, it apparently was quite unstable and proceeded readily to the tetrahydrocarbazole structures. It is well known that cyclohexanone phenylhydrazones are easily converted to the tetrahydrocarbazoles (25, 27a). Accordingly, it was felt that cyclohexanone was too reactive a carbonyl compound to provide us with an isolable dienone-imine.

The phenylhydrazones of less readily enolizeable ketones indolize with comparatively less ease (27a). Thus, acetaldehyde phenylhydrazone has not yet been cyclized to indole (50) and the phenylhydrazones of propionaldehyde (130, 131) when compared to that of cyclohexanone (25, 27a) required comparatively drastic conditions for their conversion to the final indole molecules. Therefore, it was felt that it might be possible to obtain better results with propionaldehyde as a carbonyl moiety rather than with cyclohexanone.

B. Propionaldehyde was condensed with N-methyl-2,6-dimethylphenylhydrazine hydrochloride in refluxing benzene for 19 hours, using the Dean-Stark water trap. Water was isolated, showing that the reaction had progressed at least to the enehydrazine stage.

A solid was isolated which was contaminated with dark, tarry materials. This solid was twice crystallized from 95% ethanol-ether

mixture (by solution in 95% ethanol and then addition of ether to faint turbidity). A colourless solid was obtained whose n.m.r. spectrum in D_2O showed it to be mostly ammonium chloride containing a small amount of methylammonium chloride.

The benzene solution, after removal of the above ammonium chloride by filtration, was freed from solvent and afforded a dark oil. When this was worked up and distilled, there was obtained a yellow oil, hereinafter called reaction product A.

Reaction product A was found to be a mixture of 1,3,7-trimethylindole and 3,7-dimethylindole. This was determined by the following evidence.

1. 1,3,7-Trimethylindole.

On crystallization from petroleum ether (b.p. 60-70°), this oily material (reaction mixture A) furnished a 32% yield of 1,3,7-trimethylindole.

The structure of the 1,3,7-trimethylindole was supported by its elemental analysis and by the spectroscopic evidence, illustrated below.

The infrared spectrum in CCl_4 showed no absorption in the N-H region.

The u.v. spectrum in n-hexane showed two bands — a sharp band λ_{max}, 226 mμ (ϵ, 39,200) and a broad band at λ_{max}, 281 mμ (ϵ, 6900). This u.v. spectrum was closely similar to that obtained for indole itself (132).

The n.m.r. spectrum (Fig. 25) in $CDCl_3$ provided clear

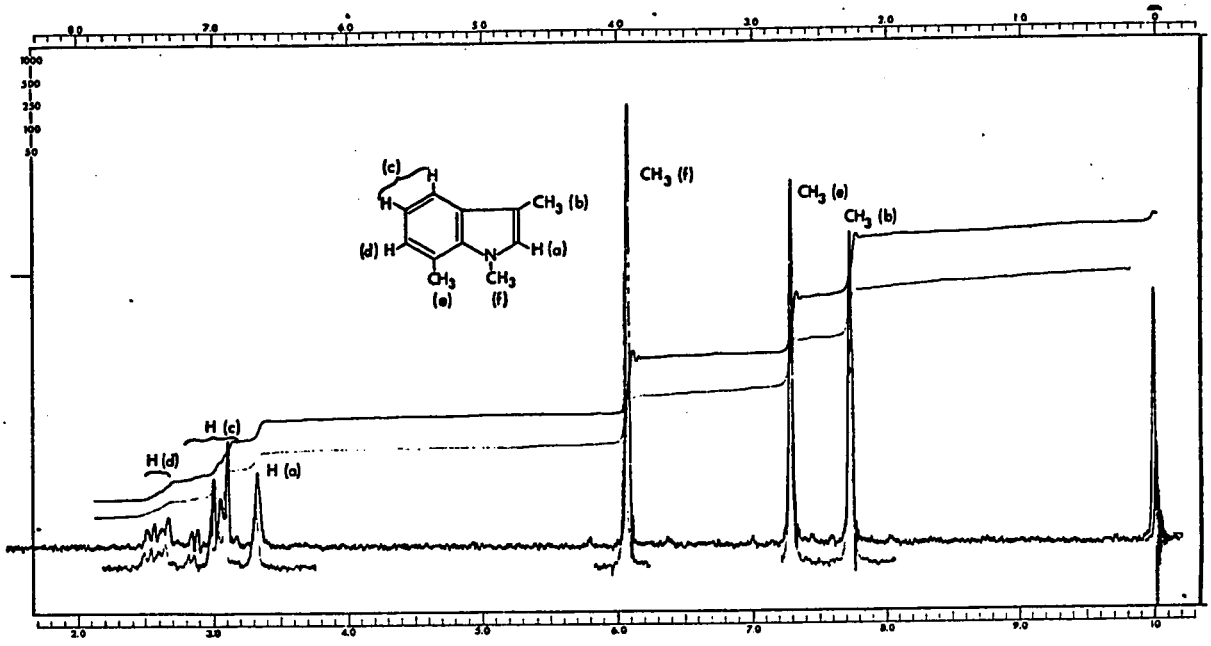
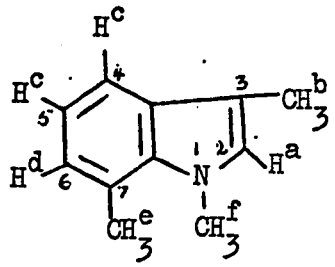


Fig. 25. N.m.r. spectrum (60 MHz) of 1,3,7-trimethylindole in $CDCl_3$. Reference, tetramethylsilane. Lower tracing obtained after the addition (with shaking) of a small amount of D_2O.

evidence that this was indeed 1,3,7-trimethylindole.



The three signals at τ 6.08 (singlet, 3H), τ 7.29 (singlet, 3H) and τ 7.73 (narrow doublet, 3H) are readily assigned to the N-methyl, C-7 methyl and C-3 methyl protons (f,e,b) respectively. The three aromatic protons (d,c) provide the multiplet at τ 2.5-3.2. The broad singlet at τ 3.32 is due to the C-2 proton (a). That C-2 rather than C-3 of the indole structure was unsubstituted, was corroborated by the large shift of the signal for this proton downfield to τ 3.05 ($\Delta\tau$ = 0.27) when the more polar solvent dimethylsulfoxide-d_6 was used. Such large signal shifts in the n.mr. spectrum due to the change in solvent are characteristic of the C-2 proton but not of the C-3 proton of the indole structure (133).

Spin-decoupling experiments (HR-100 MHz) supported the structure. Irradiation of the nucleus of H_a (τ 3.32) showed no effect on the signals of H_d (τ 2.5-2.7) but did cause a sharpening of the signals for the methyl group b at τ 7.73. Irradiation of the methyl protons, b, at τ 7.73 changed the broad singlet (w/2 ~ 3 Hz) at τ3.32 (H_a) to a sharp singlet. This, along with the solvent shift of

the signal for H_a when dimethylsulfoxide-$\underline{d}_6$ was used rather than $CDCl_3$ (133) provides evidence that H_a and CH_3 (b) give rise to the signals at τ 3.32 and τ 7.73 respectively. Irradiation at τ 7.29 (CH_3, $\underline{e}$) changed the multiplet at τ 2.5-2.7 to two doublets centered at τ 2.98 and τ 2.91 ($J \sim 2$ Hz) which are believed to be due to H_d (134). As well, some simplication occurred in the multiplet at τ 2.8-3.2 (protons c).

It was felt desirable to confirm the structure of 1,3,7-trimethylindole by an independent synthesis. The synthesis of 1,3,7-trimethylindole was achieved by the N-methylation of 3,7-dimethylindole. The synthesis of this latter compound has been reported previously (130, 131, 136). Our efforts to prepare 3,7-dimethylindole via cyclization of propionaldehyde $\underline{o}$-tolylhydrazone by following the published directions (130, 131) have not been successful. The directions given by Marion and Oldfield (130) led to an oil boiling in the range reported (130). However, the n.m.r. spectrum clearly showed that it was a mixture of substances. Of the several catalysts normally used to effect the cyclization of phenylhydrazones to indoles (10), we have found that $BF_3 \cdot Et_2O$ in acetic acid was somewhat better in this case, but this still gave a mixture. Both the procedure of Marion and Oldfield and that using the boron trifluoride etherate gave oils which showed absorptions in the infrared spectrum at 3490 cm^{-1} characteristic of the N-H absorption of indoles (121d) thus showing that the 3,7-dimethylindole had been formed as one compound in the mixture of products. Our attempts to purify it by fractional distillation or chromatography have as yet been unsuccessful.

However, a convenient route to the synthesis of 3,7-dimethylindole was devised. It involved heating a mixture of propionaldehyde and Ń-methyl-o-tolylhydrazine hydrochloride in refluxing, dry benzene, following the same method as described in Part I (135) and Part II (134) for the analogous reaction using Ń-methyl-2,6-dimethylphenylhydrazine hydrochloride. From this reaction, there was obtained in 24% yield, an oil whose i.r. and n.m.r. spectra were consistent with that expected for 3,7-dimethylindole.

The infrared spectrum of this oil in CCl_4 showed a sharp band at 3490 cm^{-1} (N-H).

The n.m.r. spectrum (Fig. 26) of this oil in $CDCl_3$ showed signals at τ 7.68 (narrow doublet, J ~ 1 Hz, 3H for CH_3 at C-3); τ 7.58 (singlet, 3H for CH_3 at C-7); a narrow multiplet at τ 3.08 (1H for H at C-2) and a multiplet between τ 2.4-3.1 for the aromatic protons and the N-H proton.

The n.m.r. spectrum as well as the elemental analysis indicated the presence of ~ 2% impurity. All attempts to eliminate these by fractional distillation or chromatography were unsuccessful.

Pure 3,7-dimethylindole was prepared by the method of Cornforth and Robinson (136)wherein7-methylindole was heated in an autoclave at 215° with sodium methoxide in methanol. The material obtained was a solid, melting at 56-57°. That reported (136) melted at 56°. Its n.m.r. spectrum in $CDCl_3$ was practically identical with that shown in Fig. 26 but devoid of the slight impurities indicated by the very weak signals in the region τ 8.7 to 9.2.

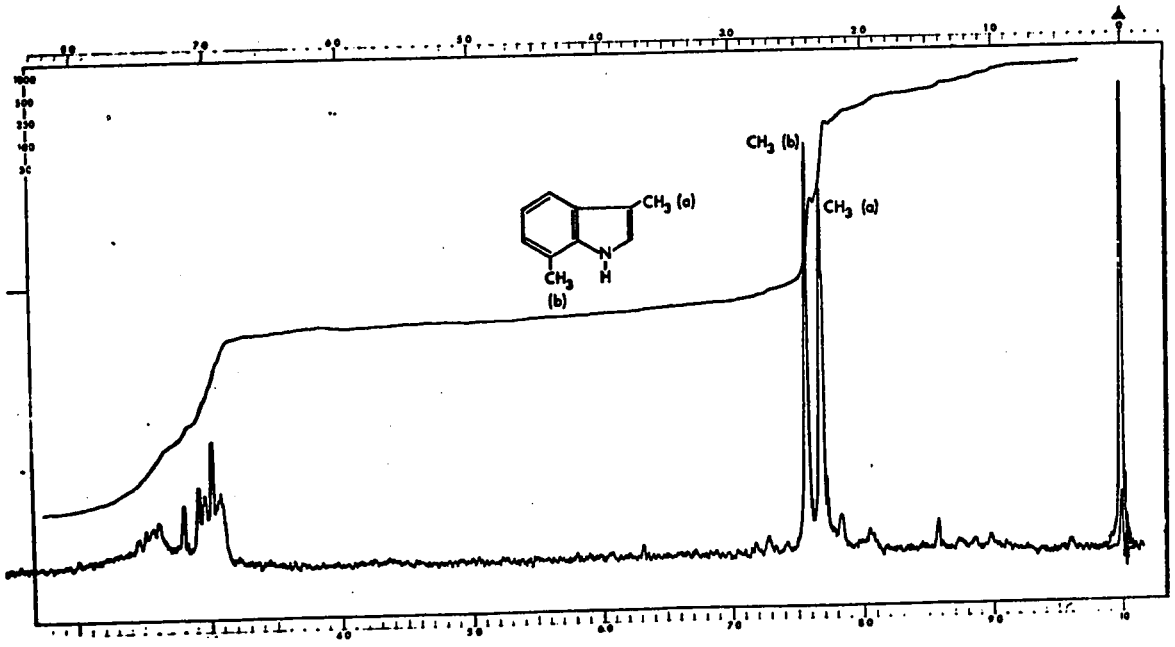


Fig. 26. N.m.r. spectrum (60 MHz) of crude 3,7-dimethylindole in $CDCl_3$. Reference, tetramethylsilane.

N-Methylation of 3,7-dimethylindole was carried out according to the method described in Part I for N-methylation of 8-methyl-1,2,3,4-tetrahycarbazole (135). It afforded in low yield, 1,3,7-trimethylindole which was identical in all respects (m.p., mixed m.p., i.r., and n.m.r.) with the sample obtained previously i.e., by the reaction of N-methyl-2,6-dimethylphenylhydrazine hydrochloride with propionaldehyde.

Thus, from the elemental analysis, spectroscopic evidence and by an independent synthesis as described above, it is confirmed that we have 1,3,7-trimethylindole.

2. Evidence for the presence of 3,7-dimethylindole in the reaction product A.

Our attempts to isolate 3,7-dimethylindole from the reaction product A were unsuccessful. Particularly, we attempted the separation by column chromatography, gas-liquid chromatography, fractional distillation, fractional crystallization and sublimation. Our attempts towards the isolation of pure 3,7-dimethylindole from this mixture were further limited due to the susceptibility of the latter to decomposition when present in air and light at room temperature. However, it may be mentioned that 3,7-dimethylindole in pure form, as obtained previously by the method of Cornforth and Robinson (136), was quite stable.

Although, pure 3,7-dimethylindole could not be isolated from the reaction product A, its presence in the latter is proved by the following evidence.

(i) The reaction product A showed N-H absorption at 3490 cm^{-1} in its infrared spectrum. An authentic sample of 3,7-dimethylindole also showed N-H absorption at 3490 cm^{-1} in its infrared spectrum.

