295. *The Fischer Indole Synthesis. Part II.*

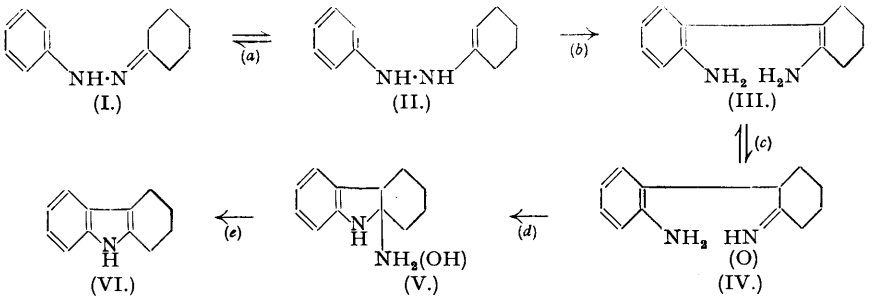
By K. H. Pausacker and C. I. Schubert.

The formation of various by-products in the preparation of tetrahydrocarbazoles is discussed. An alternative mechanism for this reaction (Pausacker and Schubert, *Nature*, in the press) is considered.

Although many mechanisms * have been advanced for the Fischer indole synthesis (cf. Hollins, "The Chemistry of Nitrogen Ring Compounds," Benn Bros., pp. 92 *et seq.*), Robinson and Robinson (*J.*, 1918, **113**, 639; 1924, **127**, 827) have propounded the most satisfactory mechanism for this reaction. A slight modification has been introduced by Allen and Wilson (*J. Amer. Chem. Soc.*, 1943, **65**, 611).

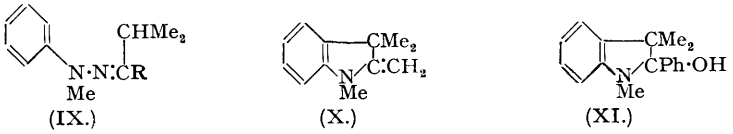
* Carlin and Fisher (*J. Amer. Chem. Soc.*, 1948, **70**, 3421) have recently proposed an entirely new mechanism for this reaction. Their results will not be discussed in the present communication.

For the cyclisation of *cyclo*hexanone phenylhydrazone (I), the modified mechanism would be represented as follows :



Additional evidence may now be cited in support of several of these stages. Grammaticakis (*Bull. Soc. chim.*, 1947, **14**, 438) has recently shown that two forms of the phenylhydrazone of *cyclo*hexanone (I and II) can be proved by spectrographic methods to coexist in equilibrium. Furthermore, the conversion of (IV) (in its hydrolysed keto-form) into (VI) is rendered probable by Reissert and Heller's observation (*Ber.*, 1904, **37**, 4369, 4375) that (VII) (formed from 1-chloro-2 : 4-dinitrobenzene and ethyl acetoacetate) is converted into 6-amino-3-carbethoxy-2-methylindole (VIII) in the presence of tin, stannous chloride, and hydrochloric acid.

The possibility of hydrolysis of the intermediate imine (IV) is also supported by the observed course of cyclisation of phenylhydrazones of type (IX), the product being (X) or (XI) according as R = CH_3 or Ph (Plancher, *Ber.*, 1898, **31**, 1496; Jennisch, *Monatsh.*, 1906, **27**, 1223).

