THE FISCHER INDOLE SYNTHESIS

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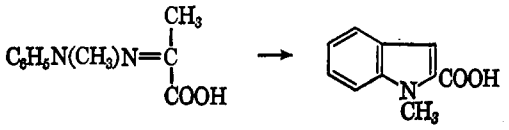
I. Introduction and Scope of the Review

The Fischer indole synthesis can be regarded as the elimination of ammonia from the arylhydrazone of an aldehyde or ketone, by treatment with an acid or various metal and anhydrous metal salt catalysts, with formation of an indole nucleus. The actual isolation of the arylhydrazone is often by-passed by subjecting an equimolar mixture of the arylhydrazine and aldehyde or ketone directly to indolization conditions. Similarly, the *in situ* generation of the arylhydrazine by reduction of the corresponding aryldiazonium salt (87) or N-nitrosoarylalkylamine (71, 139b, 189) in the presence of the carbonyl moiety leads directly to the arylhydrazone. Such methods as these are useful when the intermediate arylhydrazine or arylhydrazone is unstable.

The first indolization of an arylhydrazone was effected by Fischer and Jourdan in 1883 (92) by treatment of pyruvic acid 1-methylphenylhydrazone with alcoholic hydrogen chloride. However, it was not until the following year that Fischer and Hess (91) identified the product from this reaction as 1-methylindole-2-carboxylic acid.



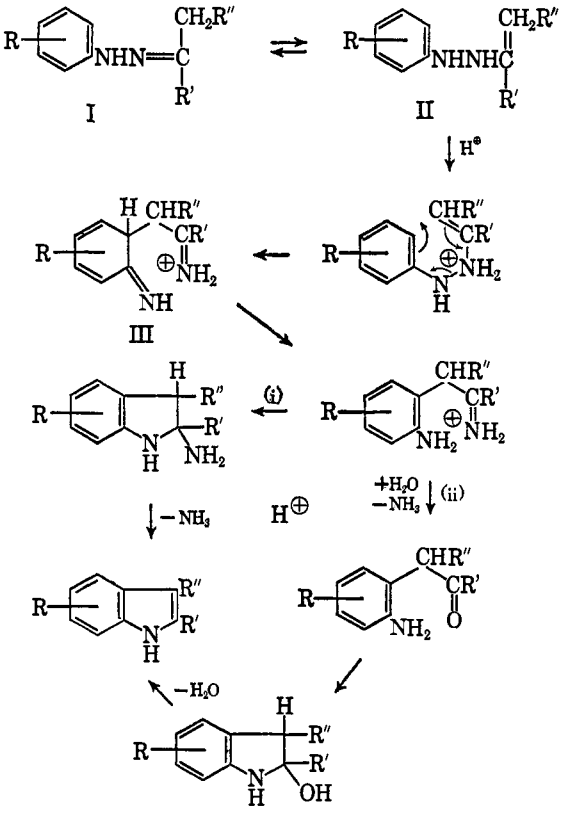
Since this discovery the reaction has been the subject of much experimental work and is now the most versatile method for the preparation of indoles. Although it has been the subject or part of the subject of a number of reviews (115a, 125a, 156, 168, 201, 217a) dating from 1924 to 1954, much work has been performed and progress made in this field since the latter date. Two recent reviews in Russian have appeared (133, 220).

Many indoles have been prepared by the Fischer method merely as intermediates in syntheses and therefore no attempt has been made in this review to tabulate all known cases of indole formation by this method. Special emphasis has, however, been laid on the mechanism of the reaction which has been the subject of much research effort over the past decade. Extensions of and exceptions and limitations to the reaction and the direction of indolization in cases where possible ambiguity exists are discussed in detail since these topics are only briefly mentioned in the previous reviews (115a, 125a, 156, 168, 201, 217a). Further related topics which have received full coverage in these reviews are briefly discussed with the inclusion of recent advances in these fields.

The literature references up to and through the 1961 issues of *Current Chemical Papers* and *Chemical Abstracts*, and several references to papers published in 1962 which were available, are included.

II. Mechanism of the Fischer Indole Synthesis

Of the four mechanisms advanced, three have been found to be inconsistent with all the experimental observations, and the one finally accepted (125a, 217a) is that proposed by Robinson and Robinson in 1918, which after further extension by Allen and Wilson in 1943 (4) and interpretation in light of modern electronic theory by Carlin and Fischer in 1948 (58) can be represented as follows. The mechanism consists essentially of three separate stages: (a) hydrazone–enehydrazine equilibrium (I⇄II); (b) formation of the new C–C bond (II→III); (c) loss of ammonia by either routes i or ii).



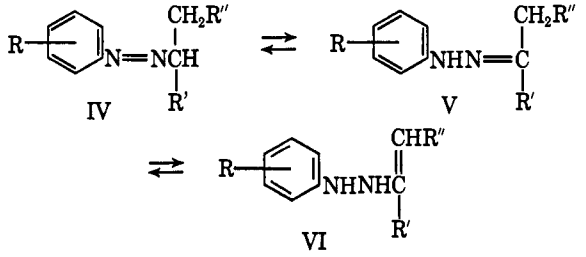
The basic principles of this mechanism, *i.e.*, *o*-benzidine conversion of the enehydrazine tautomer of the

arylhydrazone followed by indole ring formation, were first advanced by Brunner in 1898 (40) following the conversion of *o*-diaminobiphenyl into carbazole, but this paper remained completely unnoticed until 1957 (15), and until then the initial postulation of the mechanism had always been associated with the papers of Robinson and Robinson in 1918 (197) and 1924 (198). Unlike the other three proposed mechanisms, the Robinson mechanism is fully consistent with the experimental facts, and clear analogies were given for each stage when it was proposed (197). Although criticism was advanced against the mechanism because no *para*—as well as *ortho*—rearrangement could be detected during the formation of the new C–C bond (stage b) (114, 156), this criticism was invalidated (15, 198) since *para* rearrangement as opposed to *ortho* rearrangement is sterically very unlikely and, even if it was to occur, would lead to *p*-aminobenzyl alkyl (or aryl) ketones or *p*-aminophenylacetaldehydes which would be expected to lead to tars under the reaction conditions. The formation of dark tarry by-products in many Fischer indolizations may in some cases be the result of *para* rearrangement.

Subsequent to its first proposal (197), each stage of the Robinson mechanism has been well supported by experimental observations which are described below.

A. EVIDENCE FOR THE HYDRAZONE–ENEHYDRAZINE EQUILIBRIUM (STAGE A)

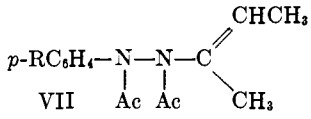
The first support for this initial stage of the Robinson mechanism arose from the observation that the enolizability of aldehydes and ketones compared directly with the ease of indolization of their arylhydrazones (197). Subsequent study of this equilibrium employed physical methods to investigate the possible isomerization of arylhydrazones among the hydrazone (V), azo (IV), and enehydrazine (VI) tautomers.



Initial ultraviolet and visible spectral work on this problem led to the conclusion that in neutral solutions in organic solvents phenylhydrazones exist in equilibrium with small amounts of the azo tautomer (109). This work was later interpreted as evidence in support of the existence of the enehydrazine tautomer under Fischer indolization conditions (172, 192), but no enehydrazine tautomer was, in fact, detectable under the experimental conditions (109), although its probable existence had been postulated earlier (108). Subsequent polarographic studies, however, supported the above azohydrazone–enehydrazine equilibrium and showed that in alcoholic solutions phenylhydrazones of aliphatic and alicyclic ketones have the enehydrazine structure in the free state, whereas those of aldehydes and aliphatic–aromatic ketones have a hydrazone structure which can most probably be converted into the enehydrazine tautomer (13, 134).

Recently (165), however, these results have been criticized and the conclusions drawn have been questioned in view of the reference compounds and experimental conditions used. No evidence for the formation of the enehydrazine tautomer from the hydrazone in neutral non-polar organic solvents could be detected by ultraviolet and nuclear magnetic resonance spectral examination of phenylhydrazones (165) and infrared and ultraviolet spectral examination of substituted phenylhydrazones (R = *p*-NO_2 and *p*-CH_3) (166), but this does not exclude its formation under Fischer indolization conditions.

Evidence for the existence of the enehydrazine intermediate VI has been obtained by trapping such an intermediate, too reactive to isolate in the free state, as its diacetyl derivative. By carrying out the *p*-toluenesulfonic acid-catalyzed indolization of ethyl methyl ketone phenylhydrazone in the presence of acetic anhydride, an excellent yield of a compound shown to have structure VII (R = H) resulted which was converted to 2,3-dimethylindole on treatment with acid or by distillation from zinc dust (227). In a similar manner

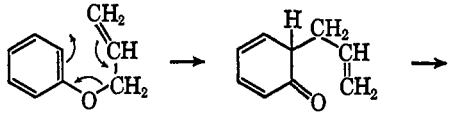


VII (R = NO_2, CH_3, and OCH_3) was prepared (226). The results of acid and base treatment of these compounds varied with substituent (see this section, B). Under similar conditions ethyl methyl ketone 1-methylphenylhydrazone gave a product from which initially (227) two and later (228) five products were isolated. These were shown (228) to be acetylmethylphenylamine, acetyl 1-methylphenylhydrazine, and three monoacetylindoles, later (225) identified as 5-, 6- and 7-monoacetyl-1,2,3-trimethylindoles by Wolff–Kishner reduction to the corresponding ethyl-1,2,3-trimethylindoles which were unambiguously synthesized. The difference in behavior of the above arylhydrazones and 1-methylphenylhydrazone was considered to be due to the fact that in the former cases acetylation of the two nitrogen atoms after enehydrazine formation stabilizes the p-electron pairs of these atoms, which retards the formation of the new C–C bond (stage b), particularly by acetylation of the 1-nitrogen atom, whereas in the latter case acetylation of the 1-nitrogen atom is not possible and the p-electron pair thus remains free to lead finally to indole formation.

This idea was not favored by the earlier report (174) that cyclohexanone acetylphenylhydrazone is indolized to 9-acetyl-1,2,3,4-tetrahydrocarbazole. However, repetition of this work showed that the product was 1,2,3,4-tetrahydrocarbazole, and thus hydrolysis of the acetyl group could have preceded Fischer indolization (226). It was supported by the previous observation (152) that the yields of indoles from 1-alkylphenylhydrazones are greater than those from the corresponding phenylhydrazones, this being attributed to the inductive effect of the 1-alkyl group in facilitating stage b of the reaction (226, 228).

B. FORMATION OF THE NEW C–C BOND (STAGE B)

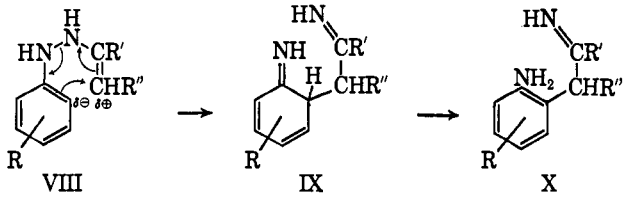
Originally an analogy was drawn between this stage of the mechanism and the *o*-benzidine rearrangement (40, 197, 198). Later (58), however, a further analogy was drawn between it and the *ortho*-Claisen rearrangement.



o-$HOC_6H_4CH_2CH{=}CH_2$

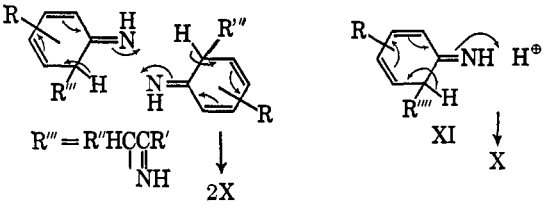
Protonation of both nitrogen atoms in the enehydrazine tautomer prior to rearrangement could occur, as in the case of the benzidine rearrangement (44). The Claisen rearrangement is a purely thermal rearrangement and does not require acid or base catalysis (229). It has also been observed (226, 227) that enehydrazine intermediates can be converted to the corresponding indoles under basic or neutral conditions on heating, and following the observation (235) that distillation of acetophenone phenylhydrazone gives 2-phenylindole, several phenylhydrazones were successfully indolized without a catalyst by refluxing in monoethylene glycol (97), this non-catalytic thermal reaction technique also being successful in the preparation of 3H-indoles (195). Phenylhydrazones have also been thermally rearranged to the corresponding indoles in the presence of sodium hydroxide with (97) and without (207) a solvent. The use of an acid catalyst in the Fischer synthesis is therefore apparently not essential if sufficiently high temperatures are used. It is likely that its use facilitates the reaction by protonation at any of all of the stages of the mechanism, but this does not fundamentally alter the above analogy with the *ortho*-Claisen rearrangement. The fact that the rate of the *ortho*-Claisen rearrangement is unaffected by substituents on the aromatic nucleus (229) whereas the ease (83, 218, 221, 222, 226) and rate (149, 173) of the Fischer indole synthesis has been found to vary with such substituents (electron-attracting groups hindering or retarding it and electron-repelling groups facilitating or accelerating it, respectively) suggests that the above analogy is erroneous. This suggestion, however, is invalidated since the former work (83, 218, 221, 222, 226) did not involve kinetic studies and in the latter work (149, 173), which did involve such studies, the rate-determining step of the reaction is unknown (53, 149) and may vary with experimental conditions (149). Therefore, an alteration in the over-all rate of indole formation on varying the substituents on the aromatic nucleus of the arylhydrazone need not arise from an alteration in the rate of stage b (53).

This formal analogy between the *o*-benzidine and *ortho*-Claisen rearrangements and the rearrangement in the Fischer indolization in which the new C–C bond is formed was made more general after consideration (15) of the conjugation and polarization of the enehydrazine intermediate formed in the first stage of the mechanism, first mentioned in 1918 (197) by Robinson and Robinson. This intermediate is polarized as shown in VIII, the polarization being further increased by protonation (in the presence of an acid) or complex formation (in the presence of a metal or metal salt) (15). Thus, atoms 1 and 6 have not only acquired opposite charge but are spatially favorable for rearrangement to occur as shown, with subsequent aromatization to X.



VIII IX X

It was concluded (15) that this, the *o*-benzidine and the *ortho*-Claisen rearrangements are only three cases of intramolecular rearrangement in a polarized 1,6-conjugated system. The polarization of such conjugated systems is probably the "driving force" behind their rearrangement. The conversion of the *o*-iminoquinone IX into the *o*-alkylaniline X was postulated (15) as probably proceeding by intermolecular proton exchange owing to the conjugation and polarization in IX, except in dilute acid media where proton-catalyzed isomerization probably operates (XI).

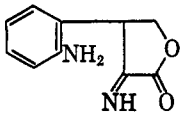


XI X

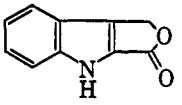
Support for the rearrangement of VIII to IX as shown, which can be regarded as an intramolecular electrophilic substitution onto the aromatic nucleus, is forthcoming from the observation (164) that in the

indolization of *m*-substituted phenylhydrazones the ratio of 4- to 6-substituted indole formed (which is independent of the rate-determining step in the mechanism) is <1 where the substituent is normally *ortho–para* directing in aromatic electrophilic substitution, and is >1 when the substituent is normally *meta–ortho* directing in aromatic electrophilic substitution.

The first isolation of an intermediate in a Fischer indole synthesis corresponding to X was effected by passing dry hydrogen chloride into an ethanolic solution of butyrolactone phenylhydrazone, when the hydrochloride of XII was isolated owing to its insolubility in the reaction medium. Subsequent heating of XII with acid gave the expected indole XIII (192, 193).



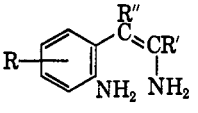
XII



XIII

Later, however, the possibility of isomerization having occurred during the verification of structure XII laid some doubt upon the correctness of the structure (227), but it was found that a further intermediate corresponding to X could be obtained as its monoacetyl derivative XIV (R = H) by treatment of VII (R = H) with potassium hydroxide (227). On treatment of XIV (R = H) with acid, 2,3-dimethylindole was obtained (227). A similar result was obtained starting with VII (R = CH_3) (226), but with VII (R = NO_2) treatment with base or acid gave only the hydrolysis products ethyl methyl ketone and *p*-nitrophenylhydrazine, whereas with VII (R = OCH_3), 5-methoxy-2,3-dimethylindole is produced in excellent yield even under basic conditions (226).