(ii) The reaction of N-methyl-2,6-dimethylphenylhydrazine hydrochloride with propionaldehyde in refluxing benzene proceeds with the formation of a large amount of ammonium chloride and a small amount of methylamine hydrochloride. By analogy with the reaction discussed in Part I (See Scheme IV), if ammonium chloride stems from the formation of 1,3,7-trimethylindole, then the methylamine hydrochloride formed in this condensation, should arise from an alternate reaction pathway (see Scheme V). This pathway, as expected, leads to the formation of 3,7-dimethylindole.

(iii) The n.m.r. spectrum (Fig. 27) of the reaction product A in $CDCl_3$ shows not only the signals for 1,3,7-trimethylindole but also signals at τ 7.60 and τ 7.69. The signals for the C-7 and C-3 methyl protons in the n.m.r. spectrum (Fig. 26) of an authentic sample of 3,7-dimethylindole appear at τ 7.58 and τ 7.68 respectively.

From the above evidence, it is concluded that 3,7-dimethylindole is present in the reaction product A.

On the basis of the above evidence, it is clear that reaction product A obtained from the Fischer reaction of propionaldehyde with N-methyl-2,6-dimethylphenylhydrazine hydrochloride contains 1,3,7-trimethylindole and 3,7-dimethylindole. The latter was a minor component in the reaction product A and defied our attempts to isolate it in a pure form.

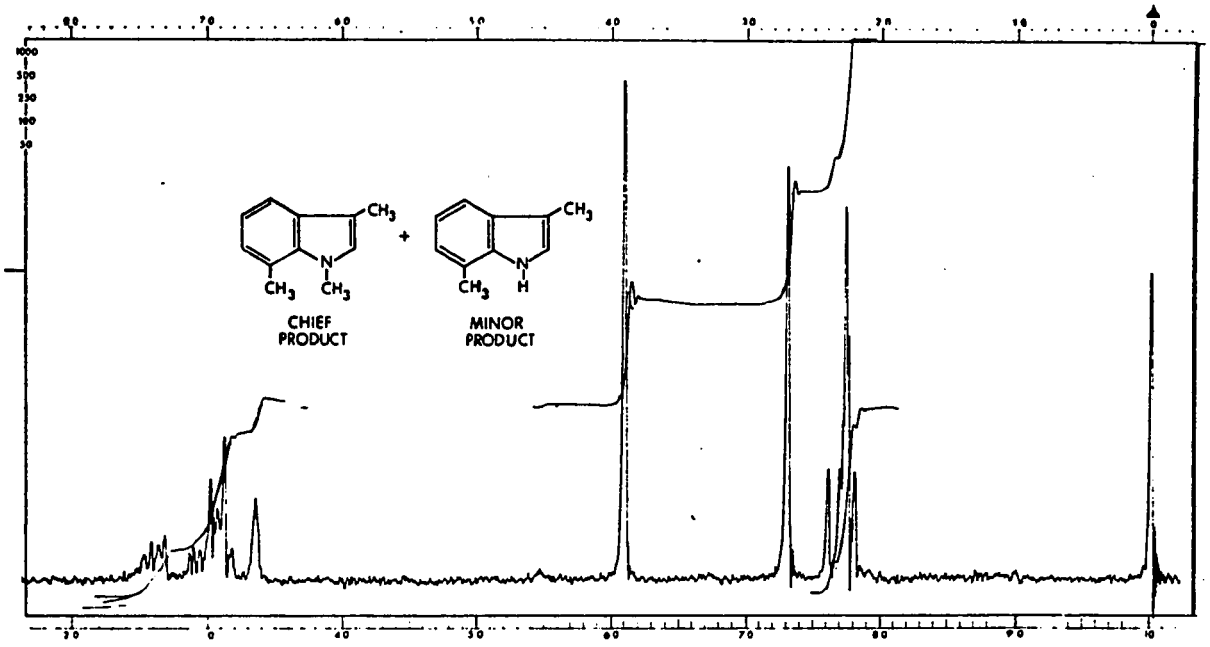


Fig. 27. N.m.r. spectrum (60 MHz) of reaction product A taken in $CDCl_3$. Reference, tetramethylsilane.

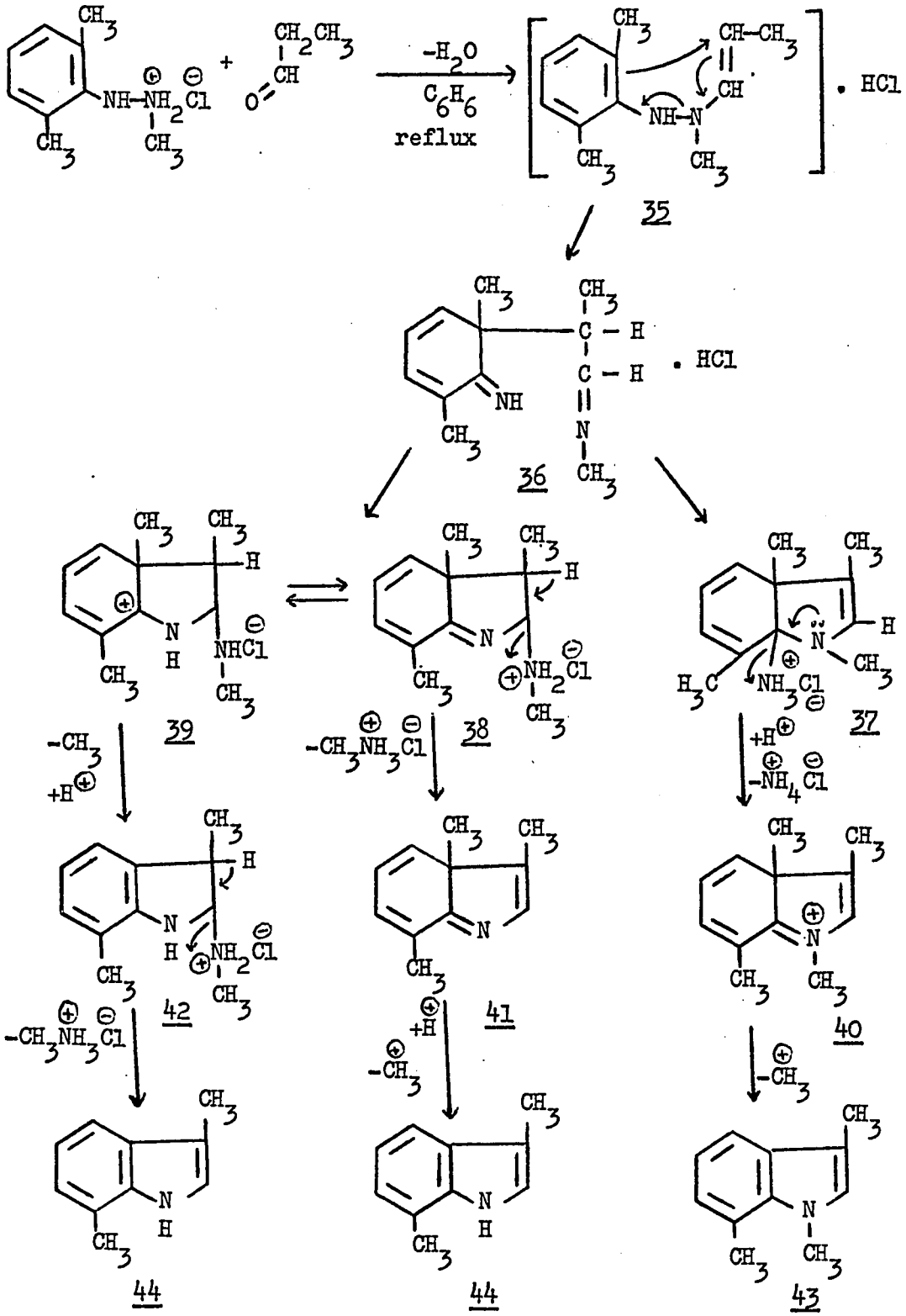
The formation of these two indoles is illustrated in Scheme XI.

C. Now, it was thought adviseable to carry out this reaction under the conditions suitable for the isolation of a dienone-imine intermediate.

Propionaldehyde was condensed with N-methyl-2,6-dimethyl-phenylhydrazine hydrochloride for 10-12 minutes in refluxing benzene using a Dean-Stark water trap. A buoyant solid was obtained which was filtered off and crystallized from 95% ethanol-ether mixture. It melted at 147-148°. A second crystallization was difficult because of tendency for decomposition. But when a minimum quantity of solvent was used and the solution was thoroughly cooled in a refrigerator for 2 days, crystals were obtained which melted at 147-148° and gave a correct analysis for $C_{12}H_{19}N_2Cl$.

The infrared spectrum of this solid hydrochloride in Nujol, showed strong bands at 1593 cm^{-1}, 1578 cm^{-1} (conjugated C=C and C=N stretching) (121c) and a band at 1632 cm^{-1} (non-conjugated C=N stretching) (121c). A weak band at 2240 cm^{-1} and a strong band at 2700 cm^{-1} indicated $\overset{\oplus}{N}H$ (121i). A broad band of medium strength in the region 3100-3300 cm^{-1} indicated N-H (bonded).

The ultraviolet (u.v.) spectrum (Fig. 28) of this material in 95% ethanol, showed a narrow band λ_{max}, 204 mμ (ϵ, 3570) and a broad band at λ_{max}, 315 mμ(ϵ, 1250). This u.v. spectrum (Fig. 28) is very closely similar to the u.v. spectrum (Fig. 20) of an authentic sample of the dienone-imine hydrochloride reported in Part II.



Scheme XI

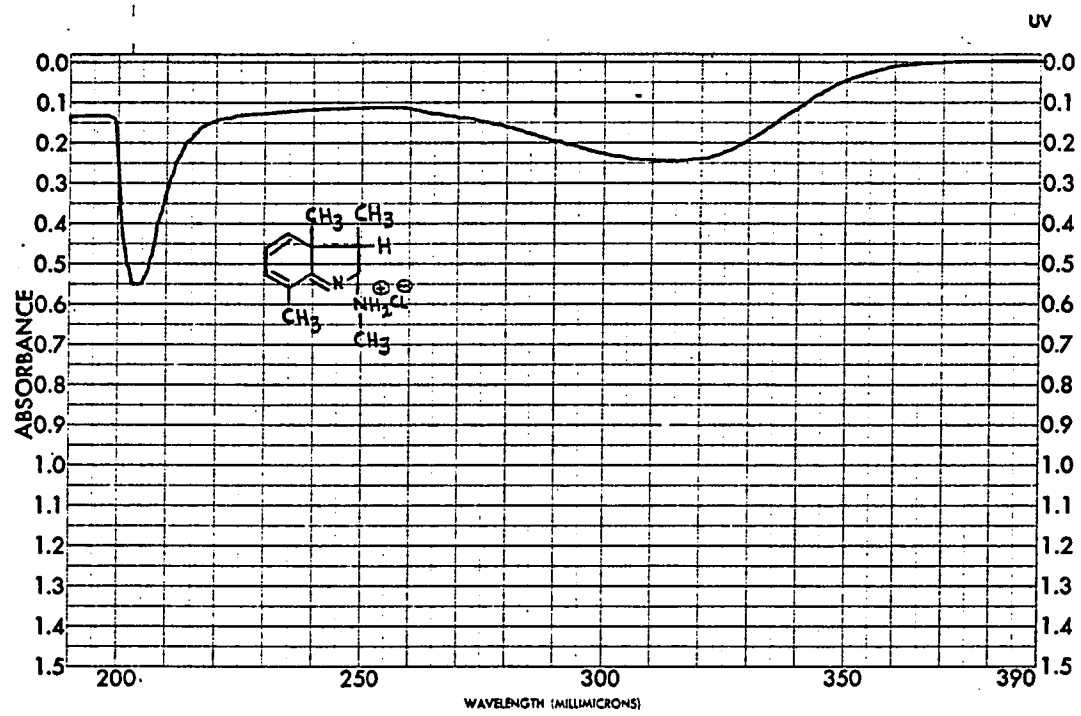


Fig. 28. U.v. spectrum taken in 95% ethanol.

The n.m.r. spectrum (Fig. 29) in D_2O clearly showed the absence of an aromatic structure (indicated by the absence of aromatic proton signals in the region τ 2.0-3.3). The n.m.r. spectrum has a general pattern similar to the n.m.r. spectrum of the authentic sample of the dienone-imine hydrochloride (Fig. 22).

It showed signals for the olefinic protons from the former aromatic ring, between τ 3.3-4.2; the high field signals for the aliphatic methyl protons between τ 8.5-9.4; the signal for the protons of the methyl group attached to a C=C (τ 8.0); the signal for the protons of a methyl group attached to nitrogen (τ 7.0-7.3) and the anomeric proton signal (s) in the region τ 4.8-5.2. The presence of two signals for $N-CH_3$ proton at τ 7.0-7.3 (Fig. 29) and the multiplicity of the signals at τ 8.5-9.3 clearly indicated that the solid contained more than one compound. Attempts to purify the material by further crystallization or by chromatography were unsuccessful because of its susceptibility to decomposition. Because the material was impure, spin-decoupling experiments were not carried out.

From the above evidence, it may be concluded that the above solid is essentially 38 contaminated with minor amount(s) of isomeric structures possibly such as 36, 37, 39 (Scheme XI).

D. This solid, melting at 147-148°, was now subjected to further reaction in order to convert it to the corresponding indole.

When a 1 gram quantity of the above solid was heated in refluxing dry benzene for 20 hours, a precipitate was obtained.