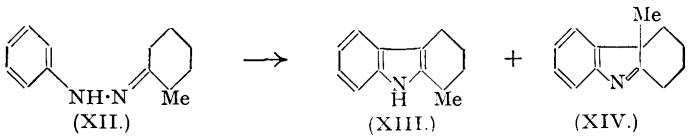


When the above evidence is combined with that already cited by Robinson and Robinson (*loc. cit.*) it is seen that only stage (*b*), involving an ortho-benzidine type rearrangement, is unsupported by very strong, experimental evidence, although even here certain analogies have been obtained. Despite a contrary statement by Robinson and Robinson, it is felt that an appreciable amount of para-rearrangement should occur concurrently, leading, as already stated by the above authors, to the formation of *p*-aminophenylacetaldehydes, which would be expected to self-condense. It may be noted that tetrahydrocarbazole can be prepared in yields exceeding 90%, indicating that here at least, para-rearrangement is inappreciable. Furthermore, the halogen atom in *o*-substituted phenylhydrazones of *cyclo*hexanone appears to be labile under the gentle conditions of cyclisation, forming hydroxytetrahydro*iso*carbazoles (see Part I, preceding paper), and this activation of halogen cannot be reconciled with the accepted interpretation of the benzidine rearrangement. However, it may be argued that the tetrahydro*iso*carbazoles are formed by an entirely different mechanism.

When an attempt was made to distinguish between an inter- and an intra-molecular mechanism for this reaction, initial results indicated that it was intermolecular in nature, thus differing from the benzidine rearrangement. In the evidence to be cited, it may be noted that the substituted phenylhydrazones of different *cyclo*hexanones were used owing to their ease of cyclisation.

After cyclising a mixture of the *p*-tolylhydrazone of *cyclo*hexanone and the phenylhydrazone of 4-methyl*cyclo*hexanone with dilute sulphuric acid, the tetrahydrocarbazole fraction was dehydrogenated with palladised charcoal, and a mixture of carbazoles was obtained. 3-Methyl- and 3 : 6-dimethyl-carbazole were separated from the mixture by fractional crystallisation and carbazole was detected by infra-red analysis. If the reaction were truly intramolecular, then

the two initial products, *i.e.*, 3-methyl- and 6-methyl-1 : 2 : 3 : 4-tetrahydrocarbazole would give the same product, *viz.*, 3-methylcarbazole, upon dehydrogenation. Further evidence was obtained from a study of the cyclisation (glacial acetic acid) of a mixture of equal weights of the *o*-tolylhydrazone of *cyclo*hexanone and the phenylhydrazone of 2-methyl*cyclo*hexanone (XII). An intramolecular reaction would lead to formation of 8-methyl- and 1-methyl-1 : 2 : 3 : 4-tetrahydrocarbazole (XIII) and the base 11-methyl-1 : 2 : 3 : 4-tetrahydrocarbazolenine (XIV) [cf. Plancher, *Atti R. Accad. Lincei*, 1900, (i), **9**, 221; Beilstein, Vol. 20, 420] :



(XII.) (XIII.) (XIV.)

On the other hand, intermolecular reaction could lead to the formation of 1 : 2 : 3 : 4-tetrahydro carbazole and its 1 : 8-*dimethyl* derivative and 8 : 11-dimethyl-1 : 2 : 3 : 4-tetrahydrocarbazolenine (XV), as well as the three products mentioned above. It was found that approximately equal weights of the basic and neutral fractions were obtained in good yield, the basic fraction consisting of an approximately equimolar mixture of (XIV) and the 8 : 11-dimethyl compound (XV). This was proved by thermal analysis of its picrate, which was also separated into the two components by fractional crystallisation. The neutral product, after dehydrogenation, yielded carbazole and 1-methylcarbazole only. Once again an intermolecular reaction was indicated.

The assumption was therefore made that fission of the N–N linkage had occurred, and the fragments formed were capable of recombination leading to indole formation. For example, the last cyclisation may be schematically represented as follows :

(A) (B) (C) (D)

0·5 A + 0·5 D ⟶ 8 : 11-Dimethyltetrahydrocarbazolenine.
0·5 C + 0·5 D ⟶ 11-Methyltetrahydrocarbazolenine.
0·5 A + 0·5 B ⟶ 1-Methylcarbazole (after dehydrogenation).
0·5 C + 0·5 B ⟶ Carbazole (after dehydrogenation).