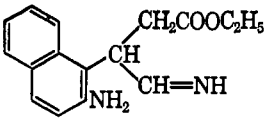
XIV



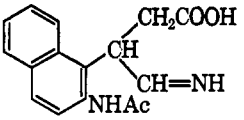
XIV

The formation of XIV (R = H and CH_3) and their subsequent conversion to the corresponding indoles casts doubt upon the suggestion (15) that in the Robinson mechanism the formation of the diamine XV need not occur, although its isolation in this instance may be incidental to acetylation.

Succinic semialdehyde 2-naphthylhydrazone on treatment with ethanolic phosphoric acid gave two products, one which after hydrolysis gave 4,5(?)-benzo-3-indoleacetic acid, and the other which when diazotized coupled with 2-naphthol to give a red colored product. This latter product was given the structure XVI without further experimental proof (32). Similarly, a mixture of 2-naphthylhydrazine hydrochloride and succinic semialdehyde on successive treatment with sodium acetate and sulfuric acid gave a product with the properties of an acetylated aromatic amine which without further proof was tentatively assigned structure XVII (32).



XVI

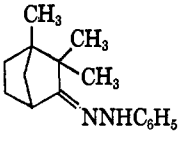


XVII

Further investigation of this work and these intermediates would be of interest.

The indolization of methyl phenyl ketone and ethyl phenyl ketone phenylhydrazones with polyphosphoric acid under milder conditions than normally used for such reactions gave, as well as the expected 2-phenylindole and 3-methyl-2-phenylindole, respectively, small yields of basic by-products in each case which were not identified (132). These could contain intermediates corresponding to X (or any other basic intermediate in the Robinson mechanism).

An observation (25) that treatment of camphenilone phenylhydrazone (XVIII) with alcoholic hydrogen chloride gives an isomeric base (characterized as its picrate and styphrate) in 13% yield was thought to be a further case of the isolation of the imine intermediate X.



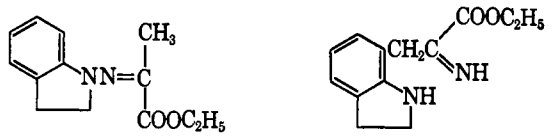
XVIII

However, since enehydrazine tautomerization of XVIII is impossible (Bredt's rule) unless methyl migration or elimination from the *gem*-dimethyl group or ring cleavage occurs, the formation in this case of such an intermediate is doubtful.

The existence of the imine intermediate X was further demonstrated (194) by subjecting the arylhydrazone XIX to Fischer indolization conditions. In this case indole ring formation in the imine intermediate XX is difficult and therefore the alternative cyclization, now possible because of the presence of the carbethoxy group, occurs, and the major product from the reaction was shown to have the structure XXI. A small yield of the indole XXII was also obtained.

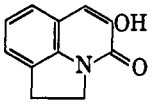
Intermediate X in the Robinson mechanism has a postulated analogy in the reductive ring contraction of cinnolines to indoles (74, 122, 160) in which the formation of a similar intermediate (XXIII) is postulated.

A study of this reaction and its mechanism with the view to isolating intermediates and to studying the

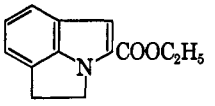


XIX

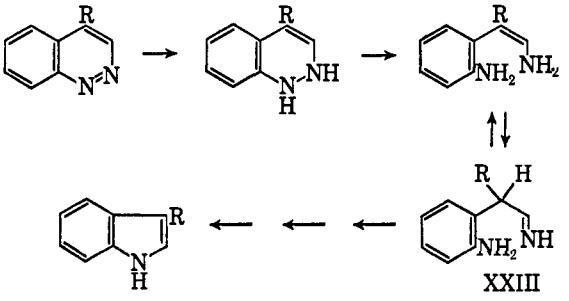
XX



XXI



XXII



XXIII

effect of varying the group R on the over-all reaction is in progress (38).

It has been suggested (3) that during the Fischer indole synthesis, formation of the new C–C bond might precede cleavage of the N–N bond and lead to an intermediate 1,2,3,4-tetrahydrocinnoline. However, the concerted cyclic nature of the rearrangement in stage b of the mechanism invalidates this suggestion.

C. LOSS OF THE NITROGEN ATOM (STAGE C)

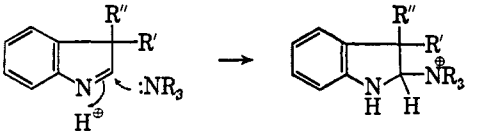
1. Determination of Which Nitrogen Atom of Arylhydrazone Is Lost during Indolization

This problem had been considered when the reaction was first discovered (89, 91, 92). It was found that 1-alkylarylhydrazones gave indoles 1-substituted with the alkyl group originally attached to the 1-nitrogen atom of the arylhydrazone. This led to the conclusion that it was the 2-nitrogen atom of the arylhydrazone which was eliminated during indolization (78, 91). This was confirmed when it was found that acetophenone 1-^{15}N-phenylhydrazone (4) and acetone 2-^{15}N-phenylhydrazone (66) on indolization gave labeled 2-phenylindole and unlabeled 2-methylindole, respectively, the ammonia produced in the latter case carrying the ^{15}N label.

2. Mechanism of 2-Nitrogen Elimination

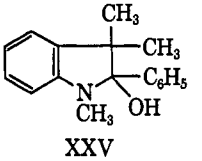
An analogy between this stage of the mechanism and the formation of piperidine from 1,5-diaminopentane dihydrochloride has been made (197).

The two possible methods, i and ii, by which ammonia can be liberated during Fischer indolization were originally suggested in 1924 (198). Later (4), elimination by method i was preferred, for although ketimines are normally very readily hydrolyzed by acid which would favor method ii, cases were known where they are stable in such media. An analogy for this method of nitrogen elimination is found in the very ready formation of 2-aminoindolines by reaction of 3H-indoles with amines (XXIV) (125d).

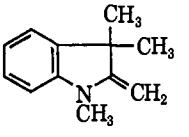


XXIV

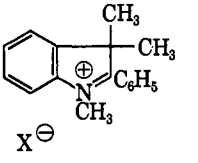
Previous observations that indolization of phenyl isopropyl ketone and methyl isopropyl ketone 1-methylphenylhydrazones lead to the formation of 2-hydroxy-1,3,3-trimethyl-2-phenylindoline (XXV) and 1,3,3-trimethyl-2-methyleneindoline (XXVI), respectively, are said to favor method ii (172), although this conclusion is erroneous as these compounds are formed by action of base on the corresponding 3H-indolium salts XXVII and XXVIII subsequent to completion of the indolization. For similar reasons, 2-hydroxy-



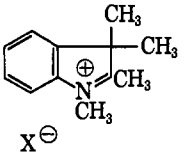
XXV



XXVI

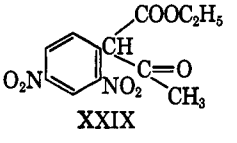


XXVII

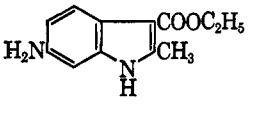


XXVIII

1,3,3-trimethylindoline is the product obtained by indolization of isobutyraldehyde 1-methylphenylhydrazone (39, 42). However, method ii was also preferred (172) since it was known that reduction of XXIX gave ethyl 6-amino-2-methylindole-3-carboxylate, this being one example of the type of ring closure employed in the Reissert indole synthesis (125b, 217b).



XXIX



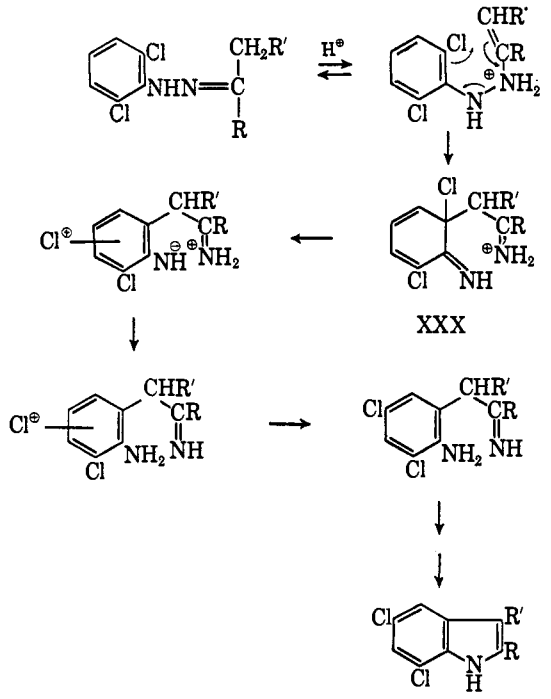
No definite conclusion can therefore be drawn as regards the precise mechanism of ammonia elimination, it being possible that variation between i and ii occurs depending upon the indolization conditions.

D. GROUP MIGRATIONS DURING INDOLIZATION OF 2,6-DISUBSTITUTED PHENYLHYDRAZONES

The Robinson mechanism has found strong support from studies of this nature carried out mainly by Carlin's school.

1. *Halogen Migration*

Treatment of 2,6-dichlorophenylhydrazones with anhydrous zinc chloride with or without added solvent led to the formation of small yields of 5,7-dichloroindoles, identified by unambiguous synthesis from the corresponding 2,4-dichlorophenylhydrazones (58). The chlorine migration was shown to occur prior to the formation of the indole ring and was found to be specific for dichlorophenylhydrazones with a 2,6-orientation (58). Similar migration was also observed in the indolization of cylohexanone 2,6-dichlorophenylhydrazone using aqueous sulfuric acid as a catalyst, which led to the formation of 6,8-dichloro-1,2,3,4-tetrahydrocarbazole (26). Further investigation (62) into the nature of the migrating chlorine atom gave no evidence that intermolecular chlorine transfer, other than possible intermolecular chlorine transfer between rearranging arylhydrazones, was occurring, but strongly suggested that the chlorine migrated in a "positive" condition, in which state it would form a π-electron complex with the aromatic ring during the migration. On this evidence and the observation that the migrating chlorine ultimately appears at the 5-position of the indole nucleus, the following mechanism was postulated (62) for the reaction.

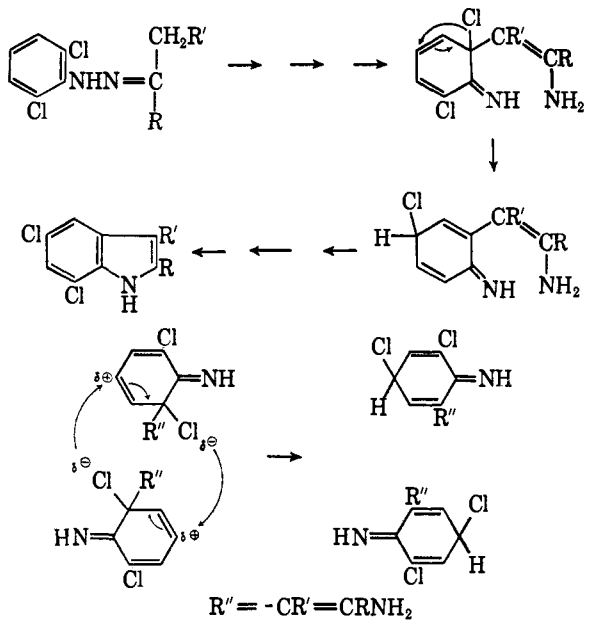


XXX

An alternative mechanism also satisfactorily embodying the experimental results was suggested (212).

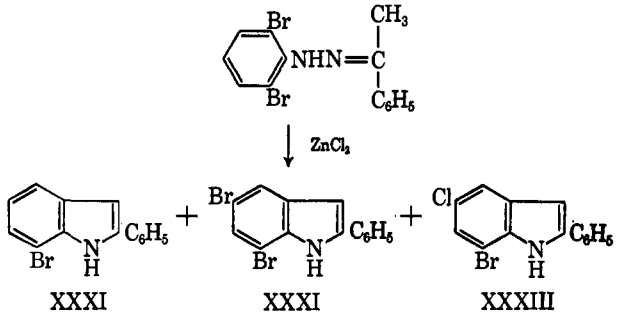
It has been proposed (15) that the polarization in the intermediate XXX could lead to the observed chlorine migration, but the validity of this mechanism is questionable, for it could not operate when halogen exchange occurs (see below).

Subsequent work (60) showed that on treatment of



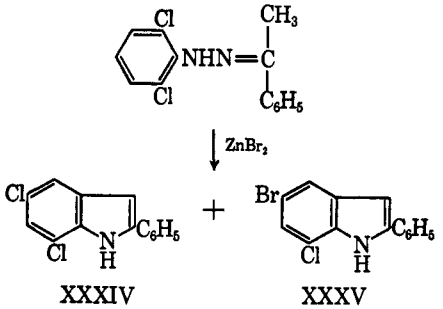
$R'' = -CR'=CRNH_2$

acetophenone 2,6-dibromophenylhydrazone with anhydrous zinc chloride in refluxing nitrobenzene, a mixture of a trace of 7-bromo-2-phenylindole (XXXI), together with approximately equimolar quantities of 5,7-dibromo-2-phenylindole (XXXII) and 7-bromo-5-chloro-2-phenylindole (XXXIII), was formed.



XXXI XXXI XXXIII

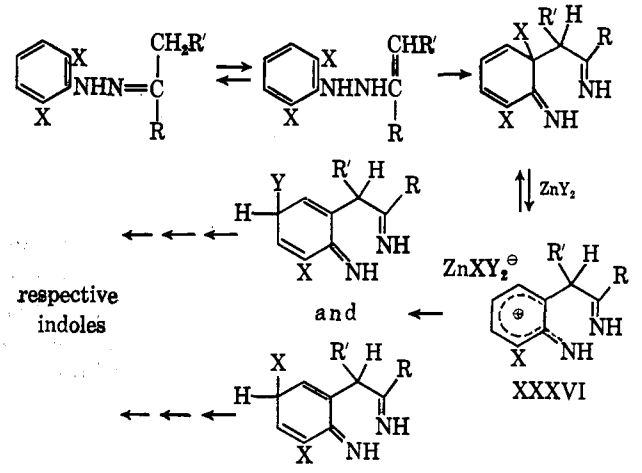
Similar treatment of acetophenone 2,6-dichlorophenylhydrazone with anhydrous zinc bromide gave a mixture of 5,7-dichloro-2-phenylindole (XXXIV) and 5-bromo-7-chloro-2-phenylindole (XXXV).



XXXIV XXXV

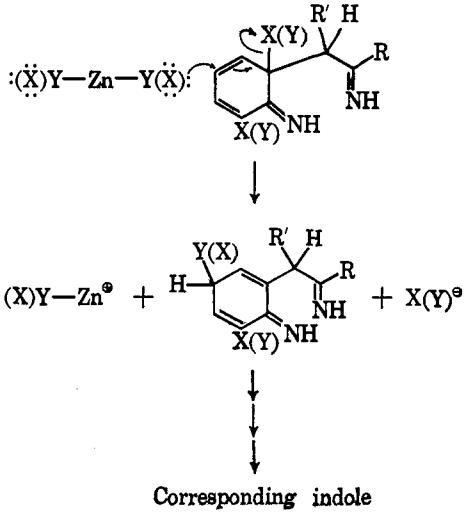
These further studies showed that not only halogen migration (to form XXXII and XXXIV) but halogen exchange (to form XXXIII and XXXV) and replacement of halogen by hydrogen (to form XXXI) can also occur under the appropriate conditions. On the basis of the previous proposed (62) mechanism for

halogen migration in these indolizations, halogen exchange is feasible between $Cl^{\oplus}$ and $ZnBr_2$ (*i.e.*, indolization of a 2,6-dichlorophenylhydrazone with zinc bromide catalyst), but in view of the relative oxidation potentials of the two halogen–halide systems it is unlikely between $Br^{\oplus}$ and $ZnCl_2$ (*i.e.*, indolization of a 2,6-dibromophenylhydrazone with zinc chloride catalyst). The following modified mechanism, in which the migrating halogen in its normal "negative" condition complexes with the zinc halide catalyst, was therefore postulated (60) to account for both halogen migrations and exchanges.

