RECENT STUDIES ON THE FISCHER INDOLE SYNTHESIS

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Contents

I. Introduction and Scope of the Review

Since the publication in *Chemical Reviews* of the initial article[1] upon the Fischer indole synthesis, about 150 papers have appeared upon various aspects of, or connected with, the reaction. It is now common practice to subject an equimolar mixture of the arylhydrazine (or a salt) and aldehyde or ketone directly to indolization conditions, thereby bypassing the isolation of the arylhydrazone. Further examples have appeared using this technique in which the actual arylhydrazine is also generated *in situ* by either diazotization, followed by reduction, of the corresponding arylamine[2] or acid hydrolysis of the corresponding arylsydnones.[2]

As in the first review,[1] special emphasis in this article has been laid upon studies related to the mechanism of the indolization, some aspects of which are still not established, upon exceptions, limitations, and extensions to the indolization, and upon the direction of indolization in cases where possible ambiguity exists. The catalysis of the reaction and alternative methods of preparing arylhydrazones (*e.g.*, the Japp–Klingemann reaction) are also discussed, as they were previously.[1]

Once again, no attempt has been made in this review to tabulate all known cases of indole formation by the Fischer synthesis, since this is outside the purpose of the article. However, the final section has been included, for along with the many examples given throughout the rest of the text, it illustrates the synthetic versatility and usefulness of the reaction and clearly establishes the Fischer reaction as the major synthetic route to indoles, even though some indole syntheses, such as the periodate oxidation of substituted 1,2,3,4-tetrahydroquinolin-3-ols,[3–5] may be competitive in reaction yields and ease of preparation as has been[5] suggested, but only in limited specific cases.

Literature references from 1962 up to and through the 1967 issues of *Current Chemical Papers* and *Chemical Abstracts* have been covered, and several references prior to 1962 have been included where necessary.

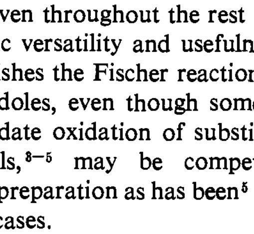
(1) B. Robinson, *Chem. Rev.*, 63, 373 (1963).

(2) D. P. Ainsworth and H. Suschitzky, *J. Chem. Soc., C*, 315 (1967).

II. Mechanism of the Fischer Indole Synthesis

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

The observations which led to the suggestion[6] that a tautomeric equilibrium existed between phenylhydrazones and phenylazoalkanes in neutral nonpolar solvents have now been shown[7] to be caused by the autoxidation of the phenylhydrazones to hydroperoxides, shown[7,8] to have structure 1, the



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formation of which does not occur *via* the corresponding phenylazoalkanes.[7] These results support pmr spectral studies[9,10] which, contrary to previous observations,[6] were

(3) F. C. Pennington, M. Jellinek, and R. Thurn, *J. Org. Chem.*, 24, 565 (1959).

(4) F. C. Pennington, L. J. Martin, R. E. Reid, and T. W. Lapp, *ibid.*, 24, 2030 (1959).

(5) F. C. Pennington, G. L. Tritle, S. D. Boyd, W. Bowersox, and O. Aniline, *ibid.*, 30, 2801 (1965).

(6) R. O'Connor, *ibid.*, 26, 4375, 5208 (1961).

(7) A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 2788 (1965).

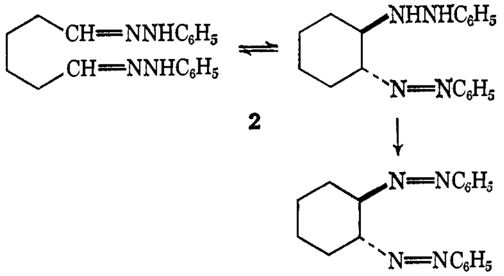
(8) H. C. Yao and P. Resnick, *J. Org. Chem.*, 30, 2832 (1965).

(9) G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, 85, 3624 (1963).

(10) G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *ibid.*, 86, 3351 (1964).

unable to detect the presence of any azo or enehydrazine tautomer in neutral solutions of phenylhydrazones.

Adipaldehyde bisphenylhydrazone was originally[11] thought to tautomerize to the 1,6-bisphenylazohexane in chloroform–methanol solution, but the product of this reaction has now[12] been shown to be *trans*-1,2-bisphenylazocyclohexane (**3**), this being formed by ring–chain tautomerism of the bisphenylhydrazone as shown in **2** followed by oxidation of the cyclic



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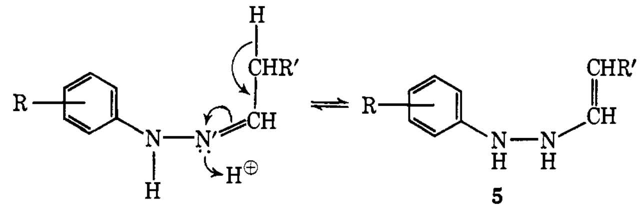
tautomer. Although attempts[12] to condense two molecules of a monohydrazone together in a similar manner in the presence of molecular oxygen failed, aldehyde phenylhydrazones do[13] give such products (along with other oxidation products depending upon reaction conditions) when active manganese dioxide is used as oxidizing agent.

The previously reported[14] intermediate cherry-red coloration produced during the boron trifluoride catalyzed indolization of cyclohexane phenylhydrazone, which was thought[14] to be caused by formation of a complex between the catalyst and the azo tautomer of the hydrazone, is unlikely to be due to such a compound.[15] In fact, under basic, radical-initiated, or mild acidic conditions, phenylazoalkanes are converted into the corresponding phenylhydrazones, which are thus probably the thermodynamically more stable form.[15] Under more vigorous acidic conditions, phenylazoalkanes are converted into indoles which are also obtained by similar treatment of the corresponding phenylhydrazones.[15]

Whereas the above failures to detect tautomerization in phenylhydrazones relate to studies carried out in neutral nonpolar media, polarographic studies carried out in more polar media (conditions which approximate more closely the acid-catalyzed Fischer indolization) indicated[16] the occurrence of azo–hydrazone–enehydrazine tautomerization in a series of ketone and aldehyde phenylhydrazones.