If hydrolytic fission of the N–N linkage occurred, then the products from *cyclo*hexanone phenylhydrazone would be either aniline and *cyclo*hexanone oxime (XVI) or phenylhydroxylamine and *cyclo*hexaneimine (which would be further hydrolysed to *cyclo*hexanone). After heating a solution of aniline and (XVI) in glacial acetic acid under reflux, only unchanged (XVI) and acetanilide could be recovered. This agrees with Robinson and Robinson's observation (*loc. cit.*) that added amines did not enter into the reaction. Similarly, tetrahydrocarbazole could not be isolated after phenylhydroxylamine and *cyclo*hexanone had been heated in glacial acetic acid solution.

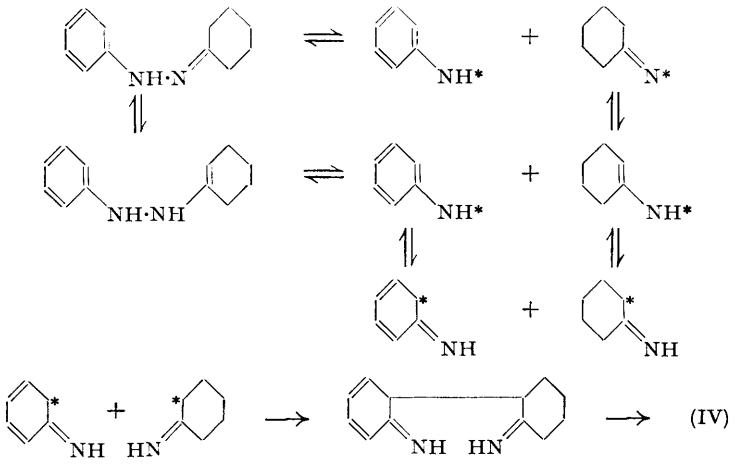
The most plausible alternative to the above involves a homolytic fission of the N–N bond, forming free radicals. The mechanism initially given would then be modified as set out at the top of the opposite page. Stages (*c*), (*d*), and (*e*) would remain unaltered.

Sir Robert Robinson (private communication) has indicated that the results obtained in the mixed cyclisation may be simply interpreted by assuming a simple hydrolysis of the hydrazone followed by condensation as shown below :

$$\left.\begin{matrix} A\cdot NH\cdot N{:}B \\ C\cdot NH\cdot N{:}D \end{matrix}\right\} \longrightarrow \left.\begin{matrix} A\cdot NH\cdot NH_2 + O{:}B \\ C\cdot NH\cdot NH_2 + O{:}D \end{matrix}\right\} \longrightarrow \left.\begin{matrix} A\cdot NH\cdot N{:}B + A\cdot NH\cdot N{:}D \\ + C\cdot NH\cdot N{:}B + C\cdot NH\cdot N{:}D \end{matrix}\right\}$$

The four phenylhydrazones thus obtained could then be cyclised each to its own indole. This hypothesis could not be tested fully but it was found at least that when the *o*-tolylhydrazone of *cyclo*hexanone was cyclised (glacial acetic acid) in the presence of phenylhydrazine, carbazole could be isolated in appreciable quantity from the dehydrogenated product. This indicates that the above suggestion is of vital importance, for it provides a simpler alternative for the free-radical mechanism. However, it is considered that tetrahydro*iso*carbazole formation, from mono- and di-*o*-substituted phenylhydrazones, takes place by the free-radical mechanism.

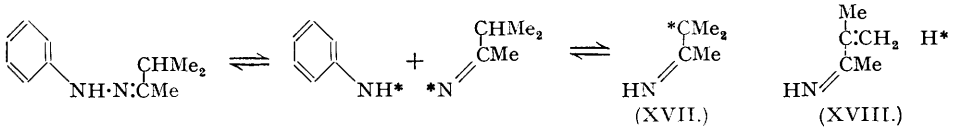
It is intended to examine the kinetics of the Fischer indole synthesis in the hope of obtaining a final decision between the two alternatives given above for stage (*b*).