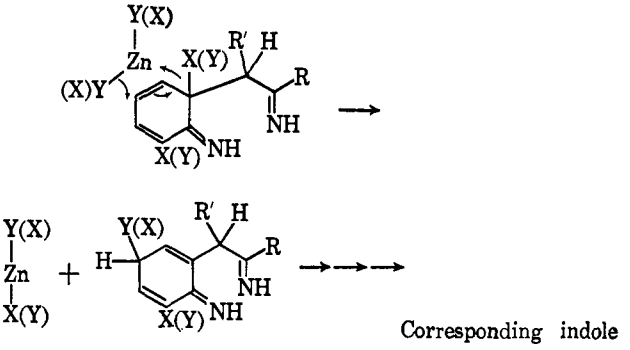


The intermediate XXXVI can also be attacked by hydroxyl anion during similar indolizations with aqueous catalysts (25, 26) to give 5-hydroxyindoles (or 6-hydroxy-1,2,3,4-tetrahydrocarbazoles) (153). Although the above mechanism agrees with the experimental observations, it does not eliminate further possibilities (60): (a) An SN1 transformation, whose only difference to the above mechanism is in the degree of separation of the migrating halogen from the organic moiety.

(b) An SN2 transformation



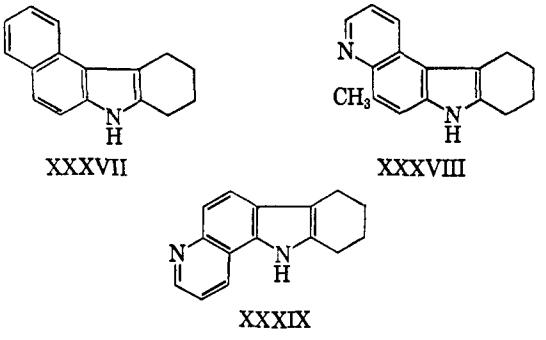
(c) The formation of a 6-membered transition state



The elimination of halogen in the indolization of 2,6-dihalogenophenylhydrazones with anhydrous zinc chloride or stannous chloride to give 7-chloro- or 7-bromoindoles (54, 60) can only be rationalized when the source of hydrogen which displaces the halogen becomes clear (60).

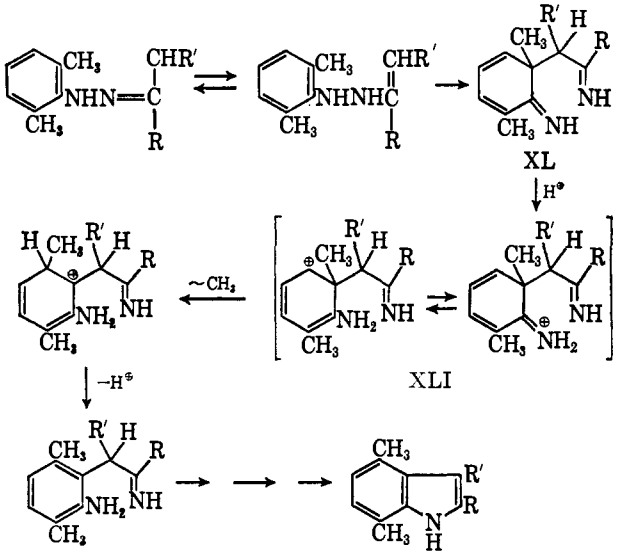
2. *Methyl Group Migration*

Similar migration to that occurring during indolization of 2,6-dihalogenophenylhydrazones occurs when ethyl pyruvate 2,6-dimethylphenylhydrazone is subjected to Fischer indolization conditions; only in this case the methyl group migrates to the 4-position of the subsequent indole nucleus, and in one instance, which could not be repeated or explained, the methyl group migrated to the indole 3-position (59). The previous observations (120) that indolization of cyclohexanone 1-methyl-2-naphthylhydrazone and 5,8-dimethyl-6-quinolylhydrazone, where methyl migration to an adjacent unsubstituted position is not possible, and cyclohexanone 6-methyl-5-quinolylhydrazone gave XXXVII, XXXVIII, and XXXIX, respectively, afford examples of methyl group elimination during Fischer indolization.

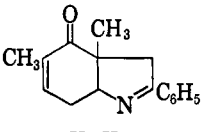


A mechanism was proposed (59) for the methyl migration in the indolization of 2,6-dimethylphenylhydrazones, which combined the Robinson mechanism for the indolization with then current views on the dienone–phenol and *para*-Claisen rearrangement and was similar in principle to the mechanism postulated previously (60) to explain halogen migration or ex-

change when 2,6-dihalogenophenylhydrazones are indolized.



Attempts were made (59) to trap the intermediates XL and XLI as the Diels–Alder addition products, but these failed, probably owing to the much more rapid conversion of these intermediates into the corresponding indoles (59). Subsequent work (56, 57) has, however, strongly supported this mechanism by the isolation of a non-aromatic intermediate XLII, corresponding to XL, from the attempted indolization of acetophenone 2,6-dimethylphenylhydrazone with anhydrous zinc chloride in nitrobenzene. From this reaction five products were isolated and were shown to be 2,6-xylidine, acetophenone, a compound $C_{24}H_{25}NO_2$ of unknown structure, 4,7-dimethyl-2-phenylindole (formed by a 1,2-migration of the methyl group as shown above) and the major component of the reaction mixture, the base XLII, whose structure was verified by degradation.

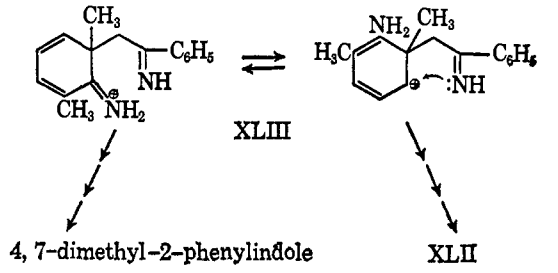


XLII

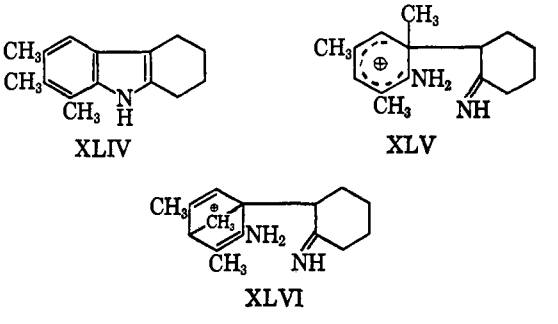
The simultaneous formation of 4,7-dimethyl-2-phenylindole and XLII can arise from the common intermediate XLIII (analogous to XLI in the above mechanism), which can undergo 1,2-methyl migration as already shown to give the indole and also new C–N bond formation, followed by loss of proton, tautomerism and hydrolysis to give XLII.

Nitrogen tracer techniques are to be employed to further investigate this mechanism, for different nitrogen atoms of the original arylhydrazone are lost in the formation of the 4,7-dimethyl-2-phenylindole and XLII (57).

Repetition (61) of earlier work (25), which had incorrectly concluded that the product resulting from the indolization of cyclohexanone mesitylhydrazone with boiling acetic acid was "1,2,3,4-tetrahydro-6,8,12-trimethylisocarbazole," has shown that the product is, in fact, 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole (XLIV). Although the formation of XLIV could possibly involve three 1,2-methyl shifts, a single 1,4-methyl shift was favored, starting with the intermediate XLV (analogous to the previous intermediates XLI and XLIII) and proceeding *via* the transition state XLVI (61).



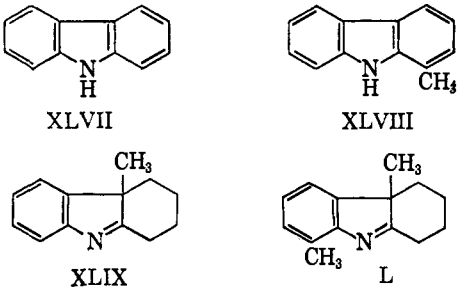
4, 7-dimethyl-2-phenylindole XLII



XLIV XLV XLVI

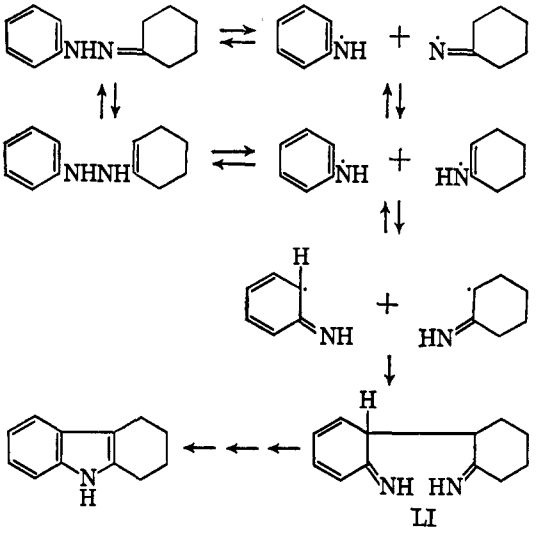
E. THE PAUSACKER MECHANISM

A new mechanistic proposal for stage b of the Robinson mechanism appeared in 1949. It was found (171, 172) that when a mixture of cyclohexanone *o*-tolylhydrazone and 2-methylcyclohexanone phenylhydrazone were subjected to indolization by boiling with glacial acetic acid, four products were obtained. The two neutral products gave carbazole (XLVII) and 1-methylcarbazole (XLVIII) upon dehydrogenation, and the two basic products were 11-methyl-2,3,4,11-tetrahydro-1H-carbazole (XLIX) and 8,11-dimethyl-2,3,4,11-tetrahydro-1H-carbazole (L). Similar results were obtained using a mixture of cyclohexanone *p*-tolylhydrazone and 4-methylcyclohexanone phenylhydrazone.



XLVII XLVIII XLIX L

From these results it was suggested (171, 172) that stage b of the Robinson mechanism was intermolecular in character and involved homolytic fission, either before or after enehydrazine formation, of the N–N bond, followed by free-radical combination leading to the formation of the new C–C bond to give LI, which then reacts according to the latter stages of the Robinson mechanism to give the indole nucleus.

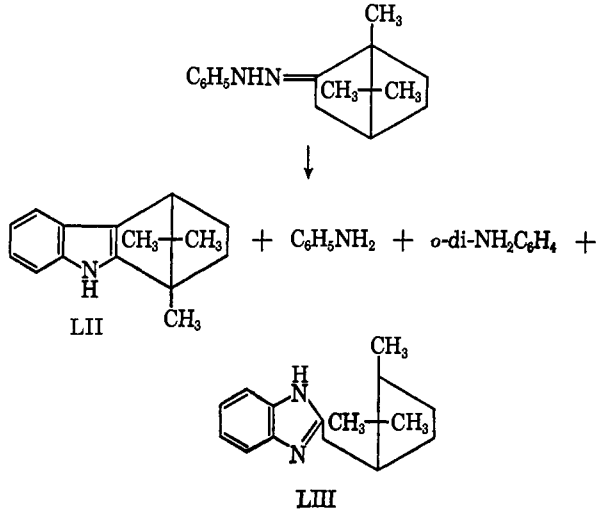


LI

The fact that anilines (as derivatives) and cyclohexanones (by odor) have been detected as by-products of such indolizations as above, together with the observation that indolization of arylhydrazones was favored when the postulated free radical associated with the ketone moiety could be stabilized, was taken as evidence in support of this theory (171, 172).

The interpretation of the above experimental results was, however, questioned, and it was suggested that they might be simply explained by assuming hydrolysis of the two initial arylhydrazones to the corresponding arylhydrazines and cyclohexanones followed by recombination, to give four arylhydrazones, and indolization (199). This was verified (103) when it was found that treatment of equimolar mixtures of acetone phenylhydrazone and cyclohexanone, cyclohexanone 2,4-dinitrophenylhydrazone and phenylhydrazine, benzaldehyde phenylhydrazone, and cyclohexanone, and a 1:5.3 molar mixture of cyclohexanone 2,4-dinitrophenylhydrazone and acetone phenylhydrazone, respectively, in glacial acetic acid, in which acetone phenylhydrazone and cyclohexanone 2,4-dinitrophenylhydrazone do not indolize, gave 1,2,3,4-tetrahydrocarbazole in 50, 10, 5, and 16% yields, respectively, 2,4-dinitrophenylhydrazine also being isolated in 31% yield from the second reaction. Later (14), following the observation that under similar conditions to those used above, mixtures of acetone phenylhydrazone with 2,4-dinitrophenylhydrazine and benzaldehyde gave excellent yields of acetone 2,4-dinitrophenylhydrazone and benzaldehyde phenylhydrazone, respectively, it was suggested that direct transhydrazonation, analogous to transesterification, rather than hydrolysis of the arylhydrazone to the arylhydrazine and ketone or aldehyde followed by recombination, might occur in such reactions.

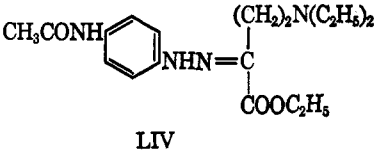
Many Fischer indole syntheses are accompanied by the formation of small amounts of the aniline derived from the arylhydrazine, and recently (214) it has been found that camphor phenylhydrazone, on treatment with anhydrous zinc chloride, gives as well as the expected indole LII, aniline, *o*-phenylenediamine and a compound shown to have structure LIII, this being formed by further reaction of the *o*-phenylenediamine.



LII LIII

The formation of anilines from arylhydrazones under indolization conditions, considered at one time (171, 172) to support the Pausacker modification of the Robinson mechanism, is probably simply an alternative decomposition of the arylhydrazone occurring simultaneously with indolization (16, 107) (see section VII, O).

The observation (29) that the only product isolable from the attempted indolization of LIV was *p*-phenylenediamine sulfate is probably an instance of such an alternative decomposition occurring exclusively.