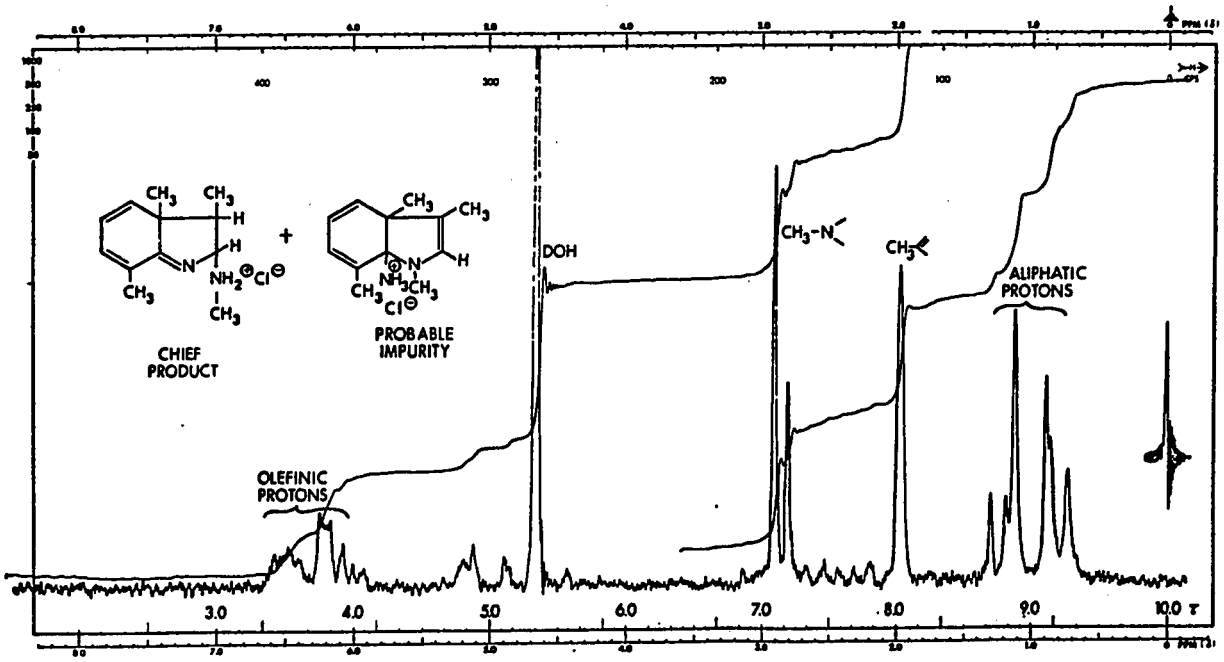


Fig. 29. N.m.r. spectrum (60 MHz) taken in D_2O. Reference, tetramethylsilane.

This was removed by filtration and dried. It melted at 299-320°. The n.m.r. spectrum of this crude material in D_2O showed only two signals — a singlet at τ 7.31 ($N-CH_3$) and a singlet at τ 5.13 (DOH). These signals and their integrated areas, along with the melting point observed above, indicated that the precipitate was a mixture of ammonium chloride and methylammonium chloride in the molar ratio of 3:1.

After the removal of the above solid by filtration, the benzene solvent was removed from the mother liquor. The residual material was a dark-yellow oil.

The n.m.r. spectrum (Fig. 30) of this dark-yellow oil in $CDCl_3$ clearly showed that the dienone-imine was converted to the corresponding indole. It showed the appearance of signals characteristic of the indole structures expected as well as signals indicative of unconsumed dienone-imine hydrochloride. From the n.m.r. spectrum, one derives the conclusion that the indoles are being formed at the expense of the dienone-imine hydrochloride.

This dark yellow oil was freed of the unreacted dienone-imine hydrochloride and furnished a yellow solid.

This yellow solid, when crystallized from petroleum ether (b.p. 60-70°), afforded a 36% yield (based on the dienone-imine hydrochloride) of pure 1,3,7-trimethylindole.

The presence of 3,7-dimethylindole in this yellow solid was again indicated by the N-H absorption at 3490 cm^{-1} in the infrared spectrum as well as by the appearance of signals at τ 7.58 (singlet) and τ 7.68 (singlet) in the n.m.r. spectrum of this yellow solid.

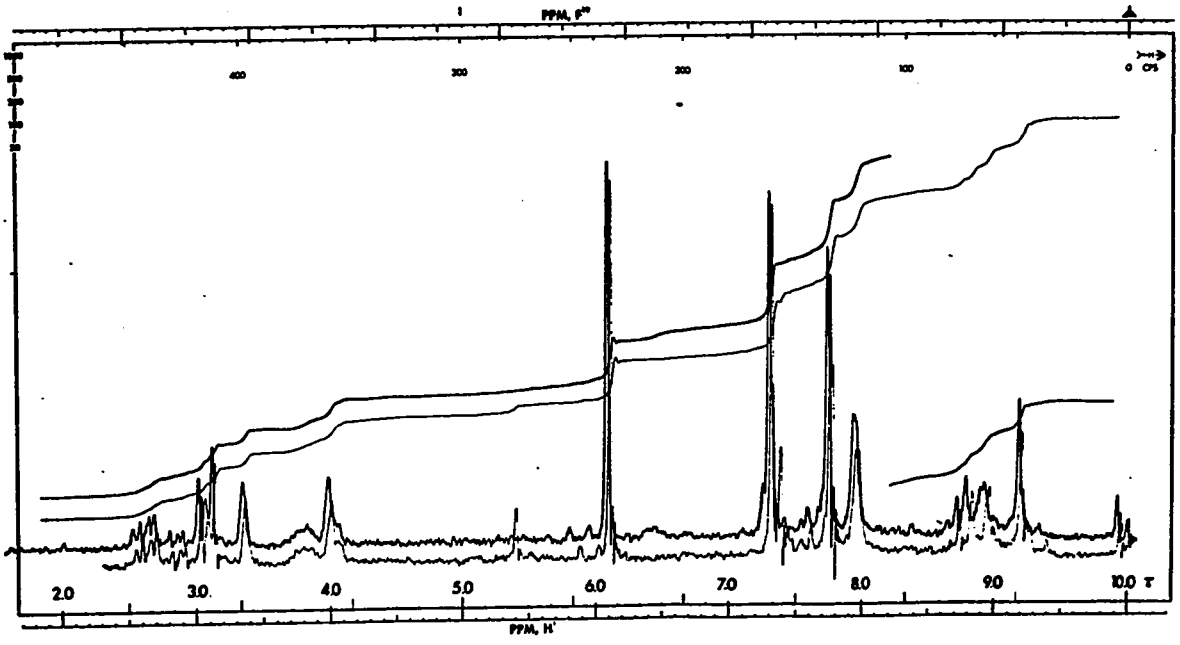


Fig. 30. N.m.r. spectrum (60 MHz) taken in $CDCl_3$. Reference, tetramethylsilane. Lower tracing obtained after the addition (with shaking) of small amount of D_2O.

As reported in the preceeding section, an authentic sample of 3,7-dimethylindole shows N-H absorption at 3490 cm^{-1} in its infrared spectrum and displays signals for C-7 and C-3 methyl protons at τ 7.58 and τ 7.68 respectively in its n.m.r. spectrum.

This 3,7-dimethylindole could not be isolated from this yellow solid in pure form. However, from the yield of methylammonium chloride ($\sim$ 9%), which is believed to arise by a reaction pathway leading to the formation of 3,7-dimethylindole, it can be concluded that the reaction mixture contains 1,3,7-trimethylindole and 3,7-dimethylindole in the proportion 80:20.

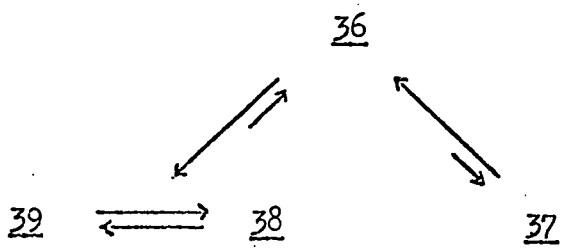
Thus, the formation of 1,3,7-trimethylindole and 3,7-dimethylindole when dienone-imine hydrochloride 38 (mixture) is allowed to react further, constitutes a sufficient proof that the reaction of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride with propionaldehyde does form a dienone-imine intermediate which then is converted to the corresponding indole.

An interesting and significant point is the correlation between the structure of the dienone-imine 38 and the products obtained from its indolization (Scheme XI). We have concluded that the mixture obtained from the condensation of propionaldehyde with N'-methyl-2,6-dimethylphenylhydrazine hydrochloride (for 10-12 minutes) contains a predominance of the dienone-imine hydrochloride 38. Possible contaminating components such as 36, 37 and 39 are present in minor amounts.

Structure 38 should then give 3,7-dimethylindole as the main product with 1,3,7-trimethylindole as the minor product. But as

actually found, the material obtained from the indolization of the dienone-imine hydrochloride 38 (mixture) contains 3,7-dimethylindole and 1,3,7-trimethylindole in the proportion of 20:80 respectively.

This suggests that Scheme XI should be modified to indicate the possibility of an equilibrium between structures 36, 37, 38 and 39, illustrated as below.



(Structures shown in Scheme XI)

If the latter could represent the equilibrium as shown above, then it is apparent that among them, structure 37 is more sterically hindered and thus thermodynamically less stable. When this mixture of four components in subjected to thermal treatment (e.g. refluxing for 19 hours in benzene), component 37 loses ammonium chloride quickly due to the steric acceleration and thus produces 40. The latter, possessing a positive charge rapidly loses a methyl group to form the neutral, fully aromatic 1,3,7-trimethylindole.

Thus, although 37 is a minor component in the equilibrated mixture, it could produce 40 at a rate faster than the combined rate at which 38 and 39 produce 41 and/or 42 respectively. Because 36, 37, 38, 39 are in equilibrium, the overall result of the thermal treatment leads to a greater build up of the 1,3,7-trimethylindole (36%) and a lesser amount of the 3,7-dimethylindole (~ 9%) in the reaction mixture. This, thus could explain the observation that 3,7-dimethylindole and 1,3,7-trimethylindole are formed in the proportion of 20:80 when dienone-imine 38 (mixture) is indolized.

From this discussion, it is apparent that a dienone-imine, proposed as an intermediate in the Fischer reaction, has been isolated and then been converted to the corresponding indoles. This supports the Robinson mechanism proposed for the Fischer indole synthesis.

EXPERIMENTAL

EXPERIMENTAL

All melting points and boiling points are uncorrected.

Infrared spectra were recorded with a Perkin-Elmer Model 421 instrument.

N.m.r. spectra were obtained with a Varian Associates Model A-60 (60 MHz) spectrometer, a Varian Associates Model A-56/60 (60 MHz) spectrometer or a Varian Associates Model HA-100 (100 MHz) spectrometer. Tetramethylsilane was used as an internal reference.

The above spectroscopic equipment was operated by Mr. Robert Swindlehurst, Mr. Glen Bigam, and their associates, Department of Chemistry, University of Alberta, Edmonton.

Ultraviolet spectra were obtained with a Perkin-Elmer Model 202 Ultraviolet-visible spectrometer.

Solvents were removed by rotary evaporator under vacuum unless otherwise stated.

Gas liquid chromatography (g.l.c.) was performed with an Aerograph Autoprep, Model A-700, equipped with 8 1/2' x 1/ 6"(I.D.) stainless steel columns. Two column packings were used: (i) Apiezon L on Gas Chrom P (60 mesh), (ii) 20% butanediol succinate on Gas Chrom P (60-80 mesh). Helium was the carrier gas used at a flow rate of 40 ml per minute. The column temperatures employed for analysis depended on the boiling points of the compounds being analyzed.

Elemental analysis were made by Mrs. Darlene Mahlow

and Mrs. Andrea Dunn, Department of Chemistry, University of Alberta, Edmonton and by Dr. C. Daessle, Organic Microanalysis, 5757 Decelles Avenue, Montreal, P.Q.

1. Preparation of phenylhydrazines.

(a) 2,6-Dimethylphenylhydrazine.

This compound was prepared according to the literature directions (74b).

With vigorous stirring, 43 g (0.36 mole) of 2,6-xylidine was added to a solution of 89 ml of concentrated hydrochloric acid in 40 ml of water. The mixture was chilled to -5° and then while stirring was maintained, a solution of 26.2 g (0.38 mole) of sodium nitrite in 40 ml of water was added dropwise over a period of 1.5 h. The clear orange solution of the diazonium salt was maintained at 0° and stirred gently while a solution of 180 g (0.80 mole) of stannous chloride dihydrate in 240 ml of a 1 : 1 solution of hydrochloric acid in water was added over a period of 4 h. The yellow slurry was stirred as it was permitted to warm to room temperature and stirring was continued for another 24 h. The pale yellow tin complex salt was collected by filtration and was washed with dry ether. This was completely dried on the funnel at room temperature. The dry complex salt was stirred into 260 ml of water and the slurry was stirred vigorously while it was treated with a solution of 90 g of sodium hydroxide in 120 ml of water. The temperature of this mixture was maintained at, or below, 15°. When the reaction was completed, the crude hydrazine was extracted from the mixture with 2 x 140 ml of ether. The ether solutions were combined, washed with 2 x 20 ml of water and dried over anhydrous magnesium sulphate for 2 h. Magnesium sulphate was removed by filtration and dry

hydrogen chloride gas was passed into the dried ethereal solution until the precipitation of the hydrazine hydrochloride was complete. The solid hydrochloride was collected and washed with dry ether and air dried. The yield of the hydrazine hydrochloride was 42 g (69%), m.p., 203-205° (dec.). Reported m.p., 204 (dec.) (74b).

(b) 2,6-Diethylphenylhydrazine.

The hydrochloride of this hydrazine was made by following the same procedure described for the preparation of 2,6-dimethylphenylhydrazine hydrochloride above. From 53 g (0.355 mole) of 2,6-diethylaniline, there was obtained 30 g (42%) of 2,6-diethylphenylhydrazine hydrochloride melting at 176-177°. An analytical sample, crystallized from a mixture of ether and 95% ethanol, melted at 191-192°.

Anal. Calcd. for $C_{10}H_{17}N_2Cl$: C, 59.80; H, 8.53; N, 13.95; Cl, 17.68

Found: C, 60.08; H, 8.68; N, 14.22; Cl, 17.70.

The i.r. spectrum of the hydrochloride in Fluorolube showed absorption at 3250 cm^{-1} (sharp, NH), 3030 cm^{-1} (aromatic =C-H stretching), 2880 cm^{-1} and 2670 cm^{-1} ($\overset{\oplus}{N}H$) and 1595 cm^{-1} (aromatic C=C).

The 60 MHz n.m.r. spectrum of the hydrochloride in D_2O showed signals at τ 2.85 (aromatic, multiplet, 3H), two overlapping quartets centered at τ 7.20 and τ 7.43 (4H for the two -$\underline{CH_2}$-CH_3 group protons) and one triplet at τ 8.85 (6H, for two -CH_2-$\underline{CH_3}$ group protons, J = 7.5 Hz).

(c) o-Methylphenylhydrazine (o-Tolylhydrazine).