It may be noted that the following examples are in harmony with the free-radical mechanism :

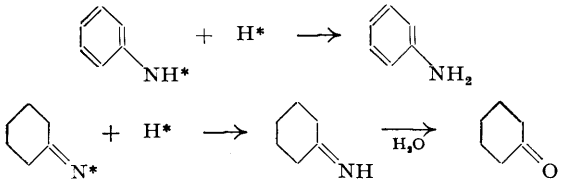
(*a*) The hydrolysis of the *o*-halogen in a substituted phenylhydrazone and the formation of tetrahydro*iso*carbazoles can be readily explained. This statement depends on the validity of the structure assigned to these compounds, which have not yet been synthesised by an unambiguous method.

(*b*) The facile cyclisation of methyl *iso*propyl ketone phenylhydrazone (Plancher, *loc. cit.*) may be explained, as the intermediate free radical (XVII) formed would be stabilised by hyperconjugative contributions of type (XVIII). In addition it may be noted that the frag-



ment D (p. 1386) should be similarly stabilised as (XIX) and not as (XX). This hypothesis is justified as it is found (*loc. cit.*) that D enters into tetrahydrocarbazolenine formation only.

(*c*) As already mentioned (see Part I), the corresponding anilines were produced in small quantities during the cyclisation of the *o*-anisyl- and *o*-chlorophenyl-hydrazones of *cyclo*hexanone. In addition, it has been found that aniline and *o*-toluidine (identified as their acetyl derivatives) were formed in the cyclisation of the phenyl- and *o*-tolyl-hydrazones of *cyclo*hexanone. Furthermore, the probable formation of small amounts of *cyclo*hexanone is also indicated, by both its odour and boiling point, in all these cyclisations. In agreement with the known properties of free radicals, the formation of these products is explained by assuming hydrogen radical abstraction from some part of the system, *i.e.* :



Of course, if the N–N bond does break, then heterolytic fission must also be considered, although it is not favoured at present for the following reasons:

(i) If (α) and (β) were first formed then it would be expected that (α) would combine with a proton present in the system forming an amine. This is invalidated by the observation that added amines do not enter into the reaction.

(α.) (β.) (γ.) (δ.)

(ii) Alternatively, the fragments (γ) and (δ) may result from initial fission. This mode of break is less probable and explains neither the production of amines during cyclisation nor the facts given in section (*b*) of the preceding discussion.

Experimental.

(All m. p.s are uncorrected. Analyses by Miss D. Wauchope. M. p.s in parentheses refer to those given in the literature.)

3 : 6-*Dimethylcarbazole.*—The *p*-tolylhydrazone of 4-methyl*cyclo*hexanone (14 g.) was cyclised with dilute sulphuric acid (Oakeshott and Plant, *J.*, 1926, 1210) and, after extraction with ether, 3 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydrocarbazole (8·7 g.) was obtained, b. p. 150—152°/0·5 mm., m. p. 106—108° (112°); picrate, m. p. 146° (147°).

The tetrahydrocarbazole was dehydrogenated (6 hrs. at 280—300°) with palladised charcoal in a stream of hydrogen, yielding 3 : 6-dimethylcarbazole, which crystallised from light petroleum (b. p. 60—90°) as small white needles, m. p. 217—218° (219°); picrate, m. p. 192° (192°).

3-*Methylcarbazole.*—3-Methyl-1 : 2 : 3 : 4-tetrahydrocarbazole was prepared according to Plant and Rosser's method (*J.*, 1928, 2454), m. p. 108° (109—110°); *picrate*, copper flakes crystallising from benzene–light petroleum (b. p. 60—90°), m. p. 134—135° (Found: N, 13·0. $C_{19}H_{18}O_7N_4$ requires N, 13·5%). Dehydrogenation with palladised charcoal gave 3-methylcarbazole, m. p. 204° (203°); picrate, m. p. 182—183° (180°).