By condensation of a number of aryl-substituted phenylhydrazine hydrochlorides with a series of acetals in warm acetic acid (which generated the arylhydrazones *in situ*), it was found[17] that the subsequent indolization which occurred under these conditions took place readily (as measured by product yield) when the original arylhydrazine had an electron-releasing substituent in the 4 position, happened less readily with such a substituent in the 2 position, and failed with the isomeric 3-substituted analogs. Under similar conditions using phenylhydrazine hydrochloride and the corresponding acetals, only low yields of indoles resulted, whereas electron-attracting substituents on the phenyl ring prevent indolization.[17]

These results were explained[17] by assuming that under the relatively mild indolization conditions used, the rate-determining step of the indolization is enehydrazine formation (*i.e.*, **4** ⇌ **5**, stage A of the proposed indolization mechanism)[1] which is facilitated by electron release from 4- (and less from 2-) electron-releasing substituents on the aromatic ring which



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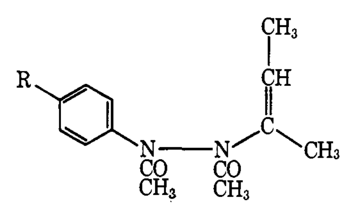
will render N′ (protonation of which can be visualized as the initial step in the tautomerization as shown) more basic than the corresponding phenylhydrazones, such mesomeric contribution from a 3-substituted electron-releasing group not being possible. In support of this postulation are the previous kinetic studies[18] which showed that under similar mild conditions cyclohexanone 4-methoxyphenylhydrazone indolizes much more rapidly than the corresponding 3 isomer, and the observations[19] that the basicities of the three isomeric methoxyphenylhydrazines are in the order **4** > **2** > **3**. However, in relation to the above studies is the suggestion[20] that in many cases, whereas electron-accepting aryl substituents hinder indolization, they also minimize side reactions, but electron-donating aryl substituents, although they facilitate indolization, also promote side reactions, and the ultimate yield of indoles from such arylhydrazones is therefore often low. The yields of indoles in such reactions, therefore, are not related to the rates of indolization, irrespective of which stage in the mechanism is rate determining.

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

Contrary to previous reports which suggested that formation of the indoles **7** (R = H, CH_3, and OCH_3) from the corresponding trapped diacetyl derivatives of the enehydrazine intermediates **6** had to be preceded by deacetylation of N in order to free the p-electron pair on this atom, it has now been found[21,22] that 1-acylindoles can be directly prepared by Fischer indolization of a mixture of N-acylated phenylhydra-



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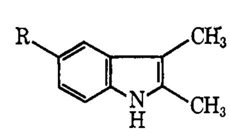

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(11) A. J. Bellamy and R. D. Guthrie, *Chem. Ind.* (London), 1575 (1964).

(12) A. J. Bellamy, R. D. Guthrie, and G. J. F. Chittenden, *J. Chem. Soc., C*, 1989 (1966).

(13) I. Bhatnagar and M. V. George, *J. Org. Chem.*, 32, 2252 (1967).

(14) H. R. Snyder and C. W. Smith, *J. Amer. Chem. Soc.*, **65**, 2452 (1943).

(15) A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 3528 (1965).

(16) Y. P. Kitaev and T. V. Troepol'skaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 454, 465 (1963); *Chem. Abstr.*, **59**, 7347 (1963).

(17) D. Desaty and D. Keglević, *Croat. Chem. Acta*, **36**, 103 (1964).

(18) K. H. Pausacker and C. I. Schubert, *J. Chem. Soc.*, 1814 (1950).

(19) H. H. Stroh and G. Westphal, *Chem. Ber.*, **96**, 184 (1963).

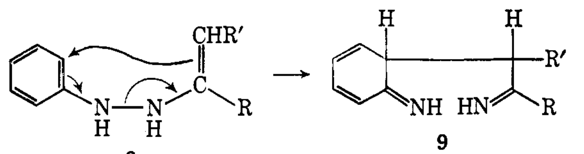
(20) L. A. Aksanova, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Obshch. Khim.*, 34, 1609 (1964); *J. Gen. Chem. USSR*, **34**, 1619 (1964).

(21) H. Yamamoto, *Bull. Chem. Soc. Jap.*, **40**, 425 (1967).

(22) H. Yamamoto, *J. Org. Chem.*, **32**, 3693 (1967).

zines and ketones in warm acetic acid. As well as constituting a useful synthesis of 1-acylindoles, these results also suggest[21,22] that 1-acetylindoles might be intermediates in the above-mentioned conversion of **6** into **7** which are subsequently hydrolyzed under the acidic indolization conditions, and that since deacylation of N is not necessary for indole formation, the N p-electron pair "hardly" participates in the formation of the new C–C bond during indolization.

Indolization of a series of 2-, 3-, and 4-nitrophenylhydrazones of several ketones afforded,[23] with the exception of ethyl methyl ketone, higher yields of indolic products from the 3-nitrophenylhydrazones than from the corresponding 2- and 4-nitrophenylhydrazones. Since a nitro substituent preferentially deactivates the positions *ortho* and *para* to it toward electrophilic attack, it was postulated[23] from these observations that formation of the new C–C bond during indolization might occur, not by intramolecular electrophilic attack on the aromatic ring of the hydrazone in the form of its enehydrazine tautomer as had previously[1] been supposed but by intramolecular nucleophilic attack upon this ring as shown in **8** → **9**.

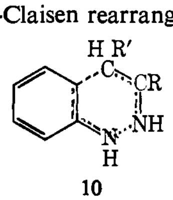


8 **9**

However, such a nucleophilic attack upon an aromatic nucleus appears to be unlikely and is based upon the two unsubstantiated assumptions from the experimental observations that this stage of the mechanism is rate determining and that the yield of indolic product is directly proportional to the velocity of the rate-determining step of the reaction.

From the above studies and those described at the end of the previous section, it is apparent that detailed kinetic studies need to be carried out upon the Fischer indole synthesis, under various conditions of catalysis, in order to further investigate the mechanism of the reaction and to establish the rate-determining stage, which is as yet unknown[24,25] and which may vary with the experimental conditions employed to effect indolization.[17,24]

The mechanism of the noncatalytic thermal indolizations of arylhydrazones (see section III.C), which are unlikely to proceed by a free-radical mechanism,[26] may involve, in the formation of the new C–C bond, a "no-mechanism" rearrangement[27,28] involving a [3,3] sigmatropic shift[29] *via* intermediate **10**, as does the *ortho*-Claisen rearrangement (see also ref 30),



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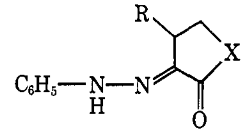
(23) A. R. Frasca, *An. Asoc. Quím. Argentina*, 50, 1 (1962).
(24) R. B. Carlin, *J. Amer. Chem. Soc.*, 74, 1077 (1952).
(25) J. McLean, S. McLean, and R. I. Reed, *J. Chem. Soc.*, 2519 (1955).
(26) A. H. Kelly, D. H. McLeod, and J. Parrick, *Can. J. Chem.*, 43, 296 (1965).
(27) E. N. Marvell, J. L. Stephenson, and J. Ong, *J. Amer. Chem. Soc.*, 87, 1267 (1965).
(28) S. J. Rhoads, "Molecular Rearrangements," P. de Mayo, Ed., Vol. 1, Interscience Publishers, New York, N. Y., 1963, Chapter 11, p 655.
(29) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, 87, 2511, 4389 (1965).
(30) K. Fukui and H. Fujimoto, *Tetrahedron Lett.*, 251 (1966).