LIV

III. CATALYSIS OF THE FISCHER INDOLE SYNTHESIS

A. NATURE OF CATALYSTS

The first indolization of an arylhydrazone was effected by the use of an alcoholic solution of hydrogen chloride (91, 92). Later, during an extension of the reaction, it was found that a more versatile reagent for effecting indolization was anhydrous zinc chloride

TABLE I

CATALYSTS USED TO EFFECT THE FISCHER INDOLE SYNTHESIS

Catalyst	References	Catalyst	References
Concd. sulfuric acid	125a, 168, 217a	Hydrogen chloride	137
Alc. concd. sulfuric acid	100	Aq. hydriodic acid	40, 41, 181, 182, 232
Dil. sulfuric acid	24, 26, 209	Alc. aq. hydrobromic acid	40
Alc. sulfuric acid	125a, 168, 217a	Aq. or aq. alc. phosphoric acid	89, 200
Dil. sulfuric acid–acetic acid	112, 119	Hydrogen bromide in glacial acetic acid	119
Alc. sulfuric acid–hydrochloric acid	219	Methanolic phosphoric acid	151, 222
Concd. hydrochloric acid	11, 20, 91, 119, 128, 152, 209	Polyphosphoric acid	132
Concd. hydrochloric acid–acetic acid	125a	Formic acid	200
Dil. hydrochloric acid	91, 113	Acetic acid	125a
Alc. hydrochloric acid	125a	Propionic acid	200
Alc. hydrogen chloride	119	Acetyl chloride in dioxane–chloroform	110
Oxalic acid in ether	40, 41	Stannous chloride–hydrogen chloride	54
Sulfosalicylic acid in aq. 2-propanol	223, 224	Boron trifluoride–benzene	125a
Zinc chloride	125a, 168, 217a	Boron trifluoride etherate	125a
Zinc bromide	60	Boron trifluoride etherate–acetic acid	125a, 163
Platinum chloride	125a, 168, 217a	Aniline salts	237
Cuprous chloride	125a, 168, 217a	Phenol	237
Cuprous bromide	125a, 168, 217a	Amberlite 1R-120 (an ion-exchange resin)	123
Copper acetylacetone complex	137	Phenylmagnesium bromide	106, 107
Copper powder	125a, 168, 217a	Ethylmagnesium bromide	105, 106, 107
Nickel chloride	125a, 168	Benzylmagnesium chloride	106, 107
Nickel chloride–acetic acid	120	Methylmagnesium iodide	106, 107
Nickel powder	125a, 168, 217a	Magnesium chloride	237
Cobalt chloride	125a, 168, 217a	Beryllium chloride	237
Cobalt powder	125a, 168, 217a	Stannous chloride	125a

in five times excess (w./w. with the arylhydrazone) (125a, 217a). The discovery of the catalytic nature of the reaction was made in 1910 by Arbuzov and Tichwinsky who found that the large amounts of anhydrous zinc chloride used previously were unnecessary, the reaction proceeding in good yield in the presence of 1% of this reagent (125a, 217a). In view of this discovery, the catalytic indolization of arylhydrazones is sometimes referred to as the Fischer–Arbuzov reaction (for example see ref. 124). Recently (33), however, it has been found that indolization of ethyl pyruvate *m*-trifluoromethylphenylhydrazone to ethyl 4- and 6-trifluoromethylindole-2-carboxylate only occurred when very large amounts of zinc chloride in glacial acetic acid at reflux temperature were used, the lack of reactivity being ascribed to the deactivating influence of the trifluoromethyl group (33).

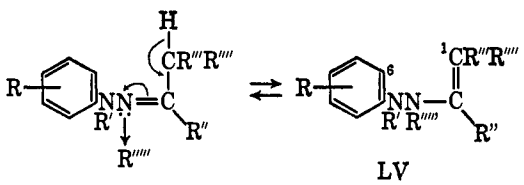
A variety of catalysts (Table I) have been used to effect the indolization of arylhydrazones, and generally speaking it may be said that acids and many compounds capable of complex formation with organic ligands may act as catalysts.

In 1911, the use of an inert solvent such as methylnaphthalene in the reaction and control of the reaction temperature was found to give increased yields of indoles (125a, 217a). To prevent aerial decomposition, Fischer indolizations have been effected in sealed tubes (69) and in a nitrogen atmosphere (100, 215).

B. MECHANISM OF CATALYSIS

In 1918, it was proposed (197) that an acid catalyst and high temperature are necessary for effecting the Fischer indole synthesis, as each successive stage in the reaction mechanism then proposed, which has been subsequently supported by much experimental work (see section II), is more basic than the preceding one, this growing basicity terminating by loss of ammonia and formation of the indole nucleus. However, it has since been found (226, 227) that after the operation of stage a of the reaction mechanism (the tautomerization of the hydrazone to the enehydrazine), indole formation is independent of acid catalysis, although it is markedly accelerated by it. Several 1,6-intramolecular rearrangements of 1,6-conjugated polarized systems similar to stage b of the Robinson mechanism are known (15) which do not require acid catalysis.

In view of this and the fact that previous observations (13, 108, 109) supporting the idea that arylhydrazones in neutral solutions might exist in equilibrium with both the azo and enehydrazine tautomers have been questioned (165), and only the presence of the azo and hydrazone tautomers in neutral solution being detected (165, 166), it would appear that the essential catalytic action is in the establishment of an equilibrium between the hydrazone and enehydrazine tautomers of the arylhydrazones and probably stabilization of the latter by either protonation (R''''' = H) or complex formation (R''''' = electron acceptor molecule) at the more basic nitrogen atom (*i.e.*, the 2-nitrogen atom) in the arylhydrazones.



LV

It has been suggested (15) that further protonation or

complex formation at the 2-nitrogen atom of LV would enhance the polarization of the 1,6-conjugated system and facilitate the rearrangement leading to the new C–C bond formation (stage b), complex formation between boron trifluoride and the azo, hydrazone, and enehydrazine tautomers having previously been suggested (211) not only to account for enehydrazine formation, but also for color changes and geometrical isomerization of arylhydrazones with this reagent. Stabilization and activation of LV are, however, unnecessary, for it need only be a transient intermediate, the equilibrium between it and the hydrazine tautomer being continuously broken in its favor by the irreversible occurrence of stage b of the mechanism. The indolization of arylhydrazones by heating with or without solvent under non-catalytic conditions (97, 195, 235) may well be explained by the formation of the transient intermediate LV (R'''''' = H) under these thermal conditions, the equilibrium being irreversibly broken in favor of indole formation.

IV. THE BORSCHE CARBAZOLE SYNTHESIS

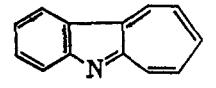
Reviews and textbooks have appeared in which this synthesis is discussed (52, 115b, 125f, 217c).

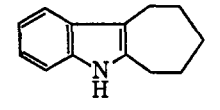
Although the phenylhydrazones of several cyclohexanones were subjected to Fischer indolization prior to 1908, the products being 1,2,3,4-tetrahydrocarbazoles, it was Borsche, Witte, and Bothe in 1908 (34) who further developed the synthesis by dehydrogenation of the 1,2,3,4-tetrahydrocarbazoles to the corresponding carbazoles by heating with lead oxide. Since then, numerous dehydrogenating agents have been successfully employed (Table II).

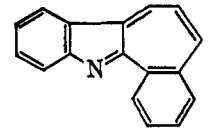
A. LIMITATIONS IN THE USE OF DEHYDROGENATING AGENTS IN THE BORSCHE SYNTHESIS

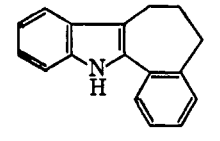
Many of the catalysts listed above are, however, of limited use. In several cases yields are low, and sometimes only black intractable tars are obtained as dehydrogenation products. In some cases substituents are removed during the dehydrogenation (*e.g.*, from 6- and 8-chloro-1,2,3,4-tetrahydrocarbazole using lead oxide and from 7-chloro- and 8-carboxy-1,2,3,4-tetrahydrocarbazole using palladized charcoal, carbazole is obtained). For a summary of these limitations see ref. 24. A catalyst which does not suffer from the drawbacks is chloranil in boiling xylene, which was found (24) to give excellent yields of the corresponding carbazoles from a large variety of substituted 1,2,3,4-tetrahydrocarbazoles. Recently (98), however, a limitation to even this catalyst has been observed in the attempted dehydrogenation of 8-trifluoromethyl-1,2,3,4-tetrahydrocarbazole to 1-trifluoromethylcarbazole which failed, the dehydrogenation being finally accomplished using sulfur in boiling quinoline.

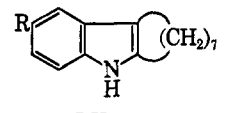
A further limitation to the dehydrogenation subsequent to indolization has been observed using homologs of 1,2,3,4-tetrahydrocarbazoles, for although 1-azo-2,3-benzazulene (LVI) and 1-azo-2,3,7,8-dibenzazulene (LVII) have been obtained by the chloranil dehydrogenation of the corresponding 2,3-cycloheptenoindole (LVIII) and benz-2,3-cycloheptenoindole (LIX) (231), attempted dehydrogenation (45), with both chloranil in boiling xylene and with selenium, of the 2,3-cyclononenoindoles (LX, R = H and CH_3) and 6,7-benz-2,3-cyclononenoindole (LXI), in an attempt to prepare the next higher fully aromatic homolog containing the group LXII, failed, as did an attempt (48) to dehydrogenate LXIII.

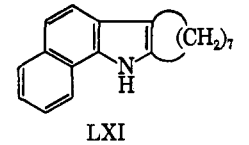

LVI

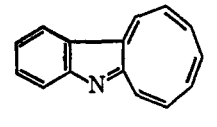

LVIII


LVII


LIX


LX


LXI


LXII

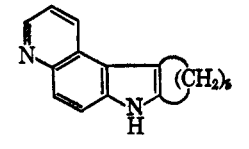

LXIII

Table II

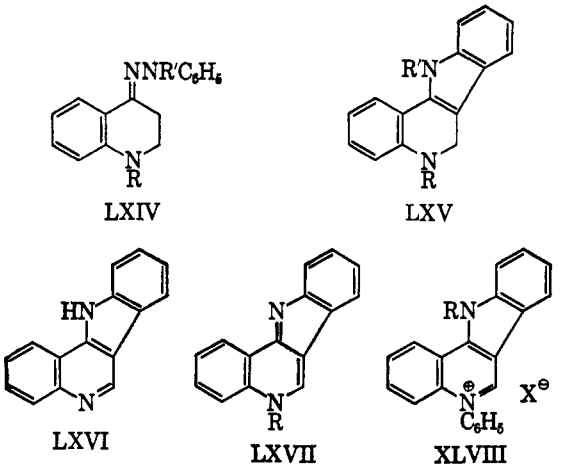
DEHYDROGENATING AGENTS USED IN THE BOSCHE CARBAZOLE SYNTHESIS

Dehydrogenating catalyst and conditions	References
Distillation over lead oxide	52, 125f, 217c
Sulfur in boiling quinoline	52, 217c
Mercurous acetate in glacial acetic acid	52, 125f, 217c
Palladous chloride in dilute hydrochloric acid	52, 217c
5% palladium on charcoal in boiling xylene	125f, 217c
Fusion with palladium and cinnamic acid	52, 125f, 217c
Heat to 200–230° with a hydrogenation catalyst in the absence of hydrogen with a phenol, aldehyde, or unsaturated aliphatic compound	125f, 217c
Chloranil in boiling xylene	52, 125f, 217c
Heat with a mixture of copper, chromium and barium oxides	217c
Naphthalene in the presence of a nickel catalyst	217c
Pallidized charcoal at elevated temp. in a stream of hydrogen	154, 172
Raney nickel in refluxing xylene	21
Sublimation over palladium–charcoal	49

B. OCCURRENCE OF SIMULTANEOUS DEHYDROGENATION WITH INDOLIZATION

In 1924 (70), it was found that indolization of 1,2,3,4-tetrahydro-4-oxoquinoline phenylhydrazone (LXIV, R = R' = H) with dilute sulfuric acid gave not the

expected indole LXV (R = R′ = H) but the fully aromatic compound LXVI, the formation of which involves the occurrence of dehydrogenation simultaneously with indolization. No further study of this observation was reported until 1949, when it was found (73) that indolization of 1,2,3,4-tetrahydro-4-oxo-1-phenylquinoline phenylhydrazone (LXIV, R = C_6H_5, R′ = H) with alcoholic hydrogen chloride gave not the expected indole LXV (R = C_6H_5, R′ = H) but the fully aromatic compound LXVII (R = C_6H_5), the structure of which was supported by analytical data (73), the yellow color of the product which disappeared on acidification owing to the formation of LXVIII (R = H) (73, 140) and the formation of a nearly colorless methiodide and ethiodide (LXVIII, R = CH_3 and C_2H_5, respectively, X = I) (140).



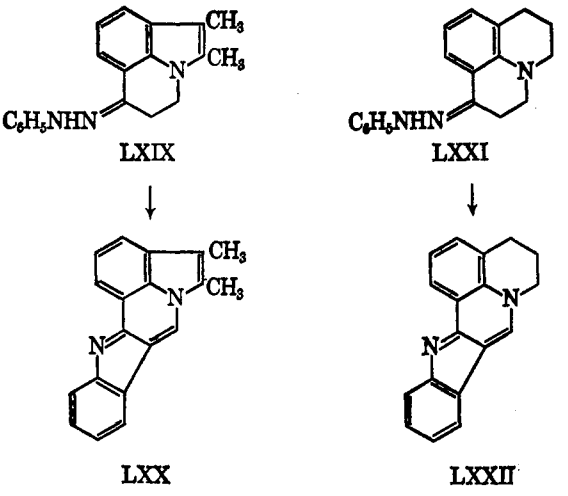
LXIV LXV LXVI LXVII XLVIII

Also, the corresponding 1-methylphenylhydrazone LXIV (R = C_6H_5, R′ = CH_3) gave on similar indolization the expected indole LXV (R = C_6H_5, R′ = CH_3), in this case dehydrogenation to the fully aromatic system being prevented by the two N-substituents (140) (see also 35, 142).

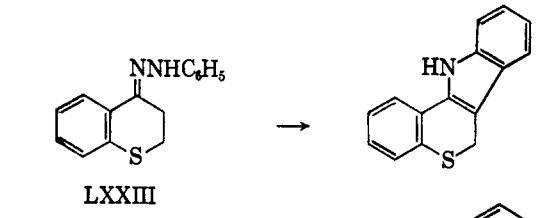
Similarly, LXIV (R = CH_3, R′ = H) gave LXVII (R = CH_3), whereas the corresponding 1-phenylphenylhydrazone LXIV (R = CH_3, R′ = C_6H_5) gave the indole LXV (R = CH_3, R′ = C_6H_5) (35).

Further examples of this simultaneous dehydrogenation with indolization were found on using the phenylhydrazones of compounds analogous to the 1,2,3,4-tetrahydro-4-oxoquinolines used above. Thus, indolization of LXIX, again using ethanolic hydrochloric acid as catalysts, gave LXX (9), and LXXI similarly afforded LXXII (142).

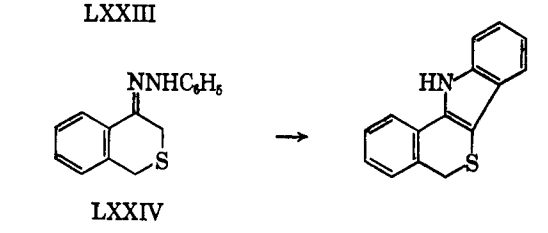
The simultaneous dehydrogenation failed to occur upon indolization of LXXIII (129), LXXIV (129), LXXV (144), LXXVI (8), LXXVII (36), LXXVIII (143) (in this case evidence suggested that the indole initially formed isomerized to give the product shown) and LXXIX (37), using as catalyst ethanolic hydrogen chloride except for the indolization of LXXV which required zinc chloride in acetic acid. In all these cases, the normal indole was produced as shown.