This compound was prepared by the same method used to make 2,6-dimethylphenylhydrazine as described above in (a). From 100 g (0.93 mole) of o-toluidine, there was obtained 80 g (54%) of o-methylphenylhydrazine hydrochloride m.p., 188-190° (from ethanol (95%)-ether).

Anal. Calcd. for $C_7H_{11}N_2Cl$: C, 52.96; H, 6.99; N, 17.67; Cl, 22.38.
Found: C, 51.58; H, 7.01; N, 17.98; Cl, 20.35.

The o-methylphenylhydrazine (o-tolylhydrazine) was obtained by the addition of base to an aqueous solution of the hydrochloride followed by the ether extraction of the mixture and removal of the solvent from the dried ether solution. It crystallized on standing. M.p., 57-58°. Literature m.p., 56° (137); 59° (138b).

(d) o-Ethylphenylhydrazine

This compound was prepared by following the same procedure as described for the preparation of 2,6-dimethylphenylhydrazine in 1(a), with the following modification.

In a three-neck, 2 liter flask was placed 189 ml of concentrated hydrochloric acid and 680 ml of water. To this was added slowly and with vigorous stirring, 113 g (0.933 mole) of o-ethylaniline within a period of 1.5 h. The slurry was brought slowly to 0° (rapid cooling solidifies the contents) and then to this was added, within a period of 2 h, a solution of 65 g (0.942 mole) of sodium nitrite in 100 ml of water. The yellow solution was maintained at this

temperature (0°) and then to this was added over a period of 3 h, a solution of 426.4 g (1.887 mole) of stannous chloride dihydrate in 520 ml of a 1 : 1 mixture of hydrochloric acid in water.

The whole mixture, while being stirred, was then allowed to come to room temperature within 4 h and then stirred for another 20 h. The slurry obtained was separated by filtration, washed with ether and dried. This white solid was dissolved in 200 ml of water and then treated with a solution of 200 g of sodium hydroxide in 260 ml of water at 10-15°. The whole solution was extracted with 2 x 200 ml of ether. The combined ethereal solution was washed with water (3 x 100 ml) and dried over anhydrous magnesium sulphate for 3 h. The solvent was removed and a yellow oil was obtained. This solidified when kept in a refrigerator overnight. Yield, 18 g (13.3%). M.p., 49-50°. Reported m.p., 49-50° (139).

A solution of o-ethylphenylhydrazine in dry ether was treated with dry hydrogen chloride gas. The colourless precipitate was removed and washed with dry ether, then dried. M.p., 183-185. Two crystallizations from 95% ethanol gave a melting point of 185-186° for o-ethylphenylhydrazine hydrochloride.

Anal. Calcd. for $C_8H_{13}N_2Cl$: C, 56.61; H, 7.53; N, 16.23; Cl, 20.05.

Found: C, 56.22; H, 7.78; N, 16.53; Cl, 19.95.

The infrared spectrum of the hydrochloride in Fluorolube showed absorptions at 3250 cm^{-1} (sharp, NH), 3030 cm^{-1} (aromatic =C-H stretching), 2880 cm^{-1} and 2690 cm^{-1} ($\overset{\oplus}{N}H$) and at 1595 cm^{-1} (aromatic C=C). The 60 MHz n.m.r. spectrum of the hydrochloride in D_2O showed signals at τ 2.55-3.15 (aromatic, multiplet, 4H),

τ 7.42 (2H, -$\underline{CH_2}$-CH_3, quartet, J=7.5 Hz), τ 8.87 (3H, -CH_2-$\underline{CH_3}$, triplet, J=7.5 Hz).

2. Preparation of N-formylphenylhydrazines.

(a) N-Formyl-2,6-dimethylphenylhydrazine.

A solution of 20 g (0.116 mole) of 2,6-dimethylphenylhydrazine hydrochloride in 80 ml of water was made alkaline by the addition of ice-cold concentrated sodium hydroxide. The liberated oil was extracted and dried (over magnesium sulphate). The ether was removed and the oily residue was dissolved in 120 ml of glacial acetic acid. Formylation was carried out by a modification of the published direction (25, 140). To the solution was added dropwise 6.6 g (0.147 mole) of formamide and the mixture then stirred for 2 h. It was cooled in an ice-bath and made alkaline by the slow addition of 5% aqueous sodium hydroxide, the temperature being kept $\sim 20^{\circ}$. The oil which separated was removed by extraction with ether (2 x 150 ml) and dried over magnesium sulphate. The filtered ether solution, when cooled in a refrigerator overnight, deposited needles which were separated and thrice crystallized from ether. Yield, 6 g (31%). M.p., 139-140°.

When the above procedure was modified by dilution of the glacial acetic acid-formamide mixture with water as previously advocated (25, 140), rather than with 5% aqueous sodium hydroxide, the yield was markedly increased (73%).

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.85; H, 7.31; N, 17.07.

Found: C, 66.28; H, 7.52; N, 16.83.

The infrared spectrum (partly discussed on page 54) in Nujol showed absorptions at 3240 cm^{-1} and 3295 cm^{-1} (two different NH), 3030 cm^{-1}

(aromatic =C-H stretching), 1670 cm^{-1} (C=O) and at 1600 cm^{-1} (aromatic C=C). The n.m.r. spectrum (Fig. 1a and 1b) in pyridine-d_5 is partly discussed on page 54 . It showed signals at τ 2.86-3.24 (multiplet, 3H aromatic + 1H for NH); τ 1.73 (singlet) and τ 1.20 (doublet, J=11 Hz) for 1H for CHO; τ -0.20 (doublet, J =11 Hz and τ -0.47, 1H for NH; two sharp signals at τ 7.62 and τ 7.72 for the methyl groups attached to the aromatic ring.

(b) N-Formyl-2,6-diethylphenylhydrazine.

N-Formylation was carried out according to the directions for N-formylation of phenylhydrazine (140). From 5 g (0.03 mole) of crude 2,6-diethylphenylhydrazine (obtained by evaporation of the solvent from the dried ether extract to which no hydrogen chloride had been added), there was obtained an oil which solidified on standing for 0.5 h. Yield, 5.5 g (94%). M.p., 61-65°. To this solid, dissolved in ether, was added some Skellysolve B (petroleum ether, b.p., 60-70°). The amorphous solid which precipitated was separated and washed with petroleum ether (b.p., 60-70°) and then with a small amount of ice cold diethyl ether. The residual colorless solid melted at 99-100°. Yield, 4 g (68%). Two further crystallizations from petroleum ether (60-70°) raised the melting point to 101°.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.39; N, 14.57.

Found : C, 68.98; H, 8.08; N, 14.78.

The infrared spectrum is discussed on page 82 . The n.m.r. spectrum (Fig. 14) is discussed on page 83 .

(c) N'-Formyl-o-tolylhydrazine.

This was made by following the procedure as described above in (b), with the following modification.

To a solution of o-tolylhydrazine (58 g, 0.475 mole) in 150 ml of glacial acetic acid was added, over a period of 0.5 h, 21.4 g (0.476 mole) of formamide. The solution was stirred for 3 h at room temperature, and then diluted with 150 ml of water and allowed to stand for about 15 minutes. The solid which accumulated was recovered and when air dried weighed 40 g and melted at 115-118°. Two crystallizations from 95% ethanol gave 35 g (49%) of N'-formyl-o-tolylhydrazine. M.p., 120°. Reported m.p., 120° (138b).

3. Preparation of Ń-alkyl-Ń-formylphenylhydrazines.

(a) Ń-Formyl-Ń-methyl-2,6-dimethylphenylhydrazine (crude).

Ń-Formyl-2,6-dimethylphenylhydrazine (4 g) was methylated according to the published directions for the preparation of Ń-methyl-Ń-formyl-2,6-dichlorophenylhydrazine (25), but using a 2:1 molar ratio of dimethyl sulphate to the hydrazine. The reaction mixture was then diluted with water and extracted with ether and dried over anhydrous magnesium sulphate. Removal of the ether gave a yellow oil (3.8 g, 87.5%). The oil was obviously a mixture according to its nuclear magnetic resonance spectrum. Fractional distillation procedures were not used due to the tendency of the material to decompose. Attempts at purification by chromatography were unsuccessful.

(b) Ń-Ethyl-Ń-formyl-2,6-dimethylphenylhydrazine (crude).

Ń-Formyl-2,6-dimethylphenylhydrazine (5 g, 0.03 mole) was ethylated by the procedure described for the methylation of Ń-formyl-2,6-dichlorophenylhydrazine (25), using equimolar quantities of diethyl sulphate and the formylated hydrazine. There was obtained a reddish yellow oil (5 g) whose nuclear magnetic resonance spectrum (Fig. 10) discussed on page 73, indicated that N-alkylation had indeed occurred. The i.r. spectrum is described on page 73.

No attempt was made to purify this material in view of the lack of success in purification of the Ń-methyl-Ń-formyl-2,6-dimethylphenylhydrazine above.

(c) Ń-Formyl-Ń-methyl-2,6-diethylphenylhydrazine (crude).

Methylation was carried out according to the directions employed for the methylation of Ń-formyl-2,6-dichlorophenylhydrazine (25) using equimolar proportions of dimethyl sulphate and the hydrazine. From 6 g (0.031 mole) of Ń-formyl-2,6-diethylphenylhydrazine, there was obtained an oil, after dilution of the reaction mixture with water, which was extracted with ether (2 x 50 ml) and dried over anhydrous magnesium sulphate. Removal of the ether from the filtered solution gave 4 g (62%) of a yellow oil. Since, the methylated Ń-formyl-2,6-dimethylphenylhydrazine had resisted attempts at purification, the methylated 2,6-diethyl homologue was not purified further.

The i.r. spectrum of this crude material in CCl_4 showed absorptions at 3450 cm^{-1} (weak, NH), 3030 cm^{-1} (aromatic =C-H stretching), 1683 cm^{-1} (C=O).

The 60 MHz n.m.r. spectrum (of crude material) in $CDCl_3$ showed signals at τ 1.47 (1H, -CH=O, singlet), τ 2.96 (3H, aromatic, multiplet), τ 3.92 (NH), two overlapping quartets centered at τ 7.05 and τ 7.45 (for two $-\underline{CH_2}-CH_3$ group protons), a triplet centered at τ 8.83 (for two $-CH_2-\underline{CH_3}$ group protons, J=5 Hz). The appearance of two singlets at τ 7.18 and τ 7.22 for the $N-\underline{CH_3}$ protons indicated it to be a mixture of more than one N-methylated product.

(d) N'-Formyl-N'-methyl-o-tolylhydrazine (crude).

N-Methylation of N-formyl-o-tolylhydrazine was carried out by following the same procedure as described above in (c), with the following modification.

To a solution of N'-formyl-o-tolylhydrazine (35 g, 0.233 mole) in 150 ml of dimethylsulfoxide was added, simultaneously in a dropwise fashion over a period of 0.5 h, equimolar quantities of dimethyl sulphate (29.5 g) and sodium hydroxide (9.3 g in 10 ml of water). The reaction mixture was stirred for 2.5 h and then diluted with 200 ml of water. The ether extract (3 x 100 ml) was washed with water and dried for 1 h over anhydrous magnesium sulphate. The drying agent was separated and the solvent removed from the filtrate. The yellow oil so obtained darkened rapidly, hence was not subjected to further purification or to elemental analysis.

The i.r. spectrum in CCl_4, showed a band of medium strength at 3320 cm^{-1} (NH) and a strong band at 1685 cm^{-1} (C=O).

The 60 MHz n.m.r. spectrum in $CDCl_3$ clearly showed that N-methylation had occurred (singlet at τ 6.93 for $N-CH_3$). But the relative areas of the signal of the aromatic methyl group at τ 7.82 (singlet) and that for $N-CH_3$ group at τ 6.93 were in the ratio 3:2, thus showing that methylation was incomplete. Hence, this oil was approximately a 1:2 mixture of N'-formyl-o-tolylhydrazine and N'-formyl-N'-methyl-o-tolylhydrazine.

4. Preparation of N'-alkylphenylhydrazine hydrochloride.

(a) N'-Methyl-2,6-dimethylphenylhydrazine hydrochloride.

The hydrolysis of N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine was carried out by following the same procedure as described for the hydrolysis of N'-formyl-N'-methyl-2,6-dichlorophenylhydrazine (25).

To a solution of 5 g of the crude N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine in 10 ml of 95% ethanol was added 10 ml of concentrated hydrochloric acid and the contents refluxed for 6 h. The cooled mixture was poured into ice cold water (80 ml) and basified with 5% aqueous sodium hydroxide. The mixture was extracted with ether, dried (over magnesium sulphate), filtered and reduced in volume to ~ 100 ml. Addition of dry hydrogen chloride gave a yellow precipitate (3.85 g) melting at 169-175° (addition of a large excess of hydrogen chloride causes some darkening and decomposition). After crystallization from ethanol-ether, it melted at 198-199°. Yield, 2.1 g (40%) of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride.

Anal. Calcd. for $C_9H_{15}N_2Cl$: C, 57.92; H, 8.04; N, 15.01; Cl, 19.01.
Found: C, 58.06; H, 8.09; N, 14.97; Cl, 19.03.

The infrared spectrum (also discussed on page 58) in Fluorolube showed absorptions at 3240 cm^{-1} (NH), 2940 cm^{-1} (CH_3), 2710 cm^{-1} ($\overset{\oplus}{N}H_2$), and 1585 cm^{-1} (aromatic C=C).

The 60 MHz n.m.r. spectrum (Fig. 2) in D_2O showed signals at τ 2.73 (3H, singlet, aromatic), τ 5.20 (DOH, broad singlet),

τ 6.98 (3H, for N-CH_3), and τ 7.59 (6H, two CH_3 attached to an aromatic ring, singlet).

The isolation of N',N'-dimethyl-2,6-dimethylphenylhydrazine hydrochloride from the mother liquor left after the filtration of the above N'-methyl-2,6-dimethylphenylhydrazine hydrochloride, will be described later in section 10 (l).

(b) N'-Ethyl-2,6-dimethylphenylhydrazine hydrochloride.

Crude N'-ethyl-N'-formyl-2,6-dimethylphenyhydrazine (30 g) was hydrolyzed by the same procedure used to hydrolyze the N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine above. There was obtained 11 g of N'-ethyl-2,6-dimethylphenylhydrazine hydrochloride. melting at 181-182°. An analytical sample was obtained by three recrystallizations from ethanol (95%)-ether and melted at 189-190°.