When α-oxobutyrolactone phenylhydrazone (**11**, R = H, X = O) is treated with hydrogen chloride in glacial acetic acid, a compound is formed which was initially formulated[31,32] as **12** and which upon treatment with a glacial acetic–concentrated sulfuric acid mixture affords the corresponding indole **13** (X = O). Further work[33] has shown that the structure of this isolated intermediate should now be corrected to **14**. Treatment of the 1-substituted pyrrolidine-2,3-dione 3-phenylhydrazones **11** [R = H; X = $N(CH_2)_2CH_3$, $N(CH_2)_3CH_3$, N-*c*-C_6H_{11}, N-C_6H_5, N-$(CH_2)_2C_6H_5$, $NCH(CH_3)CH_2C_6H_5$, and $N(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$, respectively] with hydrogen chloride in glacial acetic acid affords the corresponding indoles **13** [X = $N(CH_2)_2CH_3$, $N(CH_2)_3CH_3$, N-*c*-C_6H_{11}, NC_6H_5, $N(CH_2)_2C_6H_5$, $NCH(CH_3)CH_2C_6H_5$, and $N(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$, respectively], no intermediates corresponding to **12** or **14** being isolable.[34] However, the corresponding series



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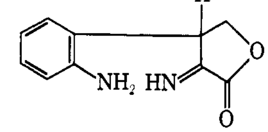

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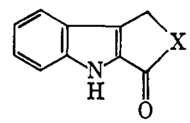

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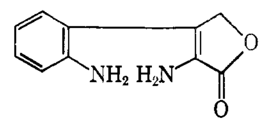

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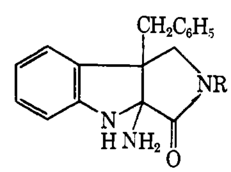
of 4-benzylpyrrolidine phenylhydrazones **11** [R = $CH_2C_6H_5$; X = NCH_3, $NCH(CH_3)_2$, N-*c*-C_6H_{11}, and N-C_6H_5, respectively] give, under similar conditions, compounds **15** [R = CH_3, $CH(CH_3)_2$, *c*-C_6H_{11}, and C_6H_5, respectively] which are indolization intermediates resulting from arrest of the reaction just prior to the final stage of the reaction, the elimination of ammonia.[35]



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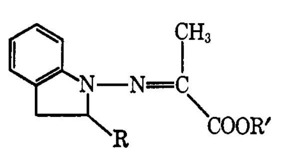
In view of the above results, the structure of similar products, which have been isolated[36,37] from the acid-catalyzed rearrangements of arylhydrazones without elimination of the elements of ammonia, should now be reinvestigated.[33]

Earlier studies have shown that the product resulting from subjection of the arylhydrazones **16** (R = H; R′ = C_2H_5) to indolization conditions is mainly **17** (R = H), formed together with a small yield of the expected indole **18** and formed preferentially to it owing to the ease of cyclization involving the carbethoxy group rather than the imino group in the intermediate **19**. Further examples of this alternative cycliza-

(31) H. Plieninger, *Chem. Ber.*, 83, 273 (1950).
(32) H. Plieninger and I. Nogradi, *ibid.*, 88, 1964 (1955).
(33) R. J. Owellen, J. A. Fitzgerald, B. M. Fitzgerald, D. A. Welsh, D. M. Walker, and P. L. Southwick, *Tetrahedron Lett.*, 1741 (1967).
(34) P. L. Southwick and R. J. Owellen, *J. Org. Chem.*, 25, 1133 (1960).
(35) P. L. Southwick, B. McGrew, R. R. Engel, G. E. Milliman, and R. J. Owellen, *ibid.*, 28, 3058 (1963).
(36) C. S. Barnes, K. H. Pausacker, and W. E. Badcock, *J. Chem. Soc.*, 730 (1951).
(37) S. Borghero and O. Finsterle, *Gazz. Chim. Ital.*, 85, 651 (1955).

tion have now[38] been investigated and the arylhydrazones **16** (R = CH_3 and C_6H_5; R′ = H and C_2H_5) have been converted exclusively into **17** (R = CH_3 and C_6H_5, respectively) under similar conditions.



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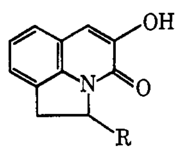

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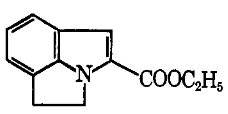

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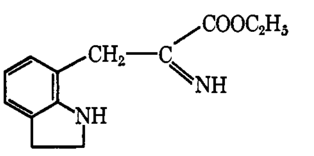

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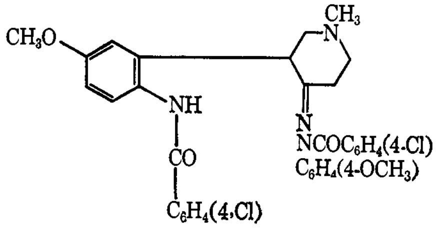

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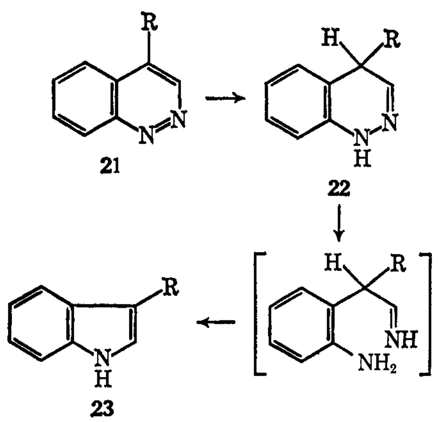

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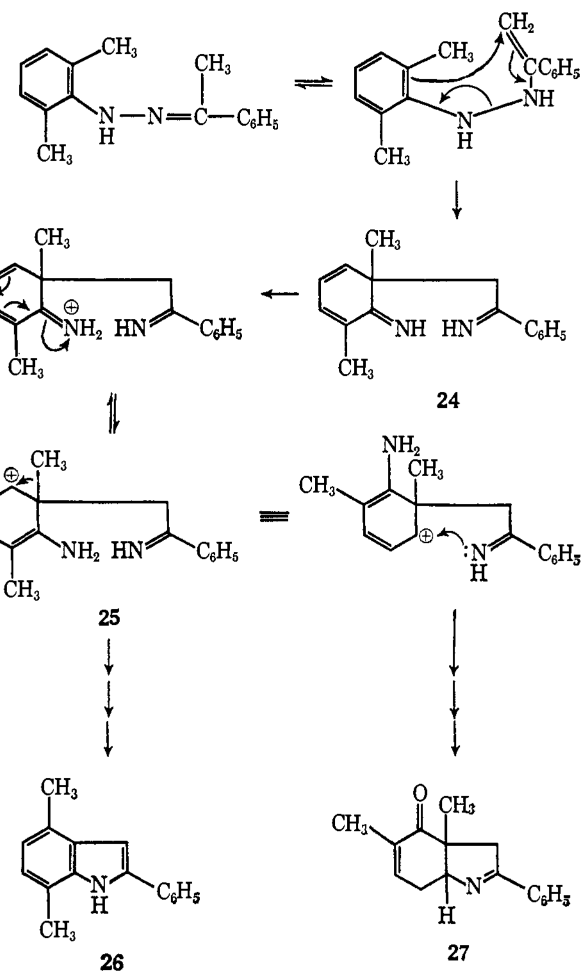
Treatment of a mixture of 1-methyl-4-piperidone and N-(4-chlorobenzoyl)-4-methoxyphenylhydrazine hydrochloride with warm acetic acid affords[22] a product, whose structure was established[22] as **20** from its pmr spectral properties and which appears to arise by hydrolysis of the imino to a keto group in an aminoimino intermediate corresponding to **12** and **19** with subsequent condensation of this keto group with starting hydrazine.