Similarly, the cyclisation of the *p*-tolylhydrazone of *cyclo*hexanone (Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 49) yielded 6-methyl-1 : 2 : 3 : 4-tetrahydrocarbazole, b. p. 160°/0·2 mm., m. p. 138° (141—142°); *picrate*, dark brown needles from benzene–light petroleum (b. p. 60—90°), m. p. 149° (Found: N, 13·2. $C_{19}H_{18}O_7N_4$ requires N, 13·5%). 3-Methylcarbazole was again obtained after dehydrogenation.

Mixed Cyclisation of the p-*Tolylhydrazone of* cyclo*Hexanone and the Phenylhydrazone of* 4-*Methyl*cyclo*hexanone.*—Equal weights of the two hydrazones were cyclised (sulphuric acid) and, after extraction with ether, the fraction of b. p. 140—148°/0·4 mm. was isolated. This was dehydrogenated (palladised charcoal) and a white solid (A) was obtained, m. p. 172—188°. A synthetic mixture composed of 2 parts of 3-methylcarbazole, 1 part of carbazole, and 1 part of 3 : 6-dimethylcarbazole melted at 173—187°, and when mixed with (A) melted at 174—187°.

After fractional crystallisation of the picrate of (A), almost pure 3 : 6-dimethylcarbazole picrate (m. p. 186—187°) was obtained which had the following m. p.s: mixed with carbazole picrate (m. p. 186°), 165—168°; mixed with 3-methylcarbazole picrate (m. p. 182—183°), 180—181°; mixed with 3 : 6-dimethylcarbazole picrate (m. p. 192°), 188—190°; mixed with last picrate and carbazole picrate, 181—182°.

The more volatile portion from the fractional vacuum sublimation of (A) yielded 3-methylcarbazole (m. p. 198—200°) after crystallisation from benzene. Mixed m. p. with an authentic specimen, 199—201°.

Thus evidence of the presence of both 3-methyl- and 3 : 6-dimethyl-carbazole in (A) has been obtained. Furthermore, Mr. A. Walsh of the Division of Industrial Chemistry, Council for Scientific and Industrial Research, has detected the presence of carbazole in (A) by infra-red spectroscopic analysis.

Cyclisation of the o-*Tolylhydrazone of* 2-*Methyl*cyclo*hexanone.*—When the above cyclisation was performed (sulphuric acid), 1 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (3·3 g., b. p. 145—148°/1 mm.) was isolated from the ethereal extract (Found: N, 6·9. $C_{14}H_{17}N$ requires N, 7·0%); *picrate*, dark red needles from light petroleum (b. p. 100—120°), m. p. 135—136° (Found: N, 13·6. $C_{20}H_{20}O_7N_4$ requires N, 13·1%). After dehydrogenation of this tetrahydrocarbazole with palladised charcoal, 1 : 8-*dimethylcarbazole* was obtained, crystallising from light petroleum (b. p. 60—90°) as white needles, m. p. 175—176° (Found: N, 7·2. $C_{14}H_{13}N$ requires N, 7·2%); *picrate*, orange needles from light petroleum (b. p. 60—90°), m. p. 174° (Found: N, 13·8. $C_{20}H_{16}O_7N_4$ requires N, 13·2%).

When the sulphuric acid solution was basified, 8 : 11-*dimethyl*-1 : 2 : 3 : 4-*tetrahydrocarbazolenine* (1·9 g.) was isolated, b. p. 120—122°/1·5 mm. (Found: N, 7·15%); *picrate*, golden-yellow plates from light petroleum (b. p. 100—120°), m. p. 175—176° (Found: N, 12·7%).