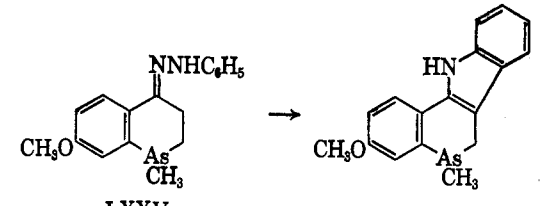
LXIX LXXI LXX LXXII



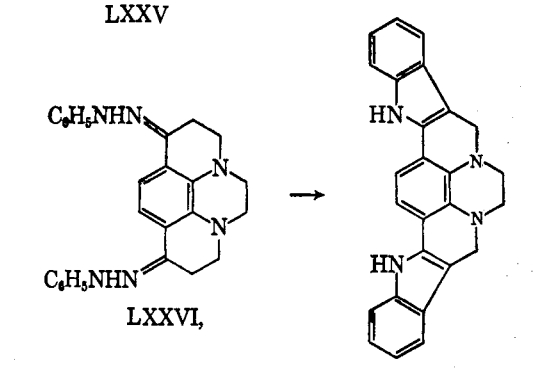
LXXIII



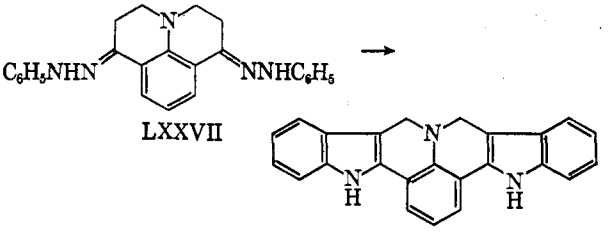
LXXIV



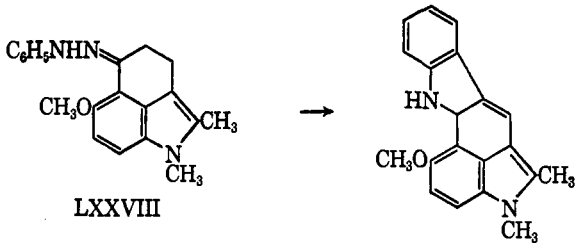
LXXV



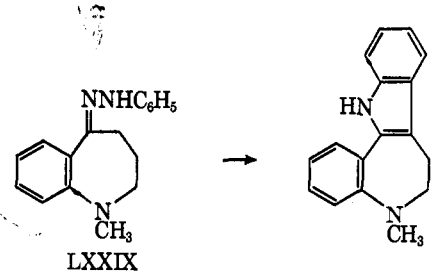
LXXVI,



LXXVII



LXXVIII

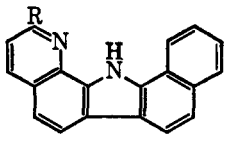


LXXIX

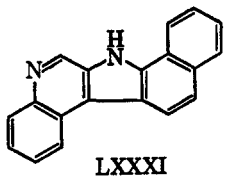
From the above results it was concluded (35, 36, 37, 144) that for the simultaneous dehydrogenation to accompany indolization as above, the following conditions had to be satisfied. (a) Aromatization to give fully aromatic cations such as LXVIII (R = H), which are the reaction products prior to working up by basification, has to be possible. (b) Conjugation between the nitrogen atom of the keto-amine and the potential indolo-nitrogen atom is necessary. (c) Orientation of the two fused hetero rings so that dehydrogenation will further conjugate the two nitrogen atoms, as shown in LXVII for example, is necessary.

Recently (49) several further instances of simultaneous dehydrogenation, involving the removal of two hydrogen atoms to give a fully aromatic polynuclear system, occurring alongside Fischer indolization have been observed, although the compounds in question and the indolization catalyst were of an entirely different nature to these used above. Thus, 1-tetralone 8-quinolylhydrazone, 2-methyl-8-quinolylhydrazone and 3-quinolylhydrazone, 1,2,3,4-tetrahydro-4-oxophenanthrene 8-quinolylhydrazone and 3-quinolylhydrazone, and 1,2,3,4-tetrahydro-1-oxophenanthrene 8-quinolylhydrazone and 3-quinolylhydrazone give directly on indolization by heating with anhydrous zinc chloride the fully aromatic polynuclear compounds LXXX (R = H and CH_3, respectively), LXXXI, LXXXII, LXXXIII, LXXXIV, and LXXXV, respectively.

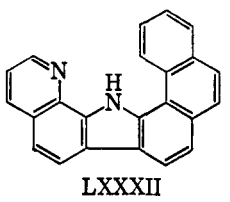
The indolization of 1,2,3,4-tetrahydro-1-oxocarbazole phenylhydrazone is also accompanied by spontaneous dehydrogenation, using glacial acetic acid as a catalyst, to give LXXXVI (30), similar dehydrogenation accompanying the later preparation (145) of an isomeric compound by indolization of 1,2,3,4-tetrahydro-4-oxocarbazole phenylhydrazone.



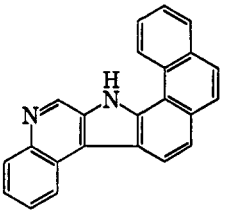
LXXX



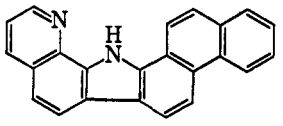
LXXXI



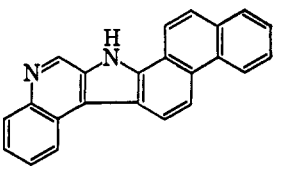
LXXXII



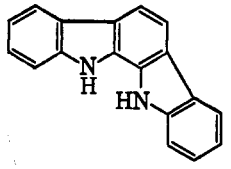
LXXXIII



LXXXIV



LXXXV

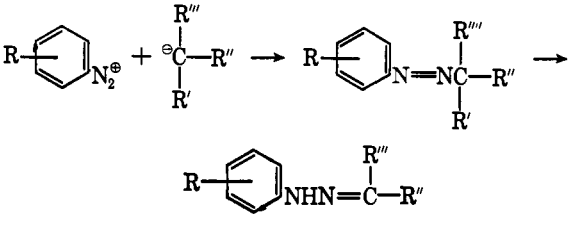


LXXXVI

V. The Japp–Klingemann Reaction

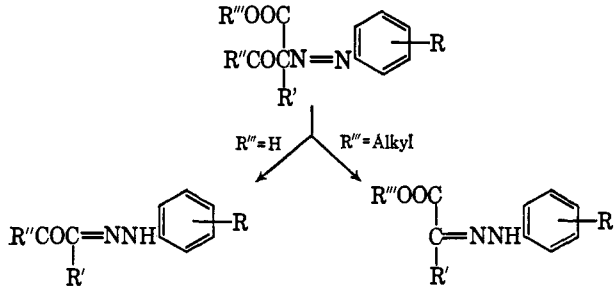
This subject was reviewed in 1959 (178).

The scope of the Fischer indole synthesis is widened by the use of the Japp–Klingemann reaction as an alternative method for the preparation of arylhydrazones. The reaction consists essentially of electrophilic attack of an aryldiazonium cation on the anionic carbon atom of an active methinyl compound to give an intermediate azo compound, which ordinarily undergoes hydrolysis under the conditions of the coupling reaction, with expulsion of one of the original carbon substituents, to give an arylhydrazone.



Although normally two or three of the carbon substituents in the active methinyl compound are electron-withdrawing groups, other labilizing influences on the proton are known (178).

Using a 2-keto ester in the reaction, cleavage of the intermediate azo compound occurs between the acyl group and the original methinyl carbon atom. Using, however, a 2-keto acid, elimination of carbon dioxide occurs.

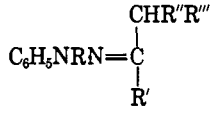


VI. DIRECTION OF INDOLIZATION

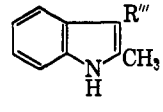
A. INDOLIZATION OF ASYMMETRICAL ACYCLIC KETONE ARYLHYDRAZONES

Arylhydrazones of this type can conceivably lead to two products on Fischer indolization.

In the case of methyl ketone phenylhydrazones (LXXXVII, R = R'' = H, R' = CH_3, R''' = alkyl or substituted alkyl, C_6H_5, $COOC_2H_5$) it is well established (50, 79, 89, 124, 126, 163, 164, 168, 204, 205) that indolization gives exclusively the corresponding 3-substituted 2-methylindoles (LXXXVIII).



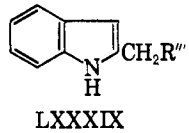
LXXXVII



LXXXVIII

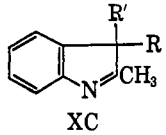
One exception, however, is the indolization of ethyl methyl ketone phenylhydrazone, which has been reported (89, 137) to give not only 2,3-dimethylindole but small amounts of 2-ethylindole.

In studying the direction of indolization of the above ketone phenylhydrazones, four methods have been used to distinguish between the two possible structures LXXXVIII and LXXXIX of the product: (i) acetyla-

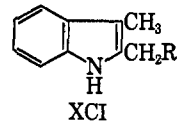


LXXXIX

tion, which gives a 1-monoacetyl and 1,3-diacetyl derivative, respectively (50); (ii) 3-monomethylation, which gives a basic 3-alkyl-2,3-dimethyl-3H-indole (XC, R = CH_3, R' = alkyl) and a non-basic 2-alkyl-3-methylindole (XCI, R = alkyl), respectively (65, 79, 90, 93, 96); (iii) oxidative scission of the indolic 2,3-C=C to yield known substituted benzene derivative (163, 204, 205); (iv) unambiguous synthesis of the indole formed by the indolization (124).

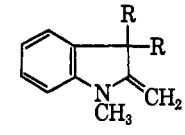


XC

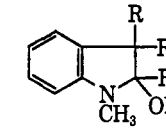


XCI

2-Methyl-3H-indoles (XC, R and R' = alkyl) can also be unambiguously synthesized, for it is known (118, 125a, 168, 217a) that indolization of ketone phenylhydrazones of the type LXXXVII (R = H, R' = CH_3, R'' and R''' = alkyl) gives exclusively XC (R and R' = alkyl). In fact, using 1-methylphenylhydrazones of such ketones (LXXXVII, R = R' = CH_3, R'' and R''' = alkyl), enamines (XCII, R and R' = alkyl) rather than the indole are formed (125c, 168, 217a). Where enamine formation is inhibited, 2-hydroxyindolines (XCIII, R = H and C_6H_5, R' and R'' = alkyl) are the products, these arising by action of base on the initially formed 3H-indolium salts (217a, 217f).



XCII



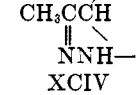
XCIII

However, in LXXXVII (R = H, R' = *n*-alkyl, R'' and R''' = alkyl, R' ≠ CH_3) indolization occurs in both possible directions and leads to a mixture of the corresponding indole and 3H-indole (182).

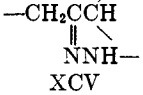
Indolization of isobutyl isopropyl ketone phenylhydrazone has been found (50) to give exclusively 2,3-diisopropylindole, whereas by analogy with the above indolization the product might have been expected to have been a mixture of this indole and the isomeric 2-isobutyl-3,3-dimethyl-3H-indole. However, the structure of the product was not verified.

The following rules have been given (182) regarding the direction of indolization of the above types of ketone arylhydrazones:

(i) A ketone arylhydrazone containing the group XCIV indolizes to give only the 3H-indole. (ii) A



XCIV



XCV

XCVI

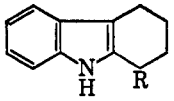
ketone arylhydrazone containing the group XCV gives both the indole and 3H-indole on indolization. (iii) A ketone arylhydrazone containing the group XCVI gives only the 3-alkyl-2-methylindole on indolization.

The direction of indolization of unsymmetrical ketone phenylhydrazones (LXXXVII, R = R'' = H, R' = alkyl containing a 1-methylene group, R'' = alkyl, R' ≠ CH_3) does not appear to have been very thoroughly investigated, although it might be expected that both possible isomeric indoles would result. However, ethyl *n*-propyl ketone phenylhydrazone has been reported (18, 19) to give only one product, but the structure was not determined. Similarly, ethyl and propyl isobutyl ketone phenylhydrazones are indolized to apparently homogeneous products, which,

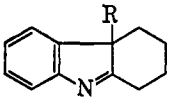
without chemical evidence but since the products were oils, were thought (50) to be 2-isobutyl-3-methylindole and 2-isobutyl-3-ethylindole, respectively. Indolization of ethyl *n*-propyl and *n*-hexyl ketone phenylhydrazones has been said (50) to give a mixture of both possible indoles in each case. Indolization of benzyl ethyl ketone *p*-tolylhydrazone, phenylhydrazone and 1-methylphenylhydrazone has been found (124) to give exclusively 2-benzyl-3,5-dimethylindole, 2-benzyl-3-methylindole and 2-benzyl-1,3-dimethylindole, respectively.

B. INDOLIZATION OF 2-ALKYLCYCLOHEXANONE ARYLHYDRAZONES

These compounds are the cyclic analogs of LXXXVII (R = H, R′, R″ and R‴ = *n*-alkyl, R′ ≠ CH_3), and just as indolization of these latter phenylhydrazones gives mixtures of the corresponding indole and 3H-indole, both the 1-alkyl-1,2,3,4-tetrahydrocarbazole (XCVII, R = alkyl) and 11-alkyl-2,3,4,11-tetrahydro-1H-carbazole (XCVIII, R = alkyl) are formed from 2-alkylcyclohexanone phenylhydrazones. Preliminary studies were carried out using

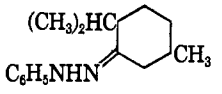


XCVII



XCVIII

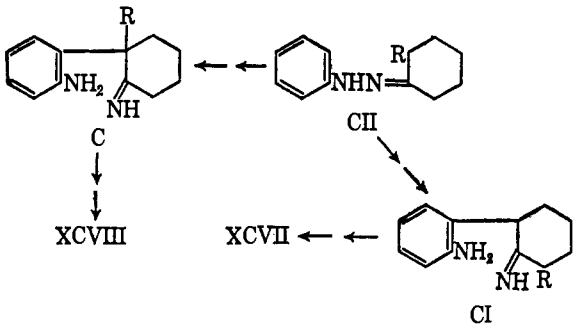
alcoholic zinc chloride (180, 185, 186) and sulfuric acid (172) as catalysts in the indolization of 2-methylcyclohexanone phenylhydrazone, when a mixture of XCVII (R = CH_3) and XCVIII (R = CH_3) resulted in each case. Menthone phenylhydrazone (XCIX) similarly gave a mixture of both possible products on indolization with alcoholic zinc chloride (183).



XCIX

It was subsequently found (149, 170) that the relative quantities of XCVII and XCVIII produced on indolization of 2-alkylcyclohexanone phenylhydrazones depended upon the catalyst used. With glacial acetic acid largely XCVIII was obtained, whereas using aqueous sulfuric acid, XCVII was the main product (R = CH_3, C_2H_5, iso-C_3H_7, cyclohexyl and C_6H_5). To explain this effect it was suggested after further study (170) that the rates of formation of C and CI (the two possible intermediates after the occurrence of stage b of the reaction mechanism) was related to the differing proton affinities of the initial phenylhydrazone CII in the indolization media used.

The preparation of a number of further 11-alkyl-2,-3,4,11-tetrahydro-1H-carbazoles (XCVIII, R = *n*-C_3H_7, *n*-C_4H_9, *n*-C_6H_{13}, and *n*-C_8H_{17}) has since been effected (45) from the corresponding 2-alkylcyclohexanone phenylhydrazones using hydrogen chloride in acetic acid as catalyst, but no attempt to isolate the possible non-basic 1-alkyl-1,2,3,4-tetrahydrocarbazoles was reported (45). The attempted indolization of 2-ethylcyclopentanone phenylhydrazone under similar conditions failed (45).



CI

C. INDOLIZATION OF 3-SUBSTITUTED CYCLOHEXANONE ARYLHYDRAZONES

The indolization of 3-methylcyclohexanone phenylhydrazone has led to conflicting results; it being claimed that both possible isomeric products, 1,2,3,4-tetrahydro-2- and 4-methylcarbazoles, are formed (184) and that only the 2-methyl isomer is formed (24, 34). The orientation of the 2-methyl isomer was verified by its dehydrogenation to 2-methylcarbazole which was unambiguously synthesized (24, 34). It need not be, however, that the observation (184) that both possible isomers are formed is incorrect, as in the latter two papers the 2-methyl isomer was isolated in low (24) and unspecified (34) yield, which suggests that the 4-methyl isomer might be produced but remains unisolated. In fact, it has been reported (107) that the indolization affords 1,2,3,4-tetrahydro-2-methylcarbazole and other products.

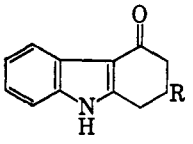
Indolization of cyclohexanone-3-carboxylic acid phenylhydrazone has been said (23) to give only 1,2,3,4-tetrahydrocarbazole-4-carboxylic acid, but structural verification of the product was lacking. Here again it could be that both isomers are formed and that one remains unisolated, or alternatively the product obtained could be a eutectic mixture of both isomers.

It would be expected that both 2- and 4-substituted 1,2,3,4-tetrahydrocarbazoles are formed by indolization of 3-substituted cyclohexanone phenylhydrazones.

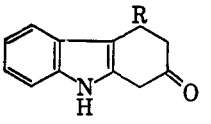
D. INDOLIZATION OF CYCLOHEXANE-1,3-DIONE ARYLHYDRAZONES

1. The Monophenylhydrazone

Cyclohexane-1,3-dione monophenylhydrazone can possibly give rise to two products, CIII (R = H) and CIV (R = H), on indolization.