The reductive ring contraction of cinnolines to indoles has been further studied,[39] the generality of the reaction being illustrated by conversion of 4-phenyl- and 4-methylcinnoline, cinnoline, and cinnoline-4-carboxylic acid (**21**, R = C_6H_5, CH_3, H, and COOH, respectively) into 3-phenylindole, skatole, and indole (**23**, R = C_6H_5, CH_3, and H, respectively), decarboxylation occurring in the latter reaction. 1,4-Dihydrocinnolines (**22**) have been isolated and have been shown[39] to be intermediates in these reactions, evidence suggesting that the most important route by which these are converted into indoles is *via* cleavage of the N–N bond to afford intermediate aminoimines as shown, analogous to those formed in the Fischer indolization. Reductive ring contraction of 4-phenyl-[2-^{15}N]cinnoline has confirmed[39] that it is the N-2 atom of the cinnoline nucleus which is eliminated during indole formation. Analogous aminoimine intermediates have been postulated[40] in the formation of indoles by catalytic reduction of 2-nitrobenzyl cyanides.

C. GROUP MIGRATION DURING INDOLIZATION OF 2,6-DISUBSTITUTED PHENYLHYDRAZONES

The mechanistic postulation (Scheme I) for the formation of 4,7-dimethyl-2-phenylindole (**26**) and **27** by treatment of acetophenone 2,6-dimethylphenylhydrazone with anhydrous zinc chloride in nitrobenzene has now[41] been verified by the use of acetophenone 2,6-dimethyl-[2-^{15}N]phenylhydrazone in the reaction. Compound **27** isolated from this reaction contained its full complement of ^{15}N, whereas the indolic product **26** contained only a trace of ^{15}N, probably owing to the presence of contaminant traces of **27**.[41]

Scheme I



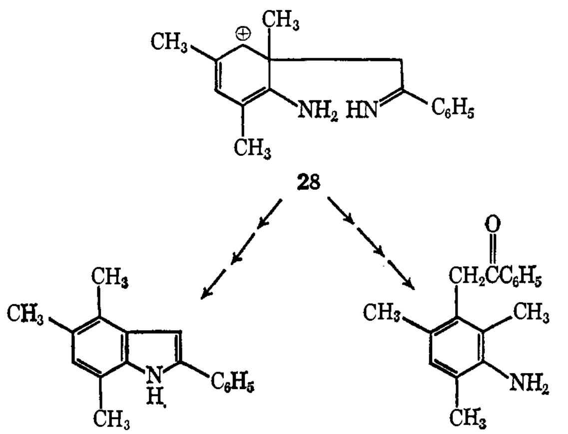
(38) L. G. Yudin, S. A. Papravko, and A. N. Kost, *Zh. Obshch. Khim.*, 32, 3586 (1962); *J. Gen. Chem. USSR*, 32, 3519 (1962).

(39) L. S. Besford and J. M. Bruce, *J. Chem. Soc.*, 4037 (1964).

(40) H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Amer. Chem. Soc.*, 80, 4622 (1958).

(41) R. B. Carlin, A. J. Magistro, and G. J. Mains, *ibid.*, 86, 5300 (1964).

In the above reaction, a 1,2 migration of the methyl group occurs in the formation of **26**, whereas similar treatment of cyclohexanone 2,4,6-trimethylphenylhydrazone results in the formation of 1,2,3,4-tetrahydro-6,7,8-trimethylcarbazole which must be formed by the 1,4 migration of a methyl group (full details of this latter work have now[42] been published). To investigate the structural differences in these two hydrazones responsible for the two different methyl group migrations, acetophenone 2,4,6-trimethylphenylhydrazone has been[43] subjected to similar reaction conditions. Four products were isolated from this reaction and were shown to be mesidine, acetophenone (both probably formed by disproportionation of the enehydrazine tautomer of the starting hydrazone), 4,5,7-trimethyl-2-phenylindole (**29**) (formed *via* a 1,2 migration of a methyl group in intermediate **28**), and 3-phenacylmesidine (**30**) (formed *via* either 1,2 or 1,4 migration of the phenacylimino group in intermediate **28**). The migration of



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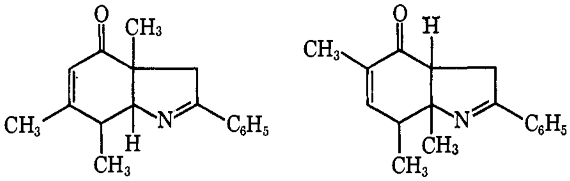
29 **30**

the phenacylimino group strongly supports[43] the suggestion that methyl group migration in the reaction leading ultimately to **29** and similar previously observed methyl group migrations occur prior to the formation of the heterocyclic ring during the indolizations.

The above 4,5,7-trimethyl-2-phenylindole (**29**) was unambiguously synthesized by indolization of acetophenone 2,4,5-trimethylphenylhydrazone, a by-product from this reaction being formulated as either **31** or **32** by comparison[43] of its uv and ir spectra with those of **27**. Unfortunately, a comparison of this by-product's pmr spectrum with that of **27** was not carried out, since this would have easily differentiated between these two structures.

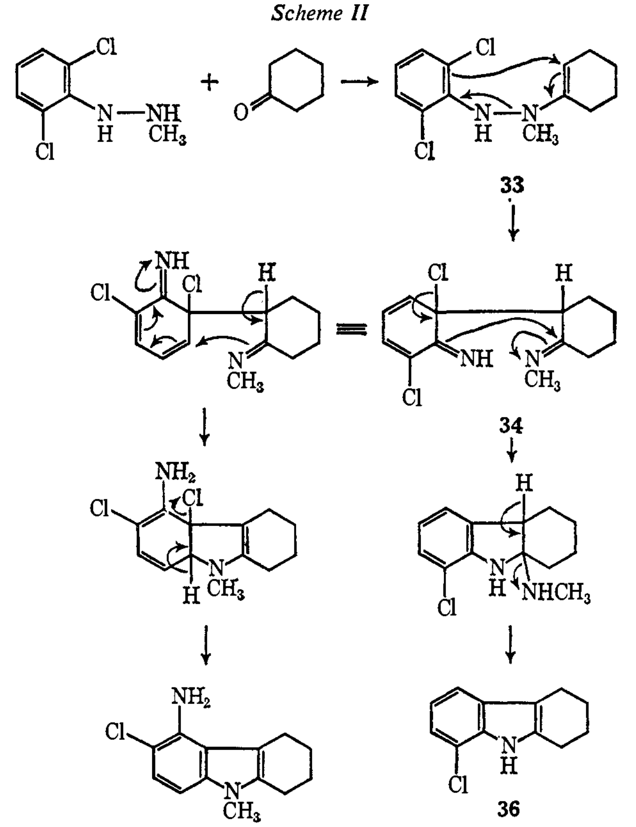


31 **32**

A further example of methyl group migration has been observed[44] when ethyl pyruvate 2-methylphenylhydrazone is indolized with a polyphosphoric acid catalyst. The resulting product, after hydrolysis and decarboxylation, afforded a mixture of 7-methylindole, resulting from the expected normal indolization, and 4-methylindole, resulting from either a 1,2 migration of the methyl group subsequent to the new C–C bond formation at the C_2 of the benzene nucleus or a less likely 1,4 migration of the methyl group subsequent to the new C–C bond formation at the C_6 of the benzene nucleus. It is interesting that in this reaction a methyl group migration occurs although the starting hydrazone has an unsubstituted 2 position, which shows that such migrations are not confined to 2,6-disubstituted phenylhydrazones as might previously have been supposed.