Anal. Calcd. for $C_{10}H_{17}N_2Cl$: C, 59.86; H, 8.48; N, 13.97; Cl, 17.46.

Found: C, 59.89; H, 8.93; N, 14.19; Cl, 17.40.

The i.r. spectrum (also discussed on page 75) in Fluorolube showed absorptions at 3245 cm^{-1} (sharp, NH), 2700 cm^{-1} ($\overset{\oplus}{NH_2}$), 1585 cm^{-1} (aromatic C=C).

The n.m.r. spectrum (Fig. 11) in D_2O is described on page 75.

(c) N'-Methyl-2,6-diethylphenylhydrazine hydrochloride.

Crude N'-formyl-N'-methyl-2,6-diethylphenylhydrazine (29 g) was hydrolyzed by the same procedure used to hydrolyze N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine above. The yield of

N-methyl-2,6-diethylphenylhydrazine hydrochloride was 6 g (20%) which melted at 170° (from 95% ethanol).

Anal. Calcd. for $C_{11}H_{19}N_2Cl$: C, 61.52; H, 8.92; N, 13.05; Cl, 16.51.
Found: C, 61.63; H, 8.73; N, 13.32; Cl, 16.07.

The i.r. spectrum is described on page 85 . The n.m.r. spectrum (Fig. 15) is described on page 85.

(d) N-Methyl-o-tolylhydrazine hydrochloride.

The hydrolysis of N-methyl-N-formyl-o-tolylhydrazine was carried out by following the procedure as described in 4 (a) above, with the following modification.

To the impure N-formyl-N-methyl-o-tolylhydrazine (14 g) was added 56 ml of a 1 : 1 solution (v/v) of concentrated hydrochloric acid and 95% ethanol and the contents refluxed for 6 h. The solution, when cooled and then allowed to stand in a refrigerator overnight, deposited a dark yellow solid (3 g) melting at 130-140°. This was thrice crystallized from 95% ethanol by the addition of ether till a faint turbidity appeared. To avoid decomposition, the crystallization had to be carried out quickly by effecting solution at room temperature and then cooling the solution in a refrigerator. In this manner, 1.5 g of a solid hydrazine hydrochloride was obtained melting at 144-146°. The strong tendency of this material to decompose made elemental analysis useless.

The infrared spectrum in Fluorolube showed two sharp bands at 3200 and 3300 cm^{-1} (NH) and a broad band at 2700 cm^{-1} ($\overset{\oplus}{N}H_2$).

The 60 MHz n.m.r. spectrum in D_2O showed a singlet at τ 7.02 (N-CH_3) and two closely spaced singlets at τ 7.80 and τ 7.82 ($\underline{CH_3}$-C≡C), as well as the DOH peak at τ 5.30 and the aromatic proton multiplet at τ 2.5-3.2. The relative area of the methyl proton signals at τ 7.02 and τ 7.80-7.82 was in the ratio 3 : 8 indicating that in the hydrolysis and crystallization, there had been some loss of N'-methylated material or more likely that N'-methylation was incomplete. Thus, the material melting at 144-146° was a mixture primarily of two substances, N'-methyl-o-tolylhydrazine hydrochloride and o-tolylhydrazine hydrochloride.

As reported before, the strong tendency of this mixture to decomposition, made attempts at its further purification and separation unsuccessful.

5. Condensation of N'-alkylphenylhydrazines (and/or) their hydrochlorides with the carbonyl compounds.

(a) i. Condensation of N'-methyl-2,6-dimethylphenylhydrazine with cyclohexanone.

A solution of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride (1 g, 0.0054 mole) in 20 ml of water was made alkaline with 5% aqueous sodium hydroxide and the resulting mixture ~~extracted~~ with ether. The ether solution was washed with water (2 x 20 ml), dried over anhydrous magnesium sulphate and then freed from solvent.

To the residual oil, in 20 ml of dry benzene, was added 0.5 g (0.0052 mole) of freshly distilled (twice) cyclohexanone. The mixture, in an apparatus equipped with a trap to collect the azeotropically distilled water (122a), was heated under reflux for 1.5 h in an atmosphere of dry nitrogen. The solution became dark. Water collected in the Dean-Stark trap and was identified by its reaction with anhydrous copper sulphate (the colourless copper sulphate became dark blue) and by its retention time on a gas-liquid chromatogram.

The reaction mixture was then freed from benzene and the residual dark oil allowed to stand at room temperature for 2-3 h. The solid which deposited, was collected and recrystallized from 95% ethanol. Needles were obtained which melted at 152-153°. Yield, 240 mg (22%) of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole. Its u.v. (Fig. 6), i.r. and n.m.r. (Fig. 5) spectra are described on pages 62-64.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.42; H, 8.54; N, 7.03.

Found: C, 84.83; H, 8.47; N, 6.89.

The sample of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole obtained by this reaction was found to be identical in all respects (i.r., u.v., n.m.r. spectra, m.p., m.m.p.) with the one obtained by synthesis described later in 8b (iii).

In a repetition of the above experiment, 2.6 g (0.014 mole) of N'-methyl-2,6-dimethylphenylhydrazine, first separated from the hydrogen chloride, was heated with cyclohexanone (1.6 g, 0.016 mole) in refluxing benzene for 1 h, using the same apparatus as above. A current of nitrogen gas was passed through the apparatus to carry away evolved gases into a trap of dry ether saturated with hydrogen chloride gas. A colourless precipitate (~80 mg) accumulated in the acidified ether. This substance decomposed at 350°. Its nuclear magnetic resonance spectrum in D_2O showed only one significant signal, that for DOH at τ 5.28. A minute peak at τ 7.3 suggested the presence and hence the formation of methylamine (as the hydrochloride). Treatment of the solid with aqueous sodium hydroxide liberated ammonia.

Water was obtained from the Dean-Stark trap and identified as such. Gas-liquid chromatography of the benzene solution, or the water or benzene obtained from the Dean-Stark trap, showed no evidence of the presence of methyl alcohol.

ii. Condensation of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride with cyclohexanone.

A mixture of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride (1 g, 0.0054 mole) and cyclohexanone (0.7 g, ~ 0.007 mole) was heated in dry refluxing benzene (30 ml) for 2.5 h in the same apparatus as was used in (i) above. The formation of water in the Dean-Stark Trap was not at all clear, but that it actually was a product of the reaction was shown in a repetition of this experiment using 3 g rather than 1 g of the hydrochloride. The refluxing solution, which did not darken, but merely changed from red to yellow, deposited a colourless solid. This was separated and air-dried (95 mg). It showed some collapse at 225°, then darkened and partly sublimed in the melting point tube and finally completely melted at 300°. The n.m.r. spectrum of this solid in D_2O showed a very large signal at τ 5.37 for DOH and a small one at τ 7.43 for N-CH_3 in the area ratio of ~ 15:1, indicating that the precipitate was essentially ammonium chloride (~ 33% yield) contaminated with a small amount of methylamine hydrochloride (~ 6%).

The yellow benzene filtrate was freed from solvent. The residual yellow oil readily deposited crystals (500 mg). Recrystallization from 95% ethanol gave 450 mg (42%) of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole melting at 151°. When 3 g of the starting material was used, the yield of the pure 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole increased to 55%.

(b) i. Condensation of N'-ethyl-2,6-dimethylphenylhydrazine with cyclohexanone.

Attempts to condense the free N'-ethyl-2,6-dimethylphenylhydrazine with cyclohexanone in refluxing benzene with or without catalytic amounts of acetic acid, boron trifluoride ethereate or p-toluenesulfonic acid in various solvents, resulted in considerable and rapid darkening of the reaction mixture. No product such as 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole could be induced to crystallize out of it. Chromatography of the reaction mixture on neutral alumina was fruitless.

ii. Condensation of N'-ethyl-2,6-dimethylphenylhydrazine hydrochloride with cyclohexanone.

A mixture of 1 g (0.005 mole) of N'-ethyl-2,6-dimethylphenylhydrazine hydrochloride and 0.5 g (0.005 mole) of cyclohexanone in 30 ml of dry benzene was heated under reflux (N_2) for 3 h in an apparatus equipped with a Dean-Stark water trap. No water was apparent in the trap but this again was no doubt due to the small amount of the starting material used. The solid precipitate (132 mg) was separated from the reaction mixture. Its n.m.r. spectrum in D_2O showed it to be essentially ammonium chloride contaminated with a small amount of ethylammonium chloride: a large signal (broad singlet) at τ 5.33 (DOH) and small signals for CH_3CH_2N discernible only under high amplification as a triplet centered at τ 8.80 and a quartet centered at τ 6.93 (J=8 Hz).

The filtrate was freed from benzene and the residual reddish-yellow oil, under vacuum in the rotatory evaporator, was subjected to a temperature of 40-50° for 4 h to complete the removal of cyclohexanone. When the residue was cooled in a salt-ice bath, yellow crystals (150 mg) were obtained. Recrystallization from 95% ethanol gave 140 mg (13%) of pure 9-ethyl-8-methyl-1,2,3,4-tetrahydrocarbazole. M.p., 55-57°.

Anal. Calcd. for $C_{15}H_{19}N$: C, 84.46; H, 8.92; N, 6.57.

Found: C, 84.35; H, 8.94; N, 6.65.

Its u.v. (Fig. 12), i.r. and n.m.r. (Fig. 13) spectra are described on page 77.

(c) i. Condensation of N′-methyl-2,6-diethylphenylhydrazine with cyclohexanone.

N′-Methyl-2,6-diethylphenylhydrazine liberated from 1 g of its hydrochloride by the usual procedure (as in 5(a) i), and 0.8 g of cyclohexanone were heated in refluxing dry benzene (40 ml) for 1 h using a Dean-Stark water trap. The solvent (benzene) was removed and the residual oily material subjected to attempts at its crystallization. The material could not be induced to crystallize.

This oil was again dissolved in 20 ml of benzene to which was then added three drops of glacial acetic acid and the solution was refluxed for another one hour. The solvent along with the unreacted cyclohexanone was removed by rotary evaporator under vacuum for 12 h at room temperature (~26°). The resiudal yellow oil, when dissolved in 2 ml of 95% ethanol and cooled in an ice-salt bath for

0.5 h, deposited crystals (40 mg, ~ 4%) of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole. M.p. 58-59°.

Anal. Calcd. for $C_{15}H_{19}N$: C, 84.46; H, 8.92; N, 6.57.

Found: C, 84.14; H, 8.99; N, 6.58.

Its u.v. (Fig. 16), i.r. and n.m.r. (Fig. 17) spectra are described on page 85-87.

ii. Condensation of N'-methyl-2,6-diethylphenylhydrazine hydrochloride with cyclohexanone.

N'-Methyl-2,6-diethylphenylhydrazine hydrochloride (1 g, 0.0047 mole) and 0.7 g (0.007 mole) of cyclohexanone were heated for 4 h in refluxing dry benzene (30 ml). The colourless solid (110 mg) obtained from the reaction mixture by filtration proved to be essentially ammonium chloride contaminated with a very small amount of methylammonium chloride.

Removal of the benzene and excess cyclohexanone from the filtrate gave a yellow oil which, when cooled, deposited a solid. Crystallization from 95% ethanol gave 380 mg (38%) of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole. M.p., 58-59°.

It was identical in all respects (u.v., i.r., n.m.r. spectra, m.p., mixed m.p.) with the sample of 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole obtained above in i.

(d) i. Condensation of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride with isobutyraldehyde. The dienone-imine hydrochloride.

A mixture of 1.0 g (0.0054 mole) of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride and 0.5 g (0.0069 mole) of isobutyraldehyde was heated for 30 min. in refluxing dry benzene in an apparatus equipped with a trap to collect the azeotropically distilled water. The mixture became yellow in 10-15 minutes. After the 30 min reflux period, a further quantity (1 g) of isobutyraldehyde was added and refluxing was continued overnight. The cooled mixture was filtered and the solid was washed with dry ether (2 x 10 ml). Yield of the crude material was 860 mg. M.p., 170-170°. This was crystallized three times by solution in 95% ethanol and addition of ether to faint turbidity. Yield of pure material was 520 mg (40%). M.p., 186°.

Anal. Calcd. for $C_{13}H_{21}N_2Cl$: C, 64.87; H, 8.73; N, 11.64; Cl, 14.74.

Found: C, 65.00; H, 8.77; N, 11.59; Cl, 14.89.

Its u.v. (Fig. 20), i.r. and n.m.r. (Fig. 22) spectra are discussed on pages 96-104.

The mother liquor, when freed from benzene gave a dark red oil (510 mg). This oil appeared to be a mixture of the starting material and some dienone-imine.

Water was collected in the Dean-Stark water trap. In an effort to obtain a "quantitative" measurement of water resulting from this condensation, 13 g of the hydrazine hydrochloride was condensed

with isobutyraldehyde under the above conditions. It afforded 0.905 g (72%) of water in the Dean-Stark water trap.

ii. Isolation of the free dienone-imine from its hydrochloride obtained above in (d, i).

A solution of the dienone-imine hydrochloride, (0.5 g) in water (30 ml) was treated with a slight excess of 0.1% aqueous sodium bicarbonate. The ether extract (2 x 50 ml) of this solution was washed with water (3 x 30 ml) and dried over anhydrous magnesium sulphate for 30 min. The magnesium sulphate was separated and the filtrate freed from ether in a rotary evaporator under vacuum for 6 h at room temperature. The residual yellow oil became crystalline when it stood in a refrigerator overnight. The crystals were washed with a 1 : 1 solution of 95% ethanol and water. Yield, 304 mg of the free dienone-imine. M.p., 37-38°.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.47; H, 9.80; N, 13.72.

Found : C, 76.48; H, 9.67; N, 13.78.

Its u.v. (Fig. 21), i.r. and n.m.r. (Fig. 23) spectra are described and discussed on pages 96-104.

(e) i. Condensation of N′-methyl-2,6-dimethylphenylhydrazine hydrochloride with propionaldehyde (for 19 h).

A quantity (10 g, 0.05 mole) of N′-methyl-2,6-dimethylphenylhydrazine hydrochloride and 3.1 g (0.053 mole) of propionaldehyde were heated in 150 ml of refluxing benzene for 19 h using the Dean-Stark apparatus. Water was isolated in the trap. The colour of the

reaction mixture become dark after about one hour.