CIII



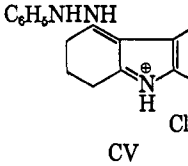
CIV

It has been found (68), however, that only one of these isomers is formed, structure CIII (R = H) being favored since the product gave a deep maroon-colored 2,4-dinitrophenylhydrazone, although this was inconclusive since possible complex formation could also give rise to a similar color. Attempts to dehydrogenate the product to the corresponding hydroxycarbazole failed (68), but following the observation (68) that the carbonyl group could be reduced to a methylene group, the following indirect evidence supporting structure CIII (R = H) was obtained. 5-Methylcyclohexane-1,3-dione monophenylhydrazone was indolized under the same conditions to those used above to give only one of the two possible isomeric products, CIII (R = CH_3) or CIV (R = CH_3). This product again gave a deep maroon-colored 2,4-dinitrophenylhydrazone, its structure being definitely established as CIII (R = CH_3) by reductive removal of the carbonyl group followed by dehydrogenation to 2-methylcarbazole (68). Thus, by analogy, the structure of the product obtained by indolization of cyclohexane-1,3-dione monophenylhydrazone is CIII (R = H) (68). The formation of CIII rather than CIV would be theoretically expected, since enehydrazine formation, the initial stage in the reaction mechanism, will be favored in the direction of the free carbonyl group.

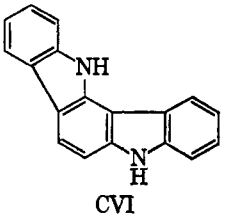
2. *The Diphenylhydrazone*

The diphenylhydrazone of not only cyclohexane-1,3-dione but also cyclohexane-1,4-dione can possibly each give rise to two isomeric products on indolization.

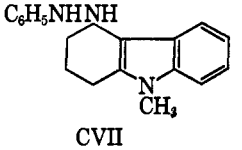
It has been found (145) that 1,2,3,4-tetrahydro-4-oxocarbazole [which is the product resulting from indolization of cyclohexane-1,3-dione monophenylhydrazone (68)] reacts with phenylhydrazine in acid solution to give CV, which on pyrolysis under reduced pressure is indolized and simultaneously dehydrogenated to CVI, previous attempts (30) to prepare the ring system of CVI by indolization of CVII having failed.



CV



CVI

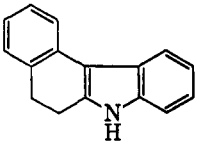


CVII

A compound which had been obtained previously (230) by a different route and which had been given structure CVI was identical with the product obtained in this case (145), which also had the same physical properties as a sample of CVI previously synthesized (111) by another alternative method.

E. INDOLIZATION OF 2-TETRALONE ARYLHYDRAZONES

Using dilute sulfuric acid as catalyst, 2-tetralone phenylhydrazone has been found to give only one of the two possible isomeric products, this being shown to have structure CVIII by dehydrogenation to 3,4-benzocarbazole (102).



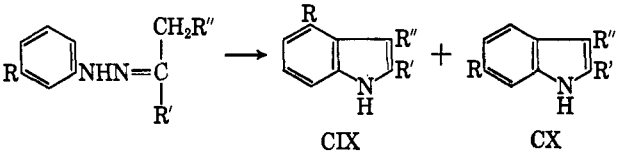
CVIII

This might be expected considering the direction of enehydrazine formation from the hydrazone in the initial stage of the reaction mechanism.

F. INDOLIZATION OF *m*-SUBSTITUTED PHENYLHYDRAZONES

This problem has occupied the attention of many schools.

After initial consideration (204, 205) of the relative amounts of 4-(CIX) and 6-(CX) isomers formed by indolization of various *m*-substituted phenylhydrazones, further examples of such ambiguous indolizations were studied (164), and the ratio CIX:CX formed in each case, alongside other examples from previous work, which gave considerable variation in R, R′ and R″, were tabulated (164). It was found (164)



CIX CX

that CIX:CX < 1 when R was a group which in electrophilic aromatic substitution is strongly *ortho–para* directing, whereas when R is normally strongly *meta–ortho* directing group CIX:CX > 1. In two cases where R was only a weakly *ortho–para* directing group (*i.e.*, Cl) only CIX was formed in one instance and only CX in the other. Thus the CIX:CX ratio/substituent relationship is in accordance with the indolization mechanism (see section II) considering the formation of the new C–C bond (stage b) as being an intramolecular electrophilic attack (164). In two instances the CIX:CX ratio did not agree with this theory, but this was attributed to either steric reasons or to the acidity of the indolization media, for in one

of these cases the correct ratio was restored by a change of catalyst (164). Several other examples, with R = OCH_3 (64, 88, 150), NO_2 (169), CF_3 (33), and F (6), have appeared in the literature in which the CIX:CX ratio/substituent relationship supports the above theory. Further apparent exceptions also occur when R = CH_3 (5, 210), CF_3 (98), F (7) and COOH (72), but again these discrepancies could be owing to one or the other of the reasons given above. In some instances the inefficiency of the separation technique used on the mixtures of 4- and 6-substituted indoles may be the cause of discrepancy, this factor requiring consideration when the CIX:CX ratio is close to unity.

Several methods have been employed to separate the two isomers formed by indolization of *m*-substituted phenylhydrazones, including fractional crystallization (6, 33, 100, 136, 169, 205, 210), fractional crystallization partially *via* picrates or acetyl derivatives (64, 72, 154, 164, 191), column chromatography (6, 7, 24, 164, 204, 205, 221), and hand separation of different crystalline forms (10).

The principal methods used to determine the orientation of such indoles or 1,2,3,4-tetrahydrocarbazoles include oxidative scission of the indole 2,3-C=C which leads to known substituted benzenes (64, 72, 136, 164, 190, 204, 205), dehydrogenation of 1,2,3,4-tetrahydrocarbazoles to carbazoles of known orientation (7, 10, 24, 99, 154), and unambiguous synthesis of 4- and 6-substituted indoles which are identified with those from the indolizations, either before or after further modification of the latter (6, 33, 72, 88, 100, 127, 150, 169, 188, 191, 210).

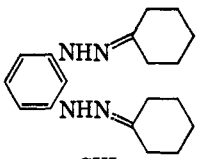
In some cases, with R = CH_3 (10), Cl (100, 154), and Br (191), both the possible 4- and 6-substituted indoles were formed but the relative yields were not determined or quoted, and in others, with R = OCH_3 (177), CH_3 (77), NO_2 (206), and Cl (216, 221), the orientation of the indolization product(s) remained undetermined.

G. INDOLIZATION OF *m*-PHENYLENEDIHYDRAZONES

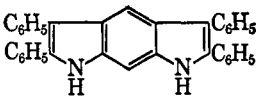
Indolization of both *m*- and *p*-phenylenedihydrazones can possibly give two isomeric products in each case.

It has been found (230) that indolization of biscyclohexanone *m*-phenylenedihydrazone (CXI) affords only one product, this being given the angular structure CXII, as opposed to the possible linear isomer, on a theoretical basis and by analogy with such reactions as the Skraup reaction with *m*-phenylenediamine. However, structural verification was obtained by dehydrogenation of CXII to the corresponding fully aromatic compound (230) which was later (11, 145) unambiguously synthesized.

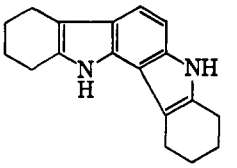
The linear structure CXIII has, however, been preferred (202) for the product obtained on indolization of bisdesoxybenzoin *m*-phenylenedihydrazone, although no structural verification was given.



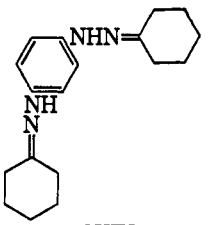
CXI



CXIII



CXII

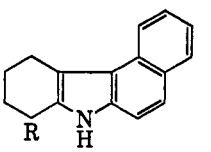


CXIV

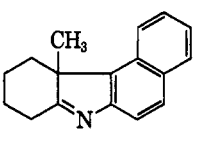
Attempts (71, 230) to indolize biscyclohexanone *p*-phenylenedihydrazone (CXIV) were unsuccessful.

H. INDOLIZATION OF 2-NAPHTHYLHYDRAZONES

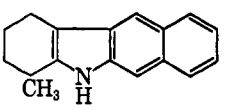
It has been found (162) that indolization of cyclohexanone 2-naphthylhydrazone gives exclusively CXV (R = H), the structure of which was verified by dehydrogenation to the known 3,4-benzocarbazole. Similarly, 2-methylcyclohexanone 2-naphthylhydrazone, initially (63) thought, without experimental verification, to give the linear isomers CXVII and CXVIII, was later (43) shown to give exclusively the angular



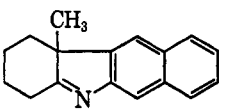
CXV



CXVI

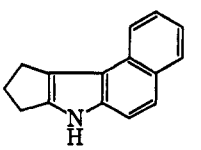


CXVII



CXVIII

isomers CXV (R = CH_3) and CXVI, and cyclopentanone 2-naphthylhydrazone was shown (43) to give exclusively CXIX.



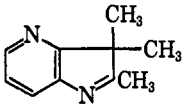
CXIX

It can be concluded that in the indolization of 2-naphthylhydrazones the formation of the new C–C bond occurs at the 1-position and not the 2′-position of the naphthalene nucleus, this being in accordance with the mechanism of the formation of the new C–C bond being an intramolecular electrophilic substitution, since elec-

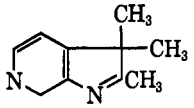
trophilic substitution into the naphthalene nucleus occurs at the 1- rather than the 2-position.

I. INDOLIZATION OF 3-PYRIDYLHYDRAZONES

It has been assumed (80) that indolization of 2-chloro-5-pyridylhydrazones gives 4-azaindoles rather than 6-azaindoles owing to the new C–C bond formation occurring at the 6- rather than at the 4-position of the pyridine nucleus. Similarly, indolization of methyl isopropyl ketone 3-pyridylhydrazone gives only one product, either CXX or CXXI (87). Support for



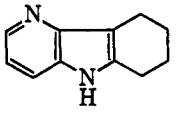
CXX



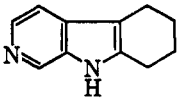
CXXI

structure CXX, which would be expected by analogy with the observation that pyridines containing an *ortho–para* directing 3-substituent undergo electrophilic substitution at the 2- rather than at the 4-position, arises from infrared spectral data, which indicate the three adjacent hydrogen atoms on the pyridine nucleus, and quaternization, which leads almost exclusively to the 1-methiodide, the difficulty in quaternization of the nitrogen atom in the pyridine nucleus being attributed to the steric hindrance of the neighboring *gem*-dimethyl group in CXX (87).

Contrary to the above observations, indolization of cyclohexanone 3-pyridylhydrazone has been found (1) to give a mixture of both possible isomeric products CXXII and CXXIII, although in agreement with the above results, ring closure at the 2-position of the pyridine nucleus predominated.



CXXII

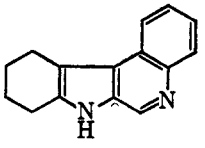


CXXIII

J. INDOLIZATION OF 3-, 6-, AND 7-QUINOLYLHYDRAZONES

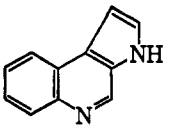
1. 3-Quinolylhydrazones

Indolization of cyclohexanone 3-quinolylhydrazone gives exclusively CXXIV, which was identified by aromatization followed by comparison with an authentic specimen of the fully aromatic product (67). Similarly,



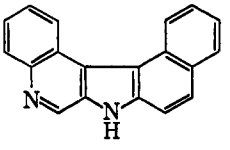
CXXIV

indolization of ethyl pyruvate 3-quinolylhydrazone with excess anhydrous zinc chloride, which also caused simultaneous hydrolysis and decarboxylation, gave only CXXV (104) whose physical constants agreed with those previously reported for this compound. 2-Tetra-

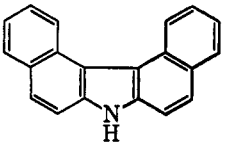


CXXV

lone 3-quinolylhydrazone also gave only one of the two possible indolization products, subsequent catalytic dehydrogenation leading to the fully aromatic polynuclear compound which was shown to have structure CXXVI, as opposed to the other possible isomer, owing to the similarity of its ultraviolet spectrum with that of the benzenoid isoster CXXVII (49).



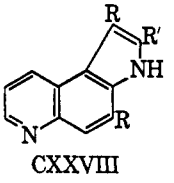
CXXVI



CXXVII

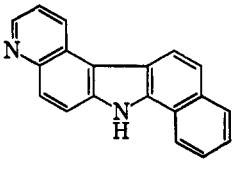
2. 6-Quinolylhydrazones

Indolization of ethyl pyruvate 6-quinolylhydrazone gives exclusively CXXVIII (R = H, R′ = $COOC_2H_5$) (233), whose structure was verified by the similarity of the ultraviolet spectrum of the hydrolyzed and decarboxylated product CXXVIII (R = R′ = H) with that of CXXVIII (R = C_2H_5, R′ = H), unambiguously synthesized from butyraldehyde 7-ethyl-6-quinolylhydrazone (116, 121, 233). Subsequently, several 6-quin-

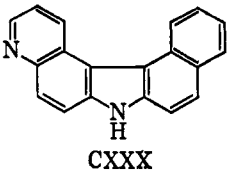


CXXVIII

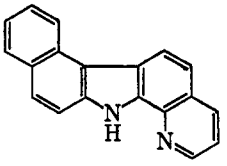
olylhydrazones were assumed to indolize in the same direction (67, 81), and recently (48) indolization of 1- and 2-tetralone 6-quinolylhydrazones has been shown to occur in the same direction, the fully aromatic polynuclear products resulting from dehydrogenation of the initial indolization products being shown to be CXXIX and CXXX, respectively, as opposed to the alternative isomers, owing to the similarity of their ultraviolet spectra with their benzenoid isosters (46, 48) and the ultraviolet spectrum of CXXIX with that of CXXXI (46).



CXXIX



CXXX

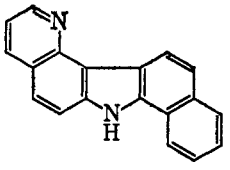


CXXXI

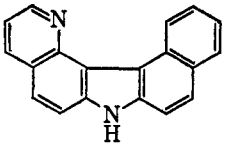
Similarly, only one product was obtained from the indolization of cyclohexanone 6-quinolylhydrazone, this being shown by unambiguous synthesis to have the angular and not the isomeric linear structure (139a).

3. *7-Quinolylhydrazones*

Indolization of 1- and 2-tetralone 7-quinolylhydrazone has been shown to give, after aromatization of the initial products, CXXXII and CXXXIII, respectively, as opposed to the possible isomeric alternatives, owing to the similarity of their ultraviolet spectra with the corresponding benzenoid isosters, and to the similarity of the ultraviolet spectrum of CXXXII with CXXXI (46). Also, cyclohexanone 7-quinolylhydrazone gives



CXXXII



CXXXIII

only the angular product on indolization, the structure being verified by unambiguous synthesis (139a).

Thus it can be concluded that during indolization of 3-, 6-, and 7-quinolylhydrazones, formation of the new C–C bond occurs between the appropriate carbon atom of the ketone or aldehyde moiety and the 4-, 5-, and 8-carbon atoms of the quinoline nucleus, respectively, this being as expected theoretically considering the mechanism of formation of the new C–C bond during indolization and the direction of electrophilic substitution in the quinoline nucleus (46, 48, 120, and references therein).

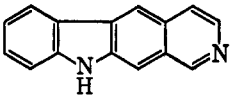
K. INDOLIZATION OF 6- AND 7-ISOQUINOLYLHYDRAZONES

1. *6-Isoquinolylhydrazones*

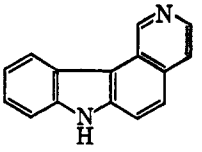
Although the indolization of 6-isoquinolylhydrazones has not been investigated owing to the failure to prepare 6-hydrazinoisoquinoline (147), the new C–C bond formation during such indolizations would be expected to occur at the 5- rather than the 7-position of the isoquinoline nucleus, since electrophilic substitution in the isoquinoline nucleus occurs predominantly at position 5 (or 8) (101).