Cyclisation of the Phenylhydrazone of 2-*Methyl*cyclo*hexanone.*—From the above cyclisation (sulphuric acid) (cf. Plancher, *loc. cit.*) 1-methyl-1 : 2 : 3 : 4-tetrahydrocarbazole [45% yield, b. p. 142—146°/0·3 mm., m. p. 69° (72°)] and 11-methyltetrahydrocarbazolenine (20% yield, b. p. 98—100°/0·3 mm.) were obtained. The latter formed a yellow picrate, m. p. 169—171° (170°). Dehydrogenation of the former with palladised charcoal gave 1-methylcarbazole, m. p. 120—121° (120·5°); picrate, m. p. 143° (143·5°).

Mixed Cyclisation of the o-*Tolylhydrazone of* cyclo*Hexanone and the Phenylhydrazone of* 2-*Methyl*cyclo*hexanone.*—A mixture (14·6 g.) of equal weights of the above two compounds was added to boiling glacial acetic acid (200 ml.). After the initial vigorous reaction, the solution was heated under reflux (15 minutes), and the acetic acid removed under reduced pressure (water-bath). Dilute hydrochloric acid was added, and the crude tetrahydrocarbazoles (7·0 g.) extracted with ether. The pure tetrahydrocarbazole fraction (B) was isolated by distillation (5·0 g., b. p. 150—152°/1·5 mm.). After basification of the acidic solution, crude tetrahydrocarbazolenines (6·2 g.) were obtained by extraction with ether. The pure fraction (C) (4·6 g.) had b. p. 120—122°/2 mm.

Fraction (B) was dehydrogenated (palladised charcoal), and the product fractionally sublimed in a vacuum. The m. p.s of the three, approximately equal, fractions were (*a*) 105—150°, (*b*) 125—195°, (*c*) 220—223°. When (*a*) was fractionally crystallised from light petroleum (b. p. 60—90°), the more soluble portion finally had m. p. 119—120° (mixed m. p. with 1-methylcarbazole, 120—121°). After repeated crystallisation of (*c*) from light petroleum (b. p. 100—120°), the less soluble fraction had m. p. 242° (mixed m. p. with carbazole, 242°). Thus (B) gives a mixture of carbazole and 1-methylcarbazole after dehydrogenation.

Fraction (C) was converted into its picrate and, after four recrystallisations from light petroleum (b. p. 100—120°), this had m. p. 167—170° (mixed m. p. with 11-methyltetrahydrocarbazolenine picrate, 168—171°). When the filtrate from the first recrystallisation was concentrated and the crystals thus obtained were recrystallised, a product, m. p. 166—168°, was obtained (mixed m. p. with 8 : 11-dimethyltetrahydrocarbazolenine picrate, 171—172°; with 11-methyltetrahydrocarbazolenine picrate, 143—159°).

Treatment of (C) (0·095 g.) with picric acid (0·109 g.) in benzene gave a picrate (shrinks 133°, m. p. 143—154°) after evaporation to dryness. This is shown to be an approximately equimolar mixture of the above two picrates by thermal analysis.

	(i.)	(ii.)	(iii.)	(iv.)	(v.)	(vi.)	(vii.)
11-Methyltetrahydrocarbazolenine picrate, %	22	34	48	56	68	79	93
Shrinking pt.	130°	127°	115°	115°	138°	148°	166°
M. p.	161—165°	149—159°	145—156°	148—158°	152—156°	159—163°	167—185°

Mixed m. p. of (iii) with the picrate of (C), 144—155° (shrinks 125°).

Cyclisation of the o-*Tolylhydrazone of* cyclo*Hexanone in the Presence of Phenylhydrazine.*—The hydrazone was added to an equimolar amount of phenylhydrazine in boiling glacial acetic acid. The tetrahydrocarbazole fraction was dehydrogenated, and the product fractionally sublimed in a vacuum (see above). The last fraction, when crystallised from benzene, had m. p. 242° (mixed m. p. with carbazole, 242°).

JOHNSON CHEMICAL LABORATORY, UNIVERSITY OF ADELAIDE. [*Received, December 29th,* 1948.]