A dark gelatinous solid (~ 1 g) was isolated by filtration and crystallized twice from 95% ethanol-ether mixture to give a solid (~ 0.7 g) melting at 290-220°. Its n.m.r. spectrum in D_2O showed it to be ammonium chloride contaminated with a small amount of methylammonium chloride.

The benzene from the above filtrate was removed and the remaining dark oil was dissolved in 150 ml of water. It was extracted with ether (3 x 100 ml). The ether solution was washed with 300 ml of dilute hydrochloric acid (50 ml of concentrated hydrochloric acid diluted to 300 ml with water). These acidic washings were mixed with the main aqueous solution left after the above ethereal extractions.

The combined ether extracts were washed with water (3 x 100 ml) and dried over anhydrous magnesium sulphate. The drying agent was separated by filtration and then the ether removed from the filtrate. It afforded an oil, weighing 4.5 g.

This oil was fractionally distilled between 80-125°/8 mm to give 1.6 g of an oil and another fraction at 136-138°/8 mm to give 2.5 g of an oil. Both these fractions showed N-H absorption at 3495 cm^{-1} in their infrared spectra. Both these fractions when allowed to crystallize from petroleum ether (b.p., 60-70°) in a refrigerator for 1-2 h, gave 0.3 g and 1.8 g respectively of 1,3,7-trimethylindole. M.p., 46°. Total yield of 1,3,7-trimethylindole, based on the starting material consumed (8 g, see below) is 31.5%.

Anal. Calcd. for $C_{11}H_{13}N$: C, 83.01; H, 8.19; N, 8.80.

Found: C, 83.10; H, 8.00; N, 8.66.

Its u.v., i.r. and n.m.r. (Fig. 25) spectra are described and discussed on pages 118-121.

The dilute hydrochloric acid washings and the main aqueous solution left after the ethereal extractions, were basified with aqueous sodium hydroxide and then this mixture was extracted with ether. The ether extract was washed with water and then dried over anhydrous magnesium sulphate. The drying agent was removed by filtration and dry hydrogen chloride gas was passed through the filtrate. Much decomposition and tar-formation occurred. However, this dark tarry material, after two crystallizations by solution in 95% ethanol and subsequent addition of ether till a slight turbidity appeared, afforded ~ 2 g of pure N'-methyl-2,6-dimethylphenylhydrazine hydrochloride. M.p., 199°. It gave no depression in the mixed m.p. with an authentic sample of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride.

ii. Condensation of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride with propionaldehyde (for 10-12 min). The dienone-imine intermediate.

A solution of 1.5 g of N'-methyl-2,6-dimethylphenylhydrazine and 0.9 g of propionaldehyde in 20 ml of dry benzene, was refluxed for 10 min. in an apparatus equipped with a Dean-Stark trap. Then, a further 1 g of the propionaldehyde was added and the solution refluxed for another 2 min.

The white, floating precipitate which was separated by

filtration from the hot reaction mixture, was washed with ether. The solid weighed 625 mg and melted at 143-145°. It was crystallized by solution in 95% ethanol and subsequent addition of ether till a slight turbidity appeared. When this was kept in a refrigerator for 3-4 h, 520 mg of a solid was obtained, melting at 147-148°. A second and similar crystallization of this solid was difficult and showed signs of decomposition. However, it was carried out successfully using the same solvents, and by placing the solution in a refrigerator for two days. The solid thus obtained melted at 147-148°.

Anal. Calcd. for $C_{12}H_{19}N_2Cl$: C, 63.58; H, 8.38; N, 12.36.
Found: C, 63.08; H, 8.37; N, 12.28.

Its u.v. (Fig. 28), i.r. and n.m.r. (Fig. 29) spectra are described and discussed on pages 127-130.

(f) Condensation of N'-methyl-o-tolylhydrazine hydrochloride with propionaldehyde. 3,7-Dimethylindole.

A mixture of impure N'-methyl-o-tolylhydrazine hydrochloride (1 g, 0.0058 mole) and propionaldehyde (0.34 g, 0.0058 mole) was heated in refluxing dry benzene (50 ml) for 17 h in an apparatus equipped to collect the azeotropically distilled water. The dark solid which was formed was separated and thrice crystallized by solution in 95% ethanol followed by addition of ether to faint turbidity. There was obtained 52 mg of pure methylamine hydrochloride melting (with sublimation) at 225-230°. The n.m.r. spectrum in D_2O showed only two signals, — a relatively large singlet at τ 7.34

($N-CH_3$) and a small singlet at τ 5.18 (DOH).

The filtrate obtained after removal of the methylamine hydrochloride was freed from benzene and the residue was dissolved in 200 ml of ether. The ether solution was washed with 2% hydrochloric acid (15 x 100 ml), then with water (3 x 100 ml) and then dried over anhydrous magnesium sulphate for 1 h. The magnesium sulphate was separated and the ether removed from the filtrate to give 500 mg of a dark oil which, according to its n.m.r. spectrum, consisted of essentially 3,7-dimethylindole. The oil was distilled and gave 200 mg of 3,7-dimethylindole boiling at 90-92°/0.5 mm. Reported b.p., 85-95°/0.5 mm (130) of what is now known by its n.m.r. spectrum to be a mixture containing some 3,7-dimethylindole.

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.75; H, 7.58; N, 9.66.

Found: C, 79.84, 80.13; H, 10.25, 10.13; N, 9.52, 10.16.

Its i.r. and n.m.r. (Fig. 26) spectra are described on page 122.

6. Preparation of the phenylhydrazones.

(a) Cyclohexanone o-methylphenylhydrazone (cyclohexanone o-tolylhydrazone).

A solution of 26 g (0.213 mole) of o-methylphenylhydrazine (o-tolylhydrazine) and 20.8 g (0.216 mole) of cyclohexanone in 100 ml of 95% ethanol, containing a small amount of acetic acid, was refluxed for 2.5 h. Removal of the alcohol left a residue which quickly deposited needles (35.5 g, crude). M.p., 60-61°. Lit. m.p., 61-62° (122b). The hydrazone had a strong tendency to decompose during attempts to crystallize it.

The 60 MHz n.m.r. spectrum in $CDCl_3$ showed signals at τ 2.45-3.42 (5H, aromatic and NH, multiplet), τ 7.88 (3H, aromatic CH_3, singlet) and two multiplets centered at τ 7.65 (4H, multiplet) and τ 8.35 (6H, multiplet) for the protons of the cyclohexanone moiety.

(b) Cyclohexanone o-ethylphenylhydrazone.

This was prepared by the same method used to synthesise cyclohexanone-o-methylphenylhydrazone above. From 11 g (0.081 mole) of o-ethylphenylhydrazine there was obtained 12 g (69%) of product. M.p., 44-46°. The hydrazone decomposed rapidly in air at room temperature, hence was not analyzed.

The 60 MHz n.m.r. spectrum in $CDCl_3$ supported the structure. The signals were at τ 2.5-3.5 (4H, aromatic multiplet), a broad

absorption centered at τ 3.55 (1H for NH, identified by deuterium exchange); τ 7.52 (quartet, 2H, for -$\underline{CH_2}$-CH_3, J=7.5 Hz); two multiplets at τ 7.5-7.9 and τ 8.0-8.5 (10H for the cyclohexanone moiety), τ 7.78 (3H, triplet for $\underline{CH_3}$-CH_2-, J=7.5 Hz).

(c) Methyl isopropyl ketone phenylhydrazone.

This was prepared according to the published directions (141) in the following way.

A solution of 30 g (0.35 mole) of methyl isopropyl ketone and 37.6 g (0.35 mole) of phenylhydrazine in 100 ml of 95% ethanol, containing three drops of glacial acetic acid, was refluxed for 3 h. The alcohol was removed and the residual oil distilled. B.p., 145° at 14 mm. Yield, 32 g (52%) of methyl isopropyl ketone phenylhydrazone. Lit. b.p., 175-176° at 47 mm (141).

The i.r. and n.m.r. spectra supported the structure indicated.

Its i.r. spectrum (film) showed absorptions at 3340 cm^{-1} (NH), 3020 cm^{-1} (aromatic =C-H stretching), 1600 cm^{-1} (aromatic C=C).

The 60 MHz n.m.r. spectrum in $CDCl_3$ showed signals at τ 2.58-3.44 (5H aromatic and 1H for NH, multiplet), τ 7.23-7.71 (1H, methine proton, multiplet), τ 8.81 and τ 8.95 (each 3H, each singlet, for the two aliphatic methyl groups), τ 8.25 (3H, singlet for =N-C-$\underline{CH_3}$).

(d) Propionaldehyde o-tolylhydrazone.

This was made by following the procedure as described above in (c). A solution of 20 g of o-tolylhydrazine and 9.4 g of propionaldehyde in 95% ethanol (100 ml) containing acetic acid as catalyst (3 drops) was refluxed. The ethanol was removed and the remaining oil distilled at 124-132°/2 mm giving 25.4 g (95% yield) of the propionaldehyde o-tolylhydrazone. Lit. b.p., 122-132°/2 mm (130).

7. (a) Cyclization of phenylhydrazones.

i. Cyclization of cyclohexanone o-tolylhydrazone.

This was cyclized according to the published directions (18, 122 b). A mixture of cyclohexanone o-tolylhydrazone (1 g) in 50 ml of 2N sulphuric acid was refluxed for 5-7 min. The dark yellow solid which appeared was separated by decantation of the liquid. When crystallized from 95% ethanol, it afforded 400 mg (44%) of 8-methyl-1,2,3,4-tetrahydrocarbazole. M.p., 95-96°. Lit. m.p., 98° (18, 122b).

Its u.v. spectrum (Fig. 8) in cyclohexane showed absorptions at λ_{max} 225 mμ (ε, 22,100) and λ_{max} 275 (ε, 3600).

Its i.r. spectrum in Nujol showed bands at 3405 cm^{-1} (NH), 1585 cm^{-1} (aromatic C=C).

Its n.m.r. spectrum (60 MHz) in $CDCl_3$ showed signals at τ 2.25-3.05 (4H, aromatic and NH protons, multiplet), at τ 7.57 (3H, aromatic CH_3, singlet) and two multiplets centered at τ 7.28 and τ 8.12 (each 4H) characteristic of the tetrahydro ring.

ii. Cyclization of cyclohexanone o-ethylphenylhydrazone.

The cyclization of cyclohexanone o-ethylphenylhydrazone was carried out by following the procedure described above in (i), with the following modification.

A mixture of 6 g of cyclohexanone o-ethylphenylhydrazone and 100 ml of 3N aqueous sulphuric acid was heated under reflux for 1.5 h. The reaction mixture was cooled and kept overnight at room

temperature. The tarry mass was extracted with ether (2 x 100 ml). The ether extract was washed with water (3 x 30 ml) and dried over anhydrous magnesium sulphate. The filtered solution was freed of solvent and gave a dark yellow oil which was distilled at 168-170° at 9 mm. The amount of product was 3.6 g. This solidified immediately to a yellow gummy mass melting at 50-52°. Two crystallizations from methanol by the addition of water to faint turbidity followed by cooling of the solution in a refrigerator for 2 h, gave colourless crystals of 8-ethyl-1,2,3,4-tetrahydrocarbazole, melting at 58-59°. Yield, 3.4 g (61%).

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03.

Found: C, 83.98; H, 8.35; N, 6.90.

The crystals began to discolor after standing at room temperature for 4-5 h.

Its u.v. (Fig. 18), i.r. and n.m.r. (Fig. 19) spectra are described on pages 87-89.

iii. Cyclization of methyl isopropyl ketone phenylhydrazone.

The methyl isopropyl ketone phenylhydrazone was converted to 2,3,3-trimethylindolenine according to the published directions (141) using an atmosphere of nitrogen rather than hydrogen.

In the actual experiment, a mixture of 20 g of the methyl isopropyl ketone phenylhydrazone and 70 g of zinc chloride in 50 ml of absolute ethanol was heated under reflux for 8 h under an atmosphere of nitrogen. The solution was cooled and diluted with

150 ml of 2% hydrochloric acid and then the vessel was scratched along the inner sides. On standing, 25 g of the crude zinc chloride salt of the indolenine was obtained. It crystallized from 95% ethanol, giving 20 g of pure zinc chloride salt of the indolenine. M.p., 225°. Reported m.p., 225° (141).

The indolenine was liberated by basifying the aqueous solution of the above zinc chloride salt of indolenine with 10% aqueous sodium hydroxide and then extracting the reaction mixture with ether. The ether solution was dried over anhydrous magnesium sulphate. The latter was separated by filtration and the ether removed to give the pure 2,3,3-trimethylindolenine as a yellow oil.

The u.v. spectrum (Fig. 9) in cyclohexane showed a strong band at λ_{max} 214 mμ (ϵ, 11600), 219 mμ (ϵ, 10200) and 252 mμ (ϵ, 3950). Lit., 216 mμ (log ϵ, 4.27), 255 mμ (log ϵ, 3.78) in 95% ethanol (142).

The infrared spectrum (film) showed a strong band at 1580 cm^{-1} (C=N). Lit., C=N, 1579 cm^{-1} (neat) (142).

The 60 MHz n.m.r. spectrum in $CDCl_3$ agreed with the structure. Signals were found at τ 2.4-3.0 (4H, aromatic, multiplet), τ 7.75 (3H, for CH_3 attached to C=N, singlet) and τ 8.73 (6H, singlet for two aliphatic CH_3 groups).

iv. Cyclization of propionaldehyde o-tolylhydrazone.

The cyclization of propionaldehyde o-tolylhydrazone was carried out in accordance with the published directions (130).

In a typical procedure, 20 g of the hydrazone was treated with

100 g of anhydrous zinc chloride and the mixture shaken thoroughly. Then this mixture was warmed slowly to ~ 40-50°. At this temperature, fumes were evolved and then immediately the temperature rose to 220°, causing charring and tar-formation. The mixture remained at this temperature for 2-3 min. and then began to cool. It was then cooled and suspended in 800 ml of 10% aqueous hydrochloric acid. The mixture was refluxed for 8 h in order to hydrolyze the uncyclized hydrazone. The solution was cooled and the supernatant liquid decanted from the tarry material. The benzene extract of the tarry residue was washed with 10% of aqueous hydrochloric acid (3 x 100 ml) and then with water (3 x 100 ml). The benzene was removed and the remaining oil distilled at 80-95°/0.5 mm. Yield, 3.3 g (~ 20%). Lit. b.p., 80-95°/0.5 mm (130).