2. *7-Isoquinolylhydrazones*

Cyclohexanone 7-isoquinolylhydrazone has been found (146) to give on indolization only one of the two possible isomeric products, which was subsequently dehydrogenated to the fully aromatic polynuclear product CXXXIV or CXXXV. Attempts (146) to



CXXXIV



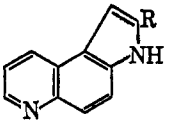
CXXXV

synthesize CXXXIV failed, but the angular structure CXXXV was theoretically favored for the dehydrogenation product, since the reactive position in 7-substituted isoquinolines toward electrophilic substitution was known to be the 8- and not the 6-position.

VII. EXCEPTIONS AND LIMITATIONS TO THE FISCHER INDOLE SYNTHESIS

A. ATTEMPTED INDOLIZATION OF ACETALDEHYDE PHENYLHYDRAZONE

Probably the most notable exception to the Fischer indole synthesis is the failure of acetaldehyde phenylhydrazone to give indole using a variety of catalysts (211), a similar negative result being obtained (196) by employing the non-catalytic method using refluxing monoethylene glycol (97), although ammonia evolution was detected in this latter case (196). On attempted indolization of pyruvic acid 6-quinolylhydrazone, decarboxylation initially occurred giving acetaldehyde 6-quinolylhydrazone which, as expected by analogy with acetaldehyde phenylhydrazone, did not indolize. However, using the ethyl ester to prevent decarboxylation, indolization was effected normally to afford CXXVI (R = $COOC_2H_5$), which after hydrolysis and decarboxylation afforded CXXXVI (R = H) (233). A



CXXXVI

similar synthetic route had been previously employed (89) in the indirect synthesis of indole by the Fischer method, which involved indolization of ethyl pyruvate phenylhydrazone to ethyl indole-2-carboxylate, subsequent hydrolysis and decarboxylation giving indole.

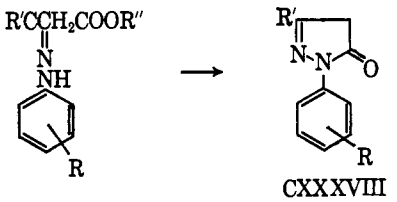
It has been suggested (226) that the absence of a terminal alkyl group in the enehydrazine tautomer of acetaldehyde phenylhydrazone (CXXXVII, R = H) is responsible for the non-indolization, the inductive effect of such a group in other aldehyde arylhydrazone enehydrazine tautomers easing the new C–C bond formation (stage b) in their indolizations.

$C_6H_4NNCH{=}CH_2$
RR
CXXXVII

However, since the validity of polarographic studies (13, 134) claiming to have detected the formation of the enehydrazine tautomer of acetaldehyde phenylhydrazone has been questioned (165), and attempts (226) to trap this tautomer as its diacetyl derivative CXXXVII (R = $COCH_3$), successful with other arylhydrazones (226, 227), have failed, it might be that the failure to indolize acetaldehyde phenylhydrazone is connected with the failure of the hydrazone–enehydrazine tautomerization (*i.e.*, stage a of the mechanism).

B. 2-KETOESTER ARYLHYDRAZONES

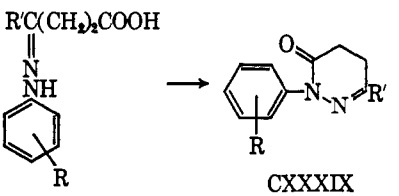
Under Fischer indolization conditions, these compounds undergo cyclization to pyrazolones (CXXXVIII) rather than indolization (125a).



CXXXVIII

C. 3-KETOACID ARYLHYDRAZONES

3-Keto and 3-aldehydo acid arylhydrazones can undergo cyclodehydration to give pyridazinones (CXXXIX) (84, 208, 224, 234). This reaction probably



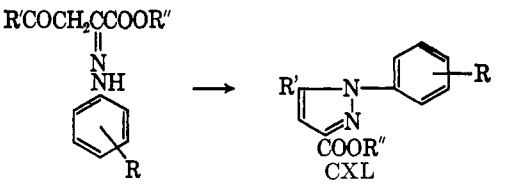
CXXXIX

explains the low yields or complete failure of formation of indoles from such arylhydrazones, where it is competitive, since the corresponding 1-alkylarylhydrazones, in which pyridazinone formation is impossible, give much improved yields of indoles (208). This technique would also be useful in preventing the cyclizations described in B and D of this section, thus allowing indolization to occur.

Pyridazinones can undergo hydrolytic ring scission affording the initial arylhydrazones which can subsequently indolize (84, 234).

D. 1,3-DIKETONE MONOARYLHYDRAZONES

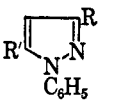
These compounds, prepared by the Japp–Klingemann reaction (178), readily cyclize to pyrazoles (CXL) (178). Similarly, the reaction of CXLI with phenylhydrazine gives a mixture of CXLII [R' = $(CH_2)_3N(C_2H_5)_2$ or CH_3 and R = CH_3 or $(CH_2)_3N(C_2H_5)_2$] (81).



CXL

$CH_3COCH_2CO(CH_2)_3N(C_2H_5)_2$

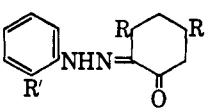
CXLI



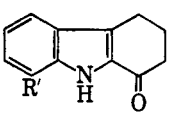
CXLII

E. CYCLOHEXANE-1,2-DIONE MONOARYLHYDRAZONES

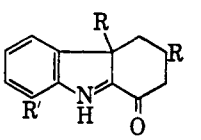
The cyclohexane-1,2-dione monophenylhydrazones CXLIII (R = H and CH_3, R' = H) are converted by concentrated sulfuric acid not to 1,2,3,4-tetrahydro-1-oxocarbazole (CXLIV, R' = H) and 2,3,4,11-tetrahydro-3,11-dimethyl-1-oxo-1H-carbazole (CXLV, R = CH_3, R' = H), respectively, but to the cinnolines (CXLVI, R = H and CH_3, R' = H) in 15 and 85% yields, respectively (155). Later work (213) confirmed



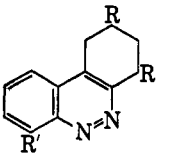
CXLIII



CXLIV



CXLV



CXLVI

these results and showed that the low yield of CXLVI (R = R' = H) was due to the formation of the normal indolization product CXLIV (R' = H) as the main product. Under similar catalytic conditions CXLIII (R = H and CH_3, R' = NO_2) gave only the normal indolization products CXLIV (R' = NO_2) and CXLV (R = CH_3, R' = NO_2), respectively (213).

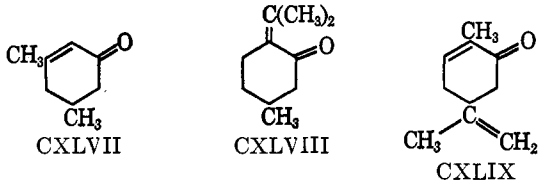
F. ISOMERIZATIONS DURING FISCHER INDOLIZATION

(a) Although phenylacetaldehyde phenylhydrazone with alcoholic hydrochloric acid gives the expected 3-phenylindole, using anhydrous zinc chloride as catalyst, 2-phenylindole is the product (76, 94, 95). Similarly, indolization of 2-tetralone phenylhydrazone, which proceeds normally in dilute sulfuric acid to give 3,4-benzo-1,2-dihydrocarbazole, gives 1,2-benzocarbazole using anhydrous zinc chloride as catalyst, in this case dehydrogenation as well as isomerization occurring (102) (see section IV, B). These migrations, and several further examples, are postulated (157, 158, 159) as occurring by a twofold Wagner–Meerwein rearrangement involving the migration of the 3-phenyl group on the indole initially produced to the indole 2-position.

(b) Although indolization of 4-alkyl-2,3-butanedione 3-phenylhydrazones to the corresponding 3-alkyl-2-acetylindoles occurs in small yields using ethanolic hydrogen chloride as catalyst, using 20% ethanolic sulfuric acid, indolization fails, but migration of the phenylhydrazine moiety occurs giving 4-alkyl-2,3-butanedione 2-phenylhydrazones (236).

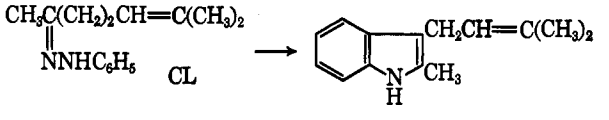
G. 1,2-UNSATURATED KETONE ARYLHYDRAZONES

Attempts (34) to indolize the *m*-nitrophenylhydrazones of 3,5-dimethylcyclohex-2-eneone (CXLVII), pulegone (CXLVIII), and *d*-carvone (CXLIX) failed, although this failure could be ascribed to the deactivating effect of the nitro substituent in the arylhydrazine moiety, the catalytic conditions for these attempted indolizations being relatively mild. Alternatively,



CXLVII CXLVIII CXLIX

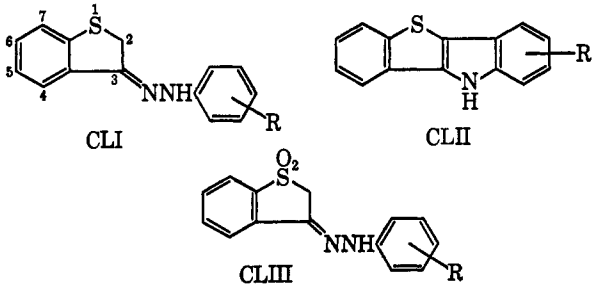
the extra conjugated unsaturation may be the decisive factor, for the 4,5-unsaturated ketone phenylhydrazone CL undergoes normal indolization (50).



CL

H. 3-OXY-1-THIOINDANE-1,1-DIOXIDE ARYLHYDRAZONES

Although arylhydrazones of 3-oxy-1-thioindane (CLI) are readily indolized to CLII, indolization of the corresponding sulfones CLIII fails (148), this failure being ascribed to (148) the fact that in the sulfones the sulfur atom is void of the two p-electrons which it possesses in CLI.

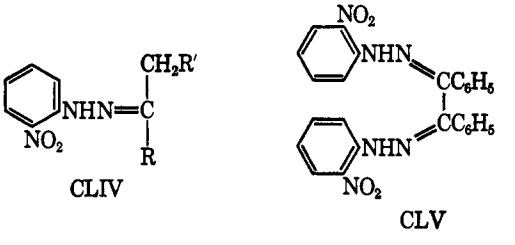


CLI CLII CLIII

I. INHIBITION BY *o*-SUBSTITUENTS

Although arylhydrazones CLI bearing 5-, 6- and 7-substituents and *m*- and *p*-substituents in the benzene ring of the arylhydrazine moiety readily indolize, both electron attracting and repelling 4- and *o*-substituents completely inhibit indolization (77), previous observations having already illustrated the inhibitory effect upon the indolization of arylhydrazones of an *o*-substituent in the arylhydrazine moiety (77 and references therein). No clear explanation of the inhibitory effect of the 4-substituents in CLI could be given, but that of the *o*-substituents in the arylhydrazine was ascribed to a steric effect (77). However, this latter inhibition is by no means general, for numerous *o*-substituted arylhydrazones have been successfully indolized.

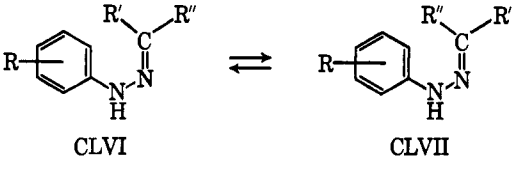
Attempts (131) to indolize desoxybenzoin *o*-nitrophenylhydrazone (CLIV, R = R′ = C_6H_5) led only to the formation of the ozazone CLV, the proposed mechanism of this reaction being related (131) in parts to the *o*-semidine rearrangement and to that proposed for osazone formation. This result and those of previous investigations of the indolization of *o*-nitrophenylhydrazones lead to the conclusion (131) that indolization of CLIV (R′ = alkyl or aryl) will occur normally when R is aliphatic, but will not occur, although this is not invariably the case, when R is aromatic, in these cases osazone formation occurring.



CLIV CLV

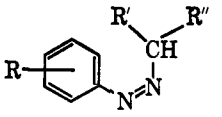
J. GEOMETRICAL ISOMERIZATION OF ARYLHYDRAZONES

In several cases arylhydrazones under conditions which normally cause indolization merely undergo geometrical isomerization between the *syn* and *anti* forms (CLVI) and (CLVII) (2, 119, 203, 211). Such geometrical isomers of the original arylhydrazones can also be isolated as by-products in successful indolizations (164, 211), and both geometrical isomers of arylhydrazones can be normally indolized under the appropriate conditions (119).



CLVI CLVII

It is suggested (211) that the interconversion between CLVI and CLVII proceeds through the azo tautomer CLVIII of the arylhydrazones, and further, since it is not necessary that the stable configuration of this azo tautomer (as a complex) be the same as that of the stable arylhydrazone; stable arylhydrazones could be converted into the labile geometrical isomers. This

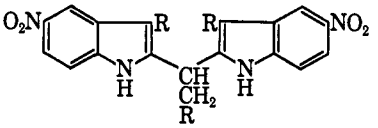


CLVIII

theory is supported by spectroscopic studies (165, 166) which verify the hydrazine–azo tautomerization in arylhydrazones. The relative stabilities of the *syn* and *anti* isomers of arylhydrazones has been studied (13, 134, 135) polarographically.

K. SUCCESSFUL INDOLIZATION WITH SUBSEQUENT FURTHER REACTION

Although indolization of aldehyde *p*-nitrophenylhydrazones occurs, the only products isolated from such reactions were found to be the condensation products CLIX (R = alkyl), formed by hydrolysis of the original *p*-nitrophenylhydrazones with subsequent condensation of the liberated aldehydes with the indole (27, 119, 209). By effecting the indolizations of such



CLIX

arylhydrazones in the presence of benzene, which permits extraction of the indole as it is formed, a 20–25% yield of the desired indole can be obtained, although considerable amounts of CLIX (R = alkyl) and other by-products still result (209). In the indolization of ketone *p*-nitrophenylhydrazones to 2,3-disubstituted indoles this undesired side reaction is not possible, for such indoles do not condense with aldehydes or ketones (161), and therefore the indoles are successfully isolated (203 and references therein).

The observation (54) that some *p*-chloroacetophenone arylhydrazones with stannous chloride as catalyst gave not only small yields of the expected indoles but also small yields of 2,4,6-tri-*p*-chlorophenylpyridine (55) was also thought (54) to be due to hydrolysis of the arylhydrazone simultaneously with indolization, three moles of the liberated *p*-chloroacetophenone reacting with the ammonia formed during indolization to give the pyridine.

L. INDOLIZATION OF 2-HYDROXYCYCLOHEXANONE ARYLHYDRAZONES

It would be expected that this reaction woud lead to a mixture of the corresponding 1,2,3,4-tetrahydro-1-hydroxycarbazole and 2,3,4,11-tetrahydro-11-hydroxy-1H-carbazole. However, using a variety of catalysts and arylhydrazines, none of these products could be isolated, simultaneous oxidation of the hydroxyl group occurring in all cases, leading to the formation of 1,2,3,4-tetrahydro-1-oxocarbazoles, bisarylhydrazones of cyclohexane-1,2-dione, and a mixture of both these products, depending on the catalyst and arylhydrazine employed (31).