Previous attempts[45] to isolate the intermediates analogous to **24** and **25** in the above type of reactions by trapping them as their Diels–Alder addition products failed, probably owing to their much more rapid conversion to the corresponding indoles under the reaction conditions. A further attempt to isolate such intermediates has been made[46] by condensing cyclohexanone with 2,6-dichloro-N′-methylphenylhydrazine at room temperature. Since it had already been shown that the enehydrazine tautomers of arylhydrazones are readily indolized under very mild conditions, it was hoped in this case to subject the enehydrazine **33** to such conditions in the hope that the apparently very labile intermediate **34** would then be isolable. However, it was found that even during the initial condensation, indolization simultaneously occurred, methylamine hydrochloride precipitating out of the reaction mixture which then afforded only 8-chloro-1,2,3,4-tetrahydrocarbazole (**36**) and 5-amino-6-chloro-1,2,3,4-tetrahydro-9-methylcarbazole (**35**), both presumably formed as shown in Scheme II.

Scheme II



(42) R. B. Carlin and M. S. Moores, *J. Amer. Chem. Soc.*, 84, 4107 (1962);
(43) R. B. Carlin and J. W. Harrison, *J. Org. Chem.*, 30, 563 (1965),
(44) B. Heath-Brown and P. Philpott, *J. Chem. Soc.*, 7185 (1965).
(45) R. B. Carlin, W. O. Henley, and D. P. Carlson, *J. Amer. Chem. Soc.*, 79, 5712 (1957).
(46) F. P. Robinson and R. K. Brown, *Can. J. Chem.*, 42, 1940 (1964).

It is suggested[46] that a readily oxidizable substance in the reaction mixture reductively removes the allylic chlorine atom in **34** to ultimately afford **36**, the formation of which is analogous to the formation of 7-chloroindoles from 2,6-dichlorophenylhydrazones under more vigorous catalytic conditions in which it is suggested[47] that traces of water in the reaction mixture (*via* the formation of complex acids with the stannous chloride catalyst) or the enehydrazine tautomer of the arylhydrazone might act as a hydrogen source.

A similar condensation of 2,6,N′-trimethylphenylhydrazine hydrochloride and cyclohexanone in boiling benzene has also failed to afford the desired intermediate but has led[48] to the isolation of 1,2,3,4-tetrahydro-8-methylcarbazole along with water and ammonium chloride. This reaction can also be effected at room temperature using the hydrazine as the free base, although in this case the yields of the indolic product are lowered.[48] In none of these reactions has the ultimate fate of the eliminated methyl group been established.[48]

III. Catalysis of the Fischer Indole Synthesis

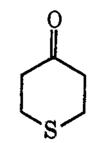
A. NEW CATALYSIS

Following the use of polyphosphate ester as a Lewis acid catalyst in other reactions, it has been[49,50] found that the use of this catalyst in boiling chloroform indolizes cyclic and acyclic ketone phenylhydrazones, usually in good yields. This catalyst is also useful in obtaining moderate yields of 3-substituted indoles from aldehyde phenylhydrazones, indolization of which with other catalysts usually affords only low yields of the desired products. If the reaction temperature is raised to 150° with this catalyst, it is found[49,50] that indolization of cyclohexanone phenylhydrazone affords 4a-ethyl-1,2,3,4-tetrahydro-4aH-carbazole, formed by 4a ethylation of the initially produced 1,2,3,4-tetrahydrocarbazole by the polyphosphate ester at the higher temperature.

B. COMPARISON OF CATALYSTS IN SPECIFIC INDOLIZATIONS

The yield of product from, and often the success or failure of, a Fischer indolization depends to a large degree upon the choice of catalyst and reaction conditions. The relative effectiveness of hydrochloric acid, hydrogen chloride, boron trifluoride, polyphosphoric acid, cuprous chloride, and varying proportions of zinc chloride in catalyzing the indolization of acetone 4-chlorophenylhydrazone has been investigated.[51] The highest yield of 5-chloro-2-methylindole was obtained using zinc chloride, in equal weight with the hydrazone, in boiling cumene. Although there were exceptions (*i.e.*, the 4-methoxy- and 4-nitrophenylhydrazones), many other acetone 4-substituted phenylhydrazones (*i.e.*, 4-fluoro-, chloro-, bromo-, and methylphenylhydrazones) and the phenylhydrazone itself were all indolized under similar conditions in high yields.[52] The observations[53] that attempted boron trifluoride etherate and polyphosphoric acid catalyzed indolization of acetone 4-bromophenylhydrazone both failed to yield the expected indolic product support the above comparative studies. However, treatment of acetone 4-chlorophenylhydrazone with polyphosphoric acid afforded a low yield of a product, which was, without verification, postulated as being 2,2′-dimethyl-5,5′-diindolyl.[51] Further studies upon comparative effectiveness of catalysts in the Fischer indolization have been reported.[54]

Many other less detailed examples of comparative catalytic studies in Fischer indolizations are known. For example, treatment of the 4-nitrophenylhydrazone of ketone **37** with glacial acetic acid failed to effect indolization whereas the reaction was successful using concentrated hydrochloric acid as catalyst,[55] but, on the other hand, attempted indolization of the phenylhydrazone of ketone **38** using hydrochloric acid led only to hydrolysis of the hydrazone, the expected indolization being effected using polyphosphoric acid.[56]



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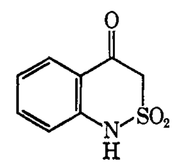

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At the present time only an empirical approach to the choice of catalyst in Fischer indolizations can usually be made (see ref 57), although it does appear[44,58–62] that where indolization involving the methyl group of a methyl ketone is required, polyphosphoric acid is usually an effective catalyst and other catalysts often fail (see also section V.A).

C. NONCATALYTIC THERMAL INDOLIZATION OF ARYLHYDRAZONES

The use of this noncatalytic indolization procedure, initially developed in 1957,[63] has been further extended[26] to the preparation from arylhydrazones of indoles which, owing to their acid sensitivity, are difficult or impossible to prepare using acid catalysts. For example, cyclopentanone phenyl- and 4-methylphenylhydrazones in boiling diethylene glycol afford 78 and 56% yields, of the corresponding indoles **39** (R = H; R′ = H and CH_3, respectively), and 2-methylcyclopentanone phenylhydrazone similarly affords a mixture of **39** (R = CH_3; R′ = H) and **40** (R = H) in the yield ratio of approximately 1:5.[26] However, contrary to this latter reaction,

(47) R. B. Carlin, Carnegie-Mellon University, Pittsburgh, Pa., personal communication, 1962.