Its infrared spectrum in CCl_4 showed a sharp band at 3495 cm^{-1} (NH) while the n.m.r. spectrum in $CDCl_3$ showed it to be a mixture. It could not be purified further.

Similar results were obtained when propionaldehyde o-tolylhydrazone was cyclized with boron trifluoride ethereate-acetic acid, 3N or 2N aqueous sulphuric acid or with p-toluenesulfonic acid as catalyst in benzene.

(b) Cyclization or indolization of the dienone-imine hydrochloride, obtained in 5e (ii).

The dienone-imine hydrochloride (1 g) was heated in 50 ml of dry benzene under reflux for 20 h in a Dean-Stark apparatus. A solid (113 mg) was isolated by filtration of the reaction mixture.

This solid showed a collapse of the structure at 180-185° and then started sublimining at 299-320° in the melting point capillary tube. Its n.m.r. spectrum in D_2O showed a broad signal at τ 5.13 (DOH) and at τ 7.28 (sharp singlet for N-CH_3) in the area ratio of 5 : 1, showing it was ammonium chloride containing about 20% of methylammonium chloride.

The benzene solution obtained above after separation of the ammonium chloride, was freed from solvent. It afforded 0.9 g of a dark oil. Its i.r. spectrum in CCl_4 showed N-H absorption at 3495 cm^{-1}. Its n.m.r. spectrum (Fig. 30) is described on page 132.

This dark oily material was dissolved in 50 ml of water and then the reaction mixture extracted with ether (2 x 50 ml). The ether extract was washed with 20 ml of 10% aqueous hydrochloric acid and then with water (3 x 20 ml). The ether solution was dried over anhydrous magnesium sulphate for 2 h and then the drying agent was separated. The ether was removed and left 310 mg of a yellow solid. This solid (crude) melted at 38-42°. It was twice crystallized from petroleum ether (b.p., 60-70°) to give 252 mg (36% yield) of 1,3,7-trimethylindole. M.p., 46°. No depression in the melting point of this indole was observed when mixed with an authentic sample of 1,3,7-trimethylindole.

8. N-Alkylation of carbazole and indole derivatives.

(a) Methylation of 1,2,3,4-tetrahydrocarbazole.

The N-methylation of 1,2,3,4-tetrahydrocarbazole was effected according to the published directions (143) for the methylation of carbazole and tetrahydrocarbazole.

The tetrahydrocarbazole (1 g) was dissolved in 30 ml of dimethyl sulfoxide (acetone also proved to be an equally good solvent). To this were added equimolar quantities of dimethyl sulphate (0.703 g) and sodium hydroxide (0.228 g dissolved in 1 ml of water) dropwise in an alternate fashion. Heat was developed. Stirring was continued for 3 h following the above addition. Then 200 ml of water was added and the reaction mixture was allowed to stand at room temperature for about 1 h. The crystals which deposited were separated by filtration. Weight, 550 mg. The solid was twice crystallized from 95% ethanol to give 490 mg (45%) of 9-methyl-1,2,3,4-tetrahydrocarbazole. M.p. 48-49°. Reported m.p., 50° (143, 144).

Similarly, when 1,2,3,4-tetrahydrocarbazole was methylated according to the procedure described later in 8 (b) iii, the yield of 9-methyl-1,2,3,4-tetrahydrocarbazole was ~ 45%.

(b) Methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole.

The methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole was attempted by the procedures published (143) for the methylation of carbazole and tetrahydrocarbazole as illustrated below in (i) and (ii).

i. The 8-methyl-1,2,3,4-tetrahydrocarbazole (140 mg) was dissolved in 15 ml of acetone. To this solution were added equimolar quantities of dimethyl sulphate (95 mg) and sodium hydroxide (30 mg, dissolved in 1 ml of water) alternately in a dropwise fashion. The reaction mixture was stirred for 3 h and then the acetone solvent was removed. The remaining contents of the flask was crystallized twice from 95% ethanol to give 125 mg of a solid, melting at 95-96°. There was no depression in the mixed m.p. when mixed with an authentic sample of 8-methyl-1,2,3,4-tetrahydrocarbazole. Its infrared spectrum in CCl_4 showed N-H abosrption characteristic of 8-methyl-1,2,3,4-tetrahydrocarbazole.

ii. In a repetition of the above experiment, the mixture was either refluxed for 3 h, or the solvent was changed from acetone to dimethyl sulfoxide and this new solution was stirred at room temperature for 3 h. Under either of these two new experimental conditions, methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole was unsuccessful.

iii. Methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole was effected by the following procedure.

To a 250 ml round bottom flask containing 1.84 g (0.0107 mole) of barium hydroxide and 1.84 g (0.012 mole) of barium oxide was added 40 ml of a 1:1 (by volume) solution of N,N-dimethylformamide and dimethyl sulfoxide. This was stirred gently and cooled to $\sim 0^{\circ}$ in a salt-ice bath. To this was added, all at once, 2 g (0.0108 mole) of 8-methyl-1,2,3,4-tetrahydrocarbazole, followed by 2.8 g (0.022 mole) of dimethyl sulphate. The reaction mixture

was stirred for 3 h at 0° and subsequently it was allowed to come to room temperature and then finally stirred for an additional 12 h at room temperature. To the solution was added 2.8 ml of concentrated ammonium hydroxide and the resulting mixture was then filtered. The filtrate, on standing at room temperature, deposited crystals (100 mg) melting at 152-153°. A second crop (50 mg) was obtained when the mother liquor was cooled for 2 days in a refrigerator. Yield, 7%.

Its u.v. (Fig. 7), i.r. and n.m.r. spectra were identical with those of the sample of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole obtained previously in 5 (a) i. There was no depression in its melting point when mixed with the sample obtained previously in 5 (a) i.

The mother liquor above, diluted with 40 ml of water was extracted with ether (2 x 50 ml). The dried (over magnesium sulphate) extract was freed from ether and gave 1.4 g of the solid, unreacted, crude 8-methyl-1,2,3,4-tetrahydrocarbazole, m.p., 83-86°. The n.m.r. spectrum of this in $CDCl_3$ showed that this was essentially 8-methyl-1,2,3,4-tetrahydrocarbazole contaminated with a small amount of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole (a very small singlet was found at τ 6.2 for the N-CH_3 protons). Yield of the N-methylated product based on the 8-methyl-1,2,3,4-tetrahydrocarbazole consumed, ~ 20%.

(c) Methylation of 8-ethyl-1,2,3,4-tetrahydrocarbazole.

The N-methylation of 8-ethyl-1,2,3,4-tetrahydrocarbazole was attempted by the procedure, illustrated in 8(b) iii above. No product

corresponding to 8-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole could be isolated from the work up of the reaction mixture.

(d) Ethylation of 8-methyl-1,2,3,4-tetrahydrocarbazole.

The N-ethylation of 8-methyl-1,2,3,4-tetrahydrocarbazole (1 g) was attempted by the same procedure described above in section 8(b)iii. No product corresponding to 8-methyl-9-ethyl-1,2,3,4-tetrahydrocarbazole could be isolated from the reaction mixture. However, 0.85 g of the 8-methyl-1,2,3,4-tetrahydrocarbazole was recovered, identical in m.p. and mixed m.p. with the starting material.

(e) Methylation of 3,7-dimethylindole.

The 3,7-dimethylindole obtained in section 5f above, was methylated in accordance with the same procedure as described in 8 (b) iii for N-methylation of 8-methyl-1,2,3,4-tetrahydrocarbazole (135). However, the work-up procedure, following the addition of concentrated ammonium hydroxide, was modified since the filtered solution failed to deposit any solid even when cooled in a refrigerator overnight. This ammoniacal filtrate was diluted with water and twice extracted with ether. The dried ether solution (over anhydrous magnesium sulphate) was freed from the solid and ether. From 0.5 g of 3,7-dimethylindole, there was obtained 0.4 g of an oil whose n.m.r. spectrum in $CDCl_3$ showed it to be a mixture of 3,7-dimethylindole and 1,3,7-trimethylindole in the approximate proportion of 55:45. A petroleum ether (b.p., 60-70°) solution of this mixture,

when cooled in an ice-salt bath for 6 h, deposited 44 mg of crystals melting at 43-46°. The n.m.r. spectrum showed that this was essentially 1,3,7-trimethylindole but contaminated with a small (~ 5%) amount of 3,7-dimethylindole. The i.r. spectrum verified this contamination, by the weak absorption band at 3490 cm^{-1}.

A second crystallization from 1 ml of petroleum ether (cooled in refrigerator overnight) gave 12 mg of pure 1,3,7-trimethylindole melting at 45-46°. Mixed m.p. with that previously obtained was undepressed. The n.m.r. spectrum in $CDCl_3$ was identical to that in Fig. 25. No absorption for N-H was evident in the infrared spectrum (CCl_4).

9. Reactions of the dienone-imine, isolated from the reaction of N-methyl-2,6-dimethylphenylhydrazine hydrochloride and isobutyraldehyde (5d,ii).

(a) Reaction with tetracyanoethylene.

i. Tetracyanoethylene (182 mg, 0.0014 mole) was dissolved in 30 ml of dry benzene. To this solution was added, dropwise, a solution of 285 mg (0.00139 mole) of the dienone-imine (isolated in 5d, ii) in 3 ml of dry benzene. The initial yellow color of the benzene solution of tetracyanoethylene turned to a deep red on addition of the dienone-imine solution. It was stirred for 3 h at room temperature and then the benzene was removed at room temperature. The remaining dark mass was crystallized thrice from 95% ethanol, to give 310 mg of a pure solid which melted at 171-172°.

Anal. Calcd. for $C_{18}H_{19}N_5$: C, 70.82; H, 6.23; N, 22.95.

Found : C, 70.54; H, 6.43; N, 23.19.

Its u.v., i.r. and n.m.r. (Fig. 24) spectra are described and discussed on pages 107-110.

ii. The solid (100 mg) of m.p. 171-172° obtained above in (i), was treated with equivalent amount (42 mg) of tetracyanoethylene in 10 ml of dry benzene. The solution turns dark after 5 min and was allowed to stand at room temperature for 3 h. The solvent was removed when a tarry material was obtained. All attempts to crystallize any solid material from this tarry material were unsuccessful.

iii. Similar results as reported in (ii) above, were obtained when the dienone-imine was treated with two equivalent amounts of tetracyanoethylene in dry benzene.

(b) Reaction with maleic anhydride.

Maleic anhydride (195 mg, 0.0019 mole) was dissolved in 30 ml of dry benzene. To this was added 300 mg (0.0014 mole) of the dienone-imine dissolved in 3 ml of dry benzene. The resulting solution became turbid after 5 min and deposited a semi-viscous solid. Weight, 400 mg. Attempts at its crystallization were unsuccessful.

Its i.r. and n.m.r. spectra are described on page 112.

(c) Reaction with acetyl chloride.

The dienone-imine (2.0 g, 0.0098 mole) was dissolved in 20 ml of dry benzene and the solution brought to boiling point. To this hot solution was added 384 mg (0.0049 mole) of acetyl chloride all at once. The white solid which appeared was separated by filtration. When dried, it weighed 1 g and melted at 185-186°. When mixed with the hydrochloride of the starting dienone-imine, there was no depression in the melting point.

The benzene solution obtained after the separation of the hydrochloride of the unreacted dienone-imine, was freed from benzene and the remaining oil was dissolved in 50 ml of water. It was extracted with ether (2 x 50 ml) and the latter washed with 10% aqueous sodium bicarbonate solution and then with water (3 x 20 ml).

(Similar washings of the benzene solution of the reaction mixture caused the formation of troublesome emulsions).

The ethereal solution was dried over anhydrous magnesium sulphate and then the drying agent was separated. Removal of the solvent gave 350 mg of a yellow oil. This was dissolved inthe minimum amount of methanol and then water was added till a faint turbidity appeared. The solution was allowed to stand in a refrigerator overnight when crystals appeared. These were separated by filtration and air-dried. Weight, 60 mg (5%), m.p., 71-74°. A second similar crystallization did not change the melting point.

Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.17; H, 8.94; N, 11.42.

Found: C, 71.17; H, 8.36; N, 11.57.

Its i.r. and n.m.r. spectra are described on page 113.

(d) i. Heating the dienone-imine in nitrobenzene with zinc chloride.

The dienone-imine (1 g) was dissolved in 10 ml of nitrobenzene and to this was added an equivalent amount (670 mg) of zinc chloride. The mixture was heated at 120-130° for 1 h. From the dark reaction mixture, nitrobenzene was removed by steam distillation and the remaining material extracted with ether (2 x 50 ml). The ether solution was freed from solvent and left a black tarry residue. All attempts to induce this to crystallize were unsuccessful.

Attempts to isolate an indole by chromatography on neutral alumina from this tarry substance, were unsuccessful.

ii. Heating the dienone-imine in benzene with hydrogen chloride.

The dienone-imine hydrochloride (1 g) was taken up in 30 ml of dry benzene and then through this solution was passed dry hydrogen chloride till a yellow colour was obtained (continued passing of hydrogen chloride darkens the reaction mixture). This was refluxed for 0.5 h and then the benzene was removed. A tarry material was left which defied attempts at its purification by crystallization or chromatography on neutral alumina.

10. Supplementary experiments.

(a) Attempted formylation of N′-formyl-2,6-dimethylphenylhydrazine.

A quantity (300 mg) of the N′-formyl-2,6-dimethylphenylhydrazine was dissolved in 3 ml of acetic acid and formamide was added dropwise in excess (1 g). This was stirred for about 3 h and then diluted with water. Crystals were isolated, weighing 250 mg and melting at 139-140°. When mixed with the original N′-formyl-2,6-dimethylphenylhydrazine, the melting point was undepressed.

(b) Preparation of pure N′-formyl-2,6-dimethylphenylhydrazine.