M. INDOLIZATION OF PYRIDYLHYDRAZONES AND QUINOLYLHYDRAZONES

1. Pyridylhydrazones

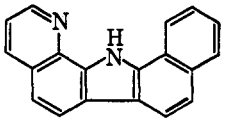
The pyridine nucleus is deactivated toward electrophilic attack not only by the inductive effect of the basic nitrogen atom but also owing to the fact that under electrophilic substitution conditions this atom carries a positive charge. This is reflected in the difficulty experienced in the indolization of pyridylhydrazones, where this effect tends to inhibit the formation of the new C–C bond (stage b). Thus, attempted indolization of acetone (82, 167), propionaldehyde (82) and pyruvic acid (82, 167) 2-pyridylhydrazones, pyruvic acid 2-methyl-3-pyridylhydrazone (69), 1,2,3,4-tetrahydro-1-methyl (and 1-phenyl) 4-oxoquinoline 4-pyridylhydrazone (141) and cyclohexane-1,2-dione bis-4-pyridylhydrazone (141) failed, although the corresponding phenylhydrazones readily indolized. However, successful indolization of cyclohexanone 2-pyridylhydrazone (167), 2-methyl-3-pyridylhydrazone (69) and 3- (1) and 4- (141) pyridylhydrazones, and desoxybenzoin 2-pyridylhydrazone (167) has been achieved using more harsh conditions than used for the indolization of the phenylhydrazones of these two ketones, which are known to indolize under very mild conditions. Similarly, whereas the attempted indolization of simple aldehyde and ketone *o*-, *m*-, and *p*-trifluoromethylphenylhydrazones (in which the trifluoromethyl substituent lowers the nucleophilicity of the aromatic nucleus) failed (98), with the exception of ethyl pyruvate *m*-trifluoromethylphenylhydrazone which indolized with difficulty (33), the corresponding cyclohexanone arylhydrazones indolized (98). It is reported (80), however, that acetone and propionaldehyde 2-chloro-5-pyridylhydrazones give the 4-azaindoles by heating with zinc chloride, and successful indolization of isopropyl methyl ketone 2-pyridylhydrazone (86), 4- and 6-methyl-2-pyridylhydrazones (85), 3-pyridylhydrazone (87), and 4-pyridylhydrazone (85) has been achieved using considerably higher temperatures than used in effecting the indolization of the corresponding phenylhydrazones.

2. Quinolylhydrazones

For a similar reason as in the pyridylhydrazones, indolization of quinolylhydrazones might be expected to be somewhat inhibited by the hetero atom.

With the hydrazine moiety in the benzenoid ring of the quinoline nucleus, the deactivating effect of the nitrogen atom in the pyridinoid ring has no marked

effect, and such quinolylhydrazones are indolized normally (46, 48, 67, 81, 116, 121, 139a, 233), although occasionally (81) more harsh conditions than used in the indolization of the corresponding phenylhydrazones are required. The difficulty experienced (49) in indolizing 1-tetralone and 1,2,3,4-tetrahydro-1- and 4-oxophenanthrene 8-quinolylhydrazones, which initially (48) failed, was attributed (48, 49) to the unfavorable steric conditions present in *cis*-biangular indolizations in the vicnity of *peri*-nitrogen atoms, *e.g.*, CLX.



CLX

However, with the hydrazine moiety in the pyridinoid ring of the quinoline nucleus, the deactivating effect of the nitrogen atom is more marked upon the indolization of quinolylhydrazones. Thus attempts to indolize acetone (176) and pyruvic acid (82) 2-quinolylhydrazones failed, although cyclohexanone (67), 1- and 2-tetralone, 1,2,3,4-tetrahydro-1- and -4-oxophenanthrene (49) 3-quinolylhydrazones, and cyclohexanone 4-quinolylhydrazone (141) have been successfully indolized, the phenylhydrazones of these latter ketones being very readily indolized.

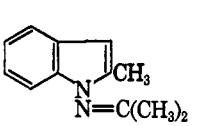
Recently (104) the 3-quinolylhydrazones of several ketones, the phenylhydrazones of which indolize with varying degrees of ease and difficulty have, however, been successfully indolized by heating with zinc chloride in *p*-cymene solution.

N. INDOLIZATION OF 2,4-DINITROPHENYLHYDRAZONES

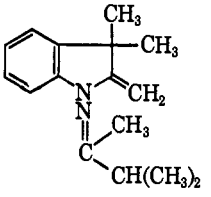
Up to a short time ago (15) it was thought that 5,7-dinitroindoles could not be prepared by indolization of 2,4-dinitrophenylhydrazones, owing to the deactivating effect of the two nitro substitutents on the benzene nucleus. However, it has since been found (79) that, using a concentrated sulfuric acid–acetic acid catalyst, methyl ethyl, diethyl and methyl propyl ketones, cylcohexanone, and 4-methylcyclohexanone 2,4-dinitrophenylhydrazones undergo normal indolization. Some limitation, however, still occurs, for attempted indolization of methyl isopropyl ketone and 2-methylcyclohexanone 2,4-dinitrophenylhydrazones to the corresponding 3H-indole and 2,3,4,11-tetrahydro-1H-carbazole, respectively, failed, although the mononitrophenylhydrazones of these two ketones indolize normally using concentrated hydrochloric acid as catalyst (79).

O. ALTERNATIVE DECOMPOSITION OF PHENYLHYDRAZONES WITH A CUPROUS CHLORIDE CATALYST

It has been observed (12) that whereas lower aldehyde phenylhydrazones, on treatment with cuprous chloride, indolize normally, higher aldehyde phenylhydrazones under similar conditions afford almost exclusively nitriles and aniline, derived from the aldehyde and phenylhydrazine moieties, respectively. Acetone phenylhydrazone also, under these conditions, did not give the expected 2-methylindole but an unknown product, ammonia and aniline. After further study (12) of this latter reaction it was suggested that ketone phenylhydrazones not containing a methylene group (excluding that in the methyl group) adjacent to the carbonyl group in the ketone moiety decompose in an analogous manner under similar conditions. Following the observations (16, 17) that the above anomalous product from acetone phenylhydrazone was basic, gave acetone on hydrolysis, had the molecular formula $C_{12}H_{14}N_2$, and acetone 1-methylphenylhydrazone did not give a similar product, structure CLXI was proposed (16) for it. Similar evidence led to the proposal of structure CLXII for the product isolated from the similar decomposition of methyl isopropyl ketone phenylhydrazone (16), although analogous



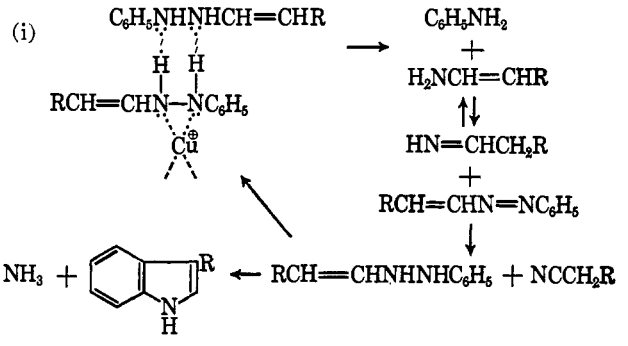
CLXI

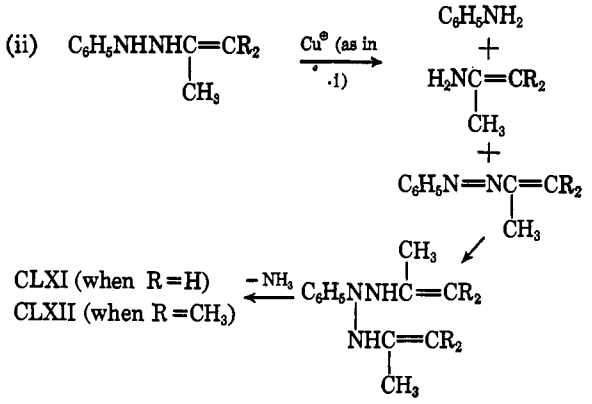


CLXII

products could not be isolated starting from the phenylhydrazones of other ketones not containing a 1-methylene group, this being attributed (16) to the decomposition of such products under the reaction conditions.

It was proposed (16) that the decompositions of the above ketone and higher aldehyde phenylhydrazones occurred by the related mechanisms i and ii, these being similar to the mechanisms proposed for the catalytic decomposition of phenylhydrazine into nitrogen, ammonia, benzene and aniline, and for the disproportionation of hydrazobenzene into azobenzene and aniline. In both cases, complexing of the cuprous ion with the enehydrazine tautomer of the phenylhydrazones causes weakening of the respective N–N bonds, thus facilitat-

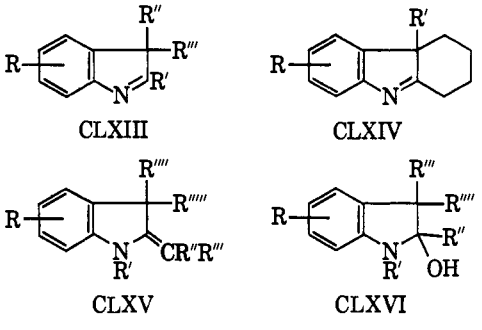




ing disproportionation, the initial stage in each mechanism (16). No reason was given, however, why such decomposition should be specific to cuprous ion catalysis (16), although it is likely to be stereochemical. A further catalyst effecting similar anomalous decompositions was found in sulfanilic acid (16).

VIII. Extensions to the Fischer Indole Synthesis

A number of these extensions have already been discussed in previous chapters. Thus, 3H-indoles (CLXIII) arise by indolization of arylhydrazones of aldehydes and ketones containing a 1-methine group (section VI, A), 2-alkylcyclohexanone arylhydrazones afford 2,3,4,11-tetrahydro-1H-carbazoles (CLXIV) (section VI, B), 2-alkylidene indolines (CLXV) [2-hydroxyindolines (CLXVI) where enamine formation is inhibited] result from 1-alkylarylhydrazones of ketones and aldehydes containing 1-methine group (sections II, C, 2, and VI, A), and the Borsche synthesis (section IV) gives a method of preparing carbazoles and other fully aromatic polynuclear compounds containing an indole nucleus.



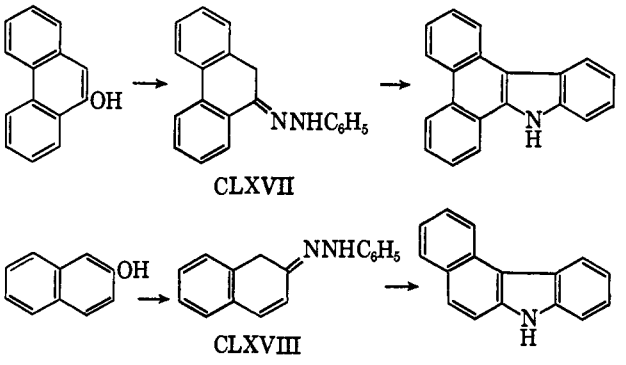
CLXIII CLXIV

CLXV CLXVI

Further extensions are now discussed, B, C, and D, although not involving the conversion of an arylhydrazone into a compound containing an indole or indole-derived nucleus, being related mechanistically to the Fischer indole synthesis.

A. The use of phenols as the carbonyl moieties of arylhydrazones

Many phenols react as their keto-tautomers on heating with arylhydrazines and give directly, *via* formation of the intermediate arylhydrazones, fully aromatic benz-substituted carbazoles (115c, 217d), this reaction thus being an alternative to that of Borsche (section IV) for the synthesis of these compounds. For example



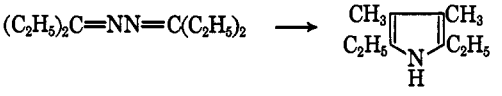
CLXVII

CLXVIII

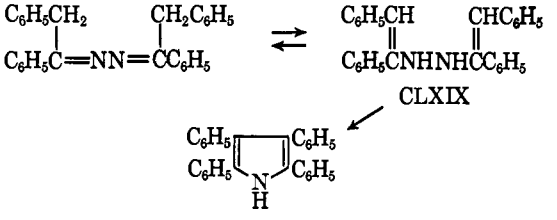
Although occasionally the reaction requires acid catalysis, it usually proceeds without a catalyst (115c, 217d), probably owing to the facile hydrazone–enehydrazine tautomerization of intermediates such as CLXVII and CLXVIII.

B. The Piloty pyrrole synthesis

In 1910 (179), Piloty observed the catalytic conversion of diethyl ketazine to 2,5-diethyl-3,4-dimethylpyrrole with zinc chloride.



It was Robinson and Robinson in 1918 (197) who first related the mechanism of this reaction to that of the Fischer indole synthesis when they cyclized phenyl benzyl ketazine to 2,3,4,5-tetraphenylpyrrole by passing dry hydrogen chloride over the molten azine. They proposed that under the influence of an acid catalyst the azine tautomerizes to the dienehydrazine CLXIX which then undergoes 1,6-rearrangement with formation of the new C–C bond, cleavage of the N–N bond, and subsequent loss of ammonia leading to pyrrole ring formation.



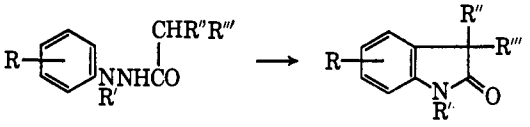
CLXIX

Several other ketazines have similarly been converted to the corresponding pyrroles under acid catalysis (22, 28, 75, 130, 138, 175, 187), but some exceptions

are known (197), for in simple aliphatic azines a competing formation of pyrazolines occur, and no pyrrole and 2,5-dimethylpyrrole could be obtained from acetaldazine and dimethylketazine, respectively.

C. THE BRUNNER OXINDOLE SYNTHESIS

In 1896, Brunner observed that on heating acylphenylhydrazines with lime, ammonia was evolved and oxindoles were formed. The reaction has subsequently found wide applicability in the synthesis of oxindoles from acylarylhydrazines using various basic catalysts (125e, 217e), from which it is concluded (125e) that acylarylhydrazines give better yields of oxindoles than do the corresponding acyl-1-methylarylhydrazines, the greatest yield resulting from the application of the reaction to the synthesis of 3-alkyl- and 3,3-dialkyloxindoles.

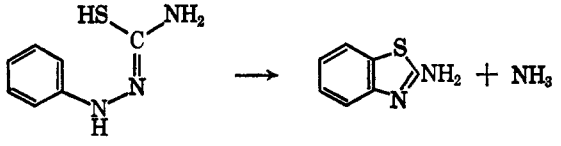


After enolization of the acylarylhydrazine under the influence of the basic catalyst to give CLXX (equivalent to the enehydrazine tautomer of the arylhydrazone in the Fischer indole synthesis), the mechanism of the reaction follows a similar pathway to that of the Fischer indole synthesis (198).

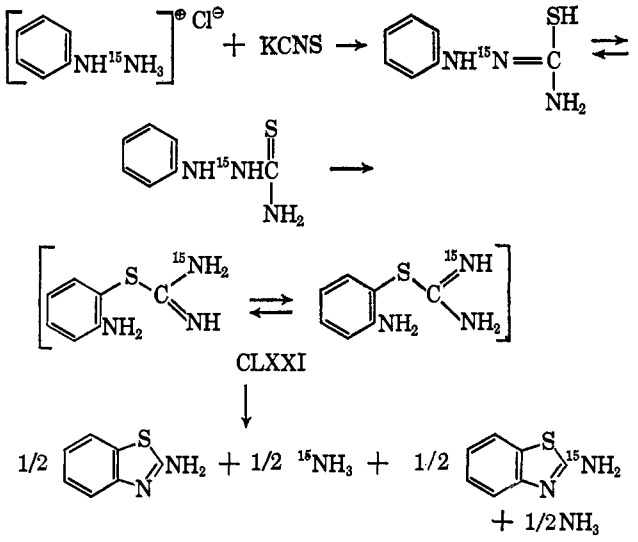
CLXX

D. THE ACID-CATALYZED CYCLIZATION OF 1-PHENYLTHIOSEMICARBAZIDE

This cyclization results in the elimination of ammonia and the formation of 2-aminobenzthiazole, the similarity of this reaction to the Fischer indolization of arylhydrazones being established in 1903 (117). Later



(66), starting from 2-^{15}N-phenylhydrazine, the cyclization afforded half the ^{15}N label in the evolved ammonia and half in the 2-aminobenzthiazole, this being attributed to the formation of the intermediate diamine CLXXI in a mechanism analogous to that of the Fischer indolization.



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