(48) R. K. Brown, University of Alberta, Edmonton, Alberta, Canada, personal communication, 1967.

(49) Y. Kanaoka, Y. Ban, K. Miyashita, K. Irie, and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), 14, 934 (1966).

(50) Y. Kanaoka, Y. Ban, O. Yonemitsu, K. Irie, and K. Miyashita, *Chem. Ind.* (London), 473 (1965).

(51) N. B. Chapman, K. Clarke, and H. Hughes, *J. Chem. Soc.*, 1424 (1965).

(52) J. W. Cornforth, G. K. Hughes, F. Lions, and R. H. Harradence, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 486 (1938); *Chem. Abstr.*, **33**, 588 (1939).

(53) W. E. Noland and C. Reich, *J. Org. Chem.*, **32**, 828 (1967).

(54) L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin.*, 687 (1967).

(55) T. E. Young, C. J. Ohnmacht, and C. R. Hamel, *J. Org. Chem.*, 32, 3622 (1967).

(56) B. Loev and K. M. Snader, *J. Heterocycl. Chem.*, 4, 403 (1967).

(57) F. J. Stevens and H. C. F. Su, *J. Org. Chem.*, 27, 500 (1962).

(58) D. P. Ainsworth and H. Suschitzky, *J. Chem. Soc.*, *C*, 1003 (1967).

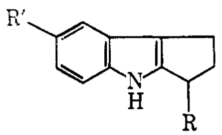
(59) N. P. Buu-Hoi, *J. Chem. Soc.*, 2882 (1949).

(60) S. P. Hiremath and S. Siddappa, *J. Indian Chem. Soc.*, **41**, 357 (1964).

(61) S. M. Parmerter, A. G. Cook, and W. B. Dixon, *J. Amer. Chem. Soc.*, 80, 4621 (1958).

(62) E. H. P. Young, *J. Chem. Soc.*, 3495 (1958).

(63) J. T. Fitzpatrick and R. D. Hiser, *J. Org. Chem.*, **22**, 1703 (1957).



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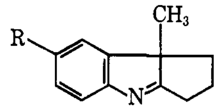

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2-methylcyclopentanone 4-benzyloxyphenylhydrazone is indolized in boiling monoethylene glycol to afford a 52% yield of 39 (R = CH_3; R′ = $OCH_2C_6H_5$), none of the corresponding 3H-indole 40 (R = $OCH_2C_6H_5$) being isolable from the total reaction product.[64] Attempts to use this technique to indolize 3-phenylcyclopent-2-en-1-one N-methylphenylhydrazone failed.[26]

Pyridyl- and pyrimidylhydrazones have also been successfully indolized[26,65] under these noncatalytic thermal conditions (see section VI.B.2).

Since thermal indolization of mixtures of cyclopentanone phenylhydrazone and cyclohexanone 4-methylphenylhydrazone and of cyclohexanone phenylhydrazone and ethyl methyl ketone 4-methylphenylhydrazone afforded no traces of "crossed" indolization products, it is suggested[26] that these thermal indolizations do not proceed by a free-radical mechanism (see also section II.B).

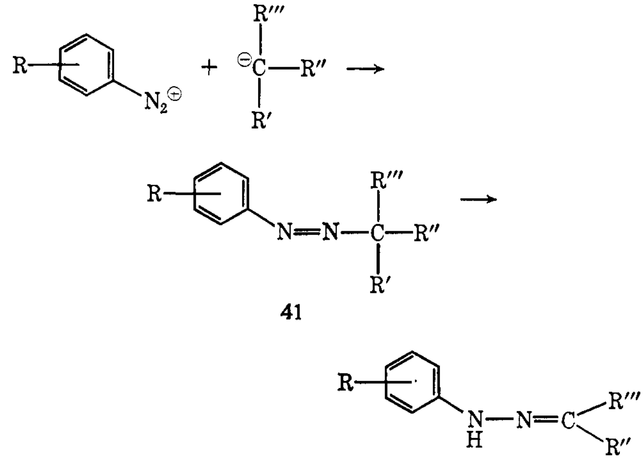
The first example of a noncatalytic indolization at room temperature has been reported,[46] although in this case the reaction was not effected upon an arylhydrazone but upon a blocked enehydrazine tautomer formed *in situ* from cyclohexanone and N′-methyl-2,6-dichlorophenylhydrazine (see section II.C).

IV. *Alternative Methods of Preparing Arylhydrazones*

A. THE JAPP–KLINGEMANN REACTION

This reaction, between an aryldiazonium cation and an activated methinyl group, affords an intermediate azo compound **41** which subsequently yields the hydrazone **42** by expulsion of one of the original carbon substituents. The intermediate azo compounds have now[66–69] been isolated from such reactions, and some compounds originally thought to be the hydrazones have been shown[44] to be the azo intermediates. Azo intermediates from the Japp–Klingemann reaction afford the corresponding hydrazones upon warming[70,71] or in alkaline[70,71] or mild acidic[44,71,72] media, but under more vigorous acidic conditions[44] spontaneous indolization of these hydrazones occurs where possible.

In some cases the Japp–Klingemann affords a mixture of both the azo compound and the hydrazone, which are easily separated since they are soluble and insoluble in petroleum



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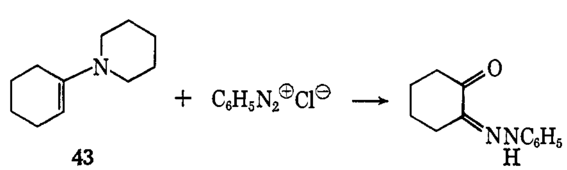
ether, respectively.[44] In slightly basic media a 1:1 molar ratio of 1,3-diketones and benzenediazonium salts affords the corresponding phenylhydrazones, whereas in strong basic conditions a similar reaction between benzenediazonium salts and 1,3-diphenylpropan-1,3-dione produces a mixture of the bisphenylazo compound, the phenylhydrazone, a formazan, and unreacted diketone.[73]

B. ENAMINE–DIAZONIUM CATION COUPLING

The Japp–Klingemann reaction is usually used to prepare the monoarylhydrazones of 1,2-diketones by coupling the appropriate aryldiazonium salt with a 1-formyl- or 1-alkoxycarbonyl-substituted ketone, with subsequent elimination of the formyl or carboxyalkyl group, respectively. An alternative synthesis of such an arylhydrazone has now[74] appeared in which cyclohexanone N-piperidinylenamine (**43**) is coupled with benzenediazonium chloride to give a 75% yield of cyclohexane-1,2-dione monophenylhydrazone (**44**). This reaction has been applied,[75] following the failure[76] of the Japp–Klingemann reaction between benzenediazonium chloride and **45** (R = CO-OCH_3), in the coupling of the pyrrolidine enamine of the ketone **45** (R = H) with benzenediazonium chloride, a reaction which affords the monophenylhydrazone **46** in 50% yield.