A solution of 1 g (0.0053 mole) of N′-methyl-2,6-dimethylphenylhydrazine hydrochloride in water (50 ml) was basified with 5% aqueous sodium hydroxide. The ether extract (2 x 50 ml) was washed with water (2 x 20 ml) and dried over anhydrous magnesium sulphate for 1 h. The drying agent was separated and the filtrate freed of solvent. To the residual yellow oil was added 6 ml of glacial acetic acid followed by 0.5 g (0.011 mole) of formamide. The mixture was stirred for 3 h at room temperature, then diluted with 20 ml of water. The benzene extract (2 x 50 ml) of this mixture was washed with 5% aqueous sodium carbonate (4 x 30 ml) and then with water (2 x 50 ml) and dried overnight (magnesium sulphate) while kept in a refrigerator (to minimise decomposition). The filtrate was freed from solvent at room temperature over a period of 6 h. The yellow oil (690 mg) solidified on standing for ~ 1.5 h. Three crystallizations from petroleum-ether (b.p., 60-70°) gave 510 mg (53%) of N′-formyl-

N'-methyl-2,6-dimethylphenylhydrazine. M.p., 60°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.92; N, 15.73.

Found: C, 67.46; H, 7.76; N, 15.74.

Its i.r. spectrum in CCl_4 showed bands at 3350 cm^{-1} (NH), 3030 cm^{-1} (aromatic =C-H stretching), 1685 cm^{-1} (C=O), 1590 cm^{-1} (aromatic C=C).

Its n.m.r. spectrum (Fig. 3) in $CDCl_3$ showed signals at τ 1.44 (1H for CH=O, singlet), τ 2.8-3.1 (3H, aromatic, multiplet), τ 3.96 (1H, for NH, broad singlet), τ 7.21 (3H, for N-CH_3, singlet), and τ 7.76 (6H, singlet for two aromatic CH_3 groups).

(c) Attempted N-methylation of N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine.

The N-methylation of N'-formyl-N'-methyl-2,6-dimethylphenylhydrazine was carried out using equimolar amounts of;

i, dimethyl sulphate and sodium hydroxide in 50 : 50 (by volume) of dimethyl sulfoxide and N,N-dimethylformamide;

ii, sodium hydride and dimethyl sulphate in tetrahydrofuran;

iii, sodium hydride and methyl iodide in tetrahydrofuran.

In the work up of the reaction mixture in all the above cases, only the starting material was recovered. No indication of the N-methylation was discernible in the infrared and n.m.r. spectra of the reaction mixtures.

(d) Raney nickel reduction of N´-formyl-2,6-dimethylphenylhydrazine.

N´-Formyl-2,6-dimethylphenylhydrazine was reduced with W-2 Raney nickel according to the published directions (119) as follows.

The formyl derivative (1 g) was dissolved in 50 ml of methanol and 1 g of W-2 Raney nickel (145) was added to it. To the gently refluxing mixture, was added an excess of hydrazine hydrate dropwise over a period of 1 h. The solution was then heated under reflux for a period of 1 h. The reaction mixture was cooled and the catalyst was separated by filtration. The solvent was removed and the oil obtained was extracted with benzene and dried over anhydrous magnesium sulphate. Removal of the benzene gave a liquid which by its infrared (film) and n.m.r. (in $CDCl_3$) spectra, was identified as 2,6-dimethylaniline. Acetylation gave a derivative which proved to be N-acetyl-2,6-dimethylaniline (138a) by its melting point and mixed melting point (176-177°).

The oil left after the extraction with benzene proved to be formamide by comparison of its infrared spectrum (film) and gas liquid chromatographic retention time with those of authentic formamide. Chromatography was done on a 100" x 0.2" (I.D.) column of Apiezon L (8 g) on Gas Chrom P (32 g) with helium as the carrier gas at a flow rate of 40 ml per minute.

(e) Preparation of pure 3,7-dimethylindole.

Pure 3,7-dimethylindole was made according to the published directions (136).

Sodium (2.4 g) was added to 30 ml of methanol over a period of 0.5 h and the solution then refluxed for another 0.5 h to complete the reaction. This methanolic solution of sodium methoxide was cooled to room temperature and then added to 2 g of commerical 7-methylindole previously placed in an auto clave. The mixture was heated for 12 h at 215° and then cooled to room temperature. It was extracted first with ether (50 ml), then with methanol (50 ml) and finally with water (20 ml). All extractions were combined and then ether and methanol removed by rotary evaporator under vacuum. The remaining aqueous extract (~20 ml) was steam-distilled and the first 350 ml of the distillate was collected. This distillate was allowed to stand for 2 h at room temperature whereupon plate-like crystals separated. They were removed by filtration, washed with water and air-dried. M.p., 56-57°. Reported m.p., 56° (136). Weight, 1 g (41.7%).

(f) Attempted Raney nickel reduction of N′-formyl-N′-methyl-2,6-dimethylphenylhydrazine.

The Raney nickel reduction of N′-formyl-N′-methyl-2,6-dimethyl-dimethylphenylhydrazine was carrried out according to the reaction conditions as described in 10 d above. No reductive cleavage of the nitrogen-nitrogen bond was discerned in this case and in all attempts, only the starting material was recovered in good yields.

(g) Condensation of N-methyl-2,6-dimethylphenylhydrazine with cyclohexanone by the azeotropic distillation of solvent at room temperature under vacuum.

N-Methyl-2,6-dimethylphenylhydrazine (2 g, 0.013 mole) and 1.3 g (0.013 mole) of dry cyclohexanone (twice distilled) were mixed in 30 ml of dry benzene. The benzene was removed under vacuum slowly at room temperature (26-30°) over a period of 4-5 h.

Water droplets could be seen in a trap (after bringing it to room temperature) cooled by a dry ice-acetone bath.

The yellow oil (~ 3 g) left after the complete evaporation of the benzene, showed in its infrared spectrum (film) the new abosrption bands at 1630 cm^{-1} and 1660 cm^{-1}. These two bands can be ascribed to the carbon-carbon double bond (non-conjugated, 121h) expected in the enehydrazine.

No vinyl proton was discernible in the n.m.r. spectrum (in $CDCl_3$) between τ 4.0-5.4. The vinyl proton in the 1-morpholino-cyclohexene-1, made in this laboratory by the usual procedure, appears at τ 5.4 and its infrared spectrum shows C=C absorption at 1645 cm^{-1}.

Further, all attempts either to isolate the pure sample of the enehydrazine or to concentrate the latter in the reaction mixture, were unsuccessful.

(h) Addition of maleic anhydride to the yellow oil obtained above in 10 g.

The yellow oil obtained above in section 10 g, was taken up in 50 ml of dry benzene and then was added 0.525 g (0.0053 mole) of maleic anhydride to it. The solution was shaken well and then warmed gently to 40-50°. The reaction mixture became dark and showed signs of decomposition. The solvent was removed and there was left a dark gelatinous, semi-solid residue. The material was chromatographed on neutral alumina (100 g neutral alumina on a column of 5/12" internal diameter). The fractions in Skellysolve B (b.p., 60-70°), and benzene were collected and mixed (due to the similarity in the i.r. spectra of the solids obtained after the evaportion of the solvents) and crystallized from 95% ethanol to furnish 216 mg (10%) of pure 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole, m.p., 152-153°. Small fractions were obtained in ether, chloroform, ethyl acetate and ethanol. They were dark and tarry. Attempts to crystallize components from these tarry fractions were unsuccessful.

(i) Alkaline hydrolysis of N′-formyl-N′-methyl-2,6-dimethylphenylhydrazine.

N′-Formyl-N′-methyl-2,6-dimethylphenylhydrazine (0.9 g) was dissolved in 50 ml of 95% ethanol and to this was added 0.5 g of sodium hydroxide dissolved in 2 ml of water. The resulting solution was refluxed for 5.5 h under a nitrogen atmosphere. The solution was

cooled and then diluted with 100 ml of water. The oily material which separated was extracted with ether (2 x 50 ml). The ether solution was dried (over anhydrous magnesium sulphate) and then dry hydrogen chloride gas was passed through it. This gave 200 mg (21%) of N'-methyl-2,6-dimethylphenylhydrazine hydrochloride melting at 196-197°.

(j) Dehydrogenation of 8-ethyl-1,2,3,4-tetrahydrocarbazole.

Dehydrogenation was carried out according to the published directions (123) with the following modifications.

A quantity (300 mg) of 8-ethyl-1,2,3,4-tetrahydrocarbazole in 3 ml of mesitylene containing 90 mg of 5% palladium on charcoal, was heated under reflux for 2.5 h. The cooled mixture was filtered and the solid washed with methyl acetate (2 x 10 ml). The combined washings and the filtrate were freed from solvent. The residual yellow oil solidified when kept in a refrigerator overnight, giving 230 mg of a material melting at 69-72°. This was crystallized by solution in methanol, addition of water to faint turbidity and cooling in a refrigerator. It afforded 190 mg of 1-ethylcarbazole. M.p., 73°. Reported m.p., 74° (123).

Its infrared spectrum in CCl_4 showed a strong, sharp band at 3480 cm^{-1} (NH), a band at 3030 cm^{-1} (aromatic =C-H stretching) and one at 1600 cm^{-} (aromatic C=C).

The 60 MHz n.m.r. spectrum in $CDCl_3$ agreed with the structure. Signals were found at τ 1.8-2.2 and τ 2.5-2.9 (two multiplets for 7 H, aromatic), τ 7.11 (2H, quartet for -$\underline{CH_2}CH_3$,

J= 7.5 Hz), τ 8.62 (3H, triplet for $\underline{CH_3}$-CH_2-, J=7.5 Hz).

(k) Isolation of N-methyl-2,6-dimethylphenylhydrazine from its hydrochloride.

The N-methyl-2,6-dimethylphenylhydrazine hydrochloride (2.6 g) was dissolved in 50 ml of water and basified with 2% aqueous sodium hydroxide. The ether extract of this mixture was washed with water (3 x 20 ml) and dried over anhydrous magnesium sulphate. The dry agent was removed by filtration and the solvent removed from the filtrate to give crude N-methyl-2,6-dimethylphenylhydrazine as an oil, $\eta_D^{25.5}$, 1.539.

The infrared spectrum in CCl_4 showed absorption bands at 3385 cm^{-1}, 3225 cm^{-1} (two NH absorptions), 3030 cm^{-1} (aromatic =C-H stretching), 2930 cm^{-1}, 2965 cm^{-1} (methyl), 1590 cm^{-1} (aromatic C=C).

The 60 MHz n.m.r. spectrum in $CDCl_3$ agreed with the structure but indicated the presence of some decomposition product(s). No evidence of the presence of the solvent, diethyl ether, was observed. It showed signals at τ 3.0-3.27 (3H, aromatic, multiplet), τ 5.51 (2H, two N-H protons, broad singlet, located by D_2O exchange), τ 7.56 (3H, N-CH_3, singlet), τ 7.78 (6H, two aromatic CH_3, singlet).

Anal. Calcd. for $C_9H_{14}N_2$: C, 72.00; H, 9.33; N, 18.66.

Found : C, 71.08, 71.53; H, 8.53, 8.24; N, 17.63.

(l) Isolation of N',N'-dimethyl-2,6-dimethylphenylhydrazine hydrochloride.

The mother liquor obtained from the acidified (hydrogen chloride gas) ether solution in 4a, after the removal of the N'-methyl-2,6-dimethylphenylhydrazine hydrochloride, was further concentrated to ~ 50 ml and kept in a refrigerator overnight. A colourless precipitate was obtained (1.5 g) melting at 180-181°. Crystallization from 95% ethanol-ether mixture failed to change the melting point.

Anal. Calcd. for $C_{10}H_{17}N_2Cl$: C, 59.86; H, 8.48; N, 13.99; Cl, 17.68.
Found: C, 59.61; H, 8.41; N, 13.72; Cl, 17.77.

Its i.r. and n.m.r. (Fig. 4) spectra are described on page 60.

The elemental analysis as well as spectroscopic evidence supported the structure of the compound as N',N'-dimethyl-2,6-dimethylphenylhydrazine hydrochloride.

When N'-formyl-2,6-dimethylphenylhydrazine was methylated with an equimolar proportions of dimethyl sulphate and sodium hydroxide rather than the 2:1 molar ratio of dimethyl sulphate and hydrazine as described in section 3a, the product obtained, following the above procedure (section 3a), was N'-methyl-2,6-dimethylphenylhydrazine hydrochloride (42%). No N',N'-dimethyl-2,6-dimethylphenylhydrazine hydrochloride was obtained.

(m) Dehydrogenation of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole.

The dehydrogenation of 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole was carried out by following the procedure as described

before in 10j.

The 8,9-dimethyl-1,2,3,4-tetrahydrocarbazole (250 mg) was dehydrogenated by heating with 90 mg at 5% palladium on charcoal for 2.5 h in refluxing mesitylene (2 ml). The hot solution was filtered, and the solid was washed with methyl acetate (2 x 10 ml). The washings (filtered) were combined with the mesitylene solution and the whole freed from solvent. The residual solid (200 mg) melted at 110-115°. Three crystallizations from 95% ethanol raised the melting point to 117°. Yield, 170 mg (69.4%) of 1,9-dimethylcarbazole.

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.15; H, 6.71; N, 7.17.

Found: C, 86.52; H, 6.95; N, 7.37.

Its infrared spectrum in CCl_4 showed absorption bands at 3030 cm^{-1} (aromatic =C-H stretching) and 1590 cm^{-1} (aromatic C=C).

The 60 MHz n.m.r. spectrum in $CDCl_3$ agreed completely with the structure. The only signals evident were a multiplet between τ 1.8-2.25 (2H) and another between τ 2.4-3.0 (5H), aromatic protons; a singlet at τ 6.0 (3H, for N-CH_3); a singlet at τ 7.23 (3H, for CH_3 attached to an aromatic ring).

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APPENDIX

The following is a list of publications taken from this thesis.

1. Fischer indole synthesis. The reaction of N′-alkyl-2,6-dialkylphenylhydrazines with cyclohexanone.
   G. S. Bajwa and R. K. Brown. Can. J. Chem. 46, 1927 (1968).

2. The dienone-imine intermediate in the Fischer indole synthesis.
   G. S. Bajwa and R. K. Brown. Can. J. Chem. 46 (1968) (in press).

3. The reaction of propionaldehyde with N′-methyl-2,6-dimethylphenylhydrazine hydrochloride. The dienone-imine intermediate in the Fischer indole synthesis and its conversion to the indole structure.
   G. S. Bajwa and R. K. Brown. Can. J. Chem. 46 (1968) (submitted).