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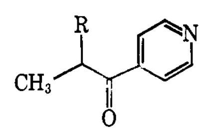

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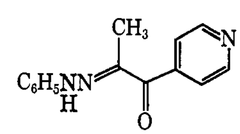


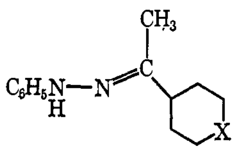
46

(64) M. Ahmed, M.Sc. Thesis, University of Manchester, Manchester, England, 1966.
(65) P. A. Crooks and B. Robinson, *Chem. Ind.* (London), 547 (1967).
(66) C. Dorée and J. A. Gardner, *J. Chem. Soc.*, **93**, 1625 (1908).
(67) C. Dorée and V. A. Petrow, *ibid.*, 1391 (1935).
(68) M. Hamana and I. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **15**, 363 (1967).
(69) L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, *Dokl. Akad. Nauk SSSR*, **169**, 361 (1966); *Chem. Abstr.*, **65**, 15376 (1966).
(70) B. Eistert and M. Regitz, *Ann. Chem.*, **666**, 97 (1963).
(71) H. C. Yao and P. Resnick, *J. Amer. Chem. Soc.*, 84, 3514 (1962).
(72) B. Eistert and M. Regitz, *Chem. Ber.*, **96**, 2290, 2304, 3120 (1963).
(73) H. C. Yao, *J. Org. Chem.*, **29**, 2959 (1964).
(74) V. I. Shvedov, L. B. Altukhova, and A. N. Grinev, *Zh. Org. Khim.*, **1**, 879 (1965); *Chem. Abstr.*, **63**, 6894 (1965).
(75) A. Jackson and J. A. Joule, *Chem. Commun.*, 459 (1967).
(76) J. A. Joule, University of Manchester, Manchester, England, personal communication, 1967.

V. Direction of Indolization

A. INDOLIZATION OF METHYL ALKYL KETONE ARYLHYDRAZONES

Contrary to what would have been expected from previous studies,[1] indolization of methyl 1-methyl-4-piperidyl ketone phenylhydrazone (**47**, X = NCH_3) and cyclohexyl methyl ketone phenylhydrazone (**47**, X = CH_2) using polyphosphoric acid as catalyst affords predominantly the 2-substituted indoles **48** (X = NCH_3 and CH_2 respectively), whereas using zinc chloride or acetic acid as catalysts in these indolizations only the corresponding 3H-indoles **49** (X = NCH_3 and CH_2, respectively) were formed,[77] as previous studies[1] would have predicted. Steric and multialkyl substitution stabilization



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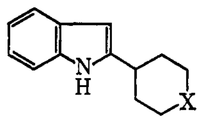

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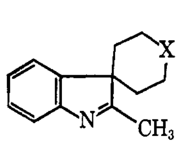

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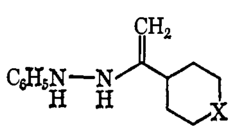
considerations of the two possible enehydrazine intermediates in these reactions led to the suggestion[77] that whereas with a "small" acid (*i.e.*, a proton derived from polyphosphoric acid) the enehydrazine intermediates **50** (X = NCH_3 and CH_2) which ultimately lead to **48** (X = NCH_3 and CH_2) are the more stable, with acids such as zinc chloride and acetic acid, the enehydrazine intermediates **51** (X = NCH_3 and CH_2; A = $ZnCl_2$ and $COCH_3$, respectively) are the more stable.



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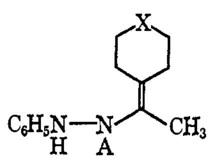

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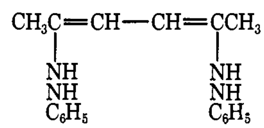
Thus, attempted prediction of the direction of indolization of such ketone arylhydrazones must include considerations of the relative steric strain in the two possible enehydrazine intermediates as well as considerations of the stabilization effected by multiple alkyl substitution of the C=C group in the enehydrazine tautomer.[77]

Further supporting these conclusions[77] it has been found[78] that a polyphosphoric acid catalyst also favors enehydrazine formation onto the methyl group, which would certainly not be expected by consideration of relative conjugative stabilization in the two possible intermediates, when it catalyzes the indolization of benzyl methyl ketone phenyl- and 4-methylphenylhydrazones preferentially to 2-benzyl- and 2-benzyl-5-methylindoles, respectively, whereas zinc chloride, boron trifluoride, and hydrogen chloride in acetic acid all catalyze these reactions in favor of 2-methyl-3-phenyl- and 2,5-dimethyl-3-phenylindoles, respectively.[78]

From the above observations it would appear that polyphosphoric acid favors indolization onto the methyl group of methyl alkyl ketone arylhydrazones.

Other factors governing the direction of indolization of methyl alkyl ketone arylhydrazones are, however, known. The thermally induced indolization of hexane-2,5-dione bisphenylhydrazone affords[79] only 2,2′-dimethyl-3,3′-diindolyl as expected, since the bisenehydrazine leading to this product is the fully conjugated system **52**, whereas the analogous intermediates which would lead to the other two possible isomeric products would consist of two nonconjugated monoenehydrazine systems and would therefore be less favorable. Acetic acid catalyzed indolization of the N-benzyl- and 4-chlorobenzylphenylhydrazones of the ketones **53** (R = CH_3 and C_2H_5; R + R = $(CH_2)_2$ and $(CH_2)_2O(CH_2)_2$) affords[80] only the corresponding 3-alkylamino-2-methylindoles as would be expected since enehydrazine formation involving the methylene group will be favored as it will involve conjugation of the p-electron pair of the nitrogen atom of the ketone moiety with the enehydrazine system.

One exception to the previous generalizations[1] that indolization of methyl alkyl ketone arylhydrazones affords exclusively 3-alkyl-2-methylindoles was the observation that indolization of ethyl methyl ketone phenylhydrazone affords, along with 2,3-dimethylindole as the major product, small amounts of 2-ethylindole. The less favored isomer can, however, be prepared exclusively by indolization of **54** to **55** which can then be desulfurized with Raney nickel to afford 2-ethylindole.[20]



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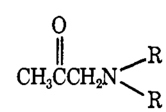

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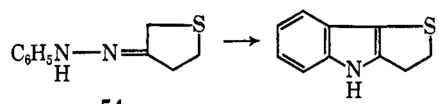
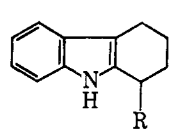


54 **55**

B. INDOLIZATION OF 2-SUBSTITUTED CYCLOHEXANONE ARYLHYDRAZONES

Thermal indolization of 2-phenylcyclohexanone and a series of 2-alkylcyclohexanone phenylhydrazones affords in each case a mixture of the corresponding 1,2,3,4-tetrahydrocarbazole **56** (R = C_6H_5 and alkyl) and 1,2,3,4-tetrahydro-4aH-carbazole **57** (R = C_6H_5 and alkyl), the ratio of the yields of



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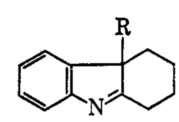

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56:**57** decreasing as the size of the group R increases,[50] these relative yields later[77] being correlated by consideration of the relative $A^{1,2}$ strain in the respective pairs of enehydrazine

(77) R. E. Lyle and L. Skarlos, *Chem. Commun.*, 644 (1966).

(78) N. P. Buu-Hoï, P. Jacquignon, and O. Périn-Roussel, *Bull. Soc. Chim. Fr.*, 32, 2849 (1965).

(79) B. Robinson, *Can. J. Chem.*, 42, 2900 (1964).

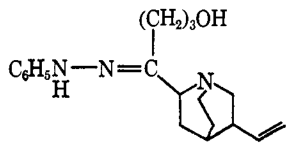
(80) F. Yoneda, T. Miyamae, and Y. Nitta, *Chem. Pharm. Bull.* (Tokyo), 15, 8 (1967).

intermediates. Similarly, 2-(2-cyanoethyl)cyclohexanone phenylhydrazone was indolized[81] by 20% sulfuric acid to afford both **56** (R = $CH_2)_2CN$) and **57** (R = $CH_2)_2CN$) in the relative yield ratios 25:9, which are in the order expected from previous studies upon the indolization of 2-alkylcyclohexanone phenylhydrazones using a sulfuric acid catalyst[1] (see also section VI.C.3). Using 98–100% formic acid as catalyst, however, indolization of 2-ethylcyclohexanone phenylhydrazone afforded mainly 4a-ethyl-1,2,3,4-tetrahydro-4aH-carbazole, although this was only isolated in low yield since it reacted with the formic acid under the indolization conditions to afford 4a-ethyl-9-formyl-1,2,3,4,4a,9a-hexahydrocarbazole.[82] Analysis by uv spectroscopy also detected the formation of small amounts of 1-ethyl-1,2,3,4-tetrahydrocarbazole.[82]

C. INDOLIZATION OF ASYMMETRICAL ACYCLIC KETONE ARYLHYDRAZONES

Further examples have appeared in which indolization of methyl *n*-alkyl[81] and methyl *sec*-alkyl[81,83] ketone phenylhydrazones afford exclusively the corresponding 2-methylindoles and 2-methyl-3H-indoles, respectively, in agreement with the previously summarized[1] conclusions (see also section V.A).

3-Hydroxypropyl 5-vinyl-2-quinuclidyl ketone phenylhydrazone (**58**) affords (+)-cinchonamine upon indolization.[84]



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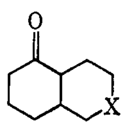
No attempts were made to isolate the corresponding 3H-indole, formation of which would be expected in this reaction by analogy with previous work.[1]

D. ENEHYDRAZINE FORMATION TOWARD A RING JUNCTION

Acetic acid catalyzed indolization of the phenylhydrazone and 2-methoxyphenylhydrazone of **59** (X = CH_2) (*trans* isomer) and the phenylhydrazone of **59** (X = $NCOCH_3$) (probably *trans* isomer) occurs toward the ring junction in each case, affording the 3H-indoles **60** (R = H, X = CH_2; R = OCH_3, X = CH_2; and R = H, X = $NCOCH_3$, respectively).[85] However, hydrogen chloride catalyzed indolization of the phenylhydrazones of both the (+) and (−) isomers of **61** and **62** affords[86] only **63** and **64**, respectively (see also ref 87), in each case the corresponding optically active and racemic isomers



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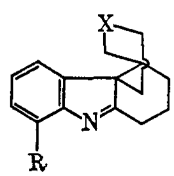

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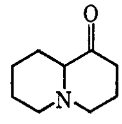

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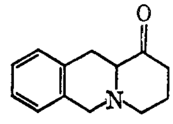

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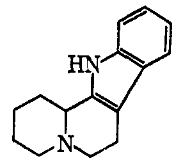

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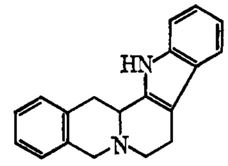

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being produced (compound (−)-**63** has been isolated[88] from natural sources, but the optical rotation of the natural base[88] is appreciably less than that of the synthetic compound,[86] suggesting that the natural base could be partially racemized; this would account for the differences between the quoted[86,88] melting points of the natural and synthetic compounds). Both **63** and **64** are produced by indolization subsequent to enehydrazine formation away from the ring junction, whereas enehydrazine formation toward the ring junction, which would ultimately afford the corresponding 3H-indoles, should be the preferred direction of this tautomerization, since it would involve a tertiary rather than a secondary carbon atom and would also conjugate the p-electron pair of the nitrogen atom at the ring junction (see section V.A). This latter direction of tautomerization must occur to some extent since both **63** and **64** are in part produced as their racemates. However, it could be that the presence of the terminal nitrogen atom on such enehydrazine systems greatly retards the intramolecular electrophilic attack which leads to new C–C bond formation, relative to the analogous rearrangements in the alternative tautomers, the formation of which, although least favored, can ultimately lead to **63** and **64**. With acyclic analogs, indolization subsequent to enehydrazine tautomerization toward the nitrogen atom occurs exclusively,[80] although in all these cases so far studied[80] indolization in the alternative direction would be onto a methyl group, which is not favored in most cases (see section V.A).

However, both the indole **65**[89] and the 3H-indole **66**[90,91] are obtained by indolization of the 2-methoxyphenylhydrazone of **67** (R = H) in acetic acid, although the phenylhydrazone of **67** (R + R = O) affords[92] only the corresponding indolic product under similar conditions. In this case enehydrazine formation toward the ring junction (which would ultimately lead to the 3H-indole) would produce a five-membered ring containing three trigonal atoms, this being reduced to one in the corresponding tautomer of **67** (R = H).[92]

(81) A. N. Kost, L. G. Yudin, and C. Yii-Chou, *Zh. Obshch. Khim.*, **34**, 3444 (1964); *J. Gen. Chem. USSR*, **34**, 3487 (1964).

(82) Y. Ban, T. Oishi, Y. Kishio, and I. Iijima, *Chem. Pharm. Bull.* (Tokyo), **15**, 531 (1967).

(83) H. J. Teuber and D. Cornelius, *Chem. Ber.*, **98**, 2111 (1965).

(84) C. Chang-pai, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, 30, 2085 (1960); *J. Gen. Chem. USSR*, **30**, 2066 (1960).

(85) V. Georgian, *Chem. Ind.* (London), 1124 (1957).

(86) S. Yamada and T. Kunieda, *Chem. Pharm. Bull.* (Tokyo), **15**, 449 (1967).

(87) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 617 (1946).

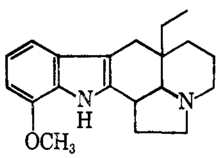
(88) S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Chem. Commun.*, 421 (1966).

(89) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanoaka, *Tetrahedron Lett.*, 2261 (1965).

(90) Y. Ban and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **13**, 1073 (1965).

(91) F. Sparatore, *Gazz. Chim. Ital.*, 88, 755 (1958).

(92) G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, **85**, 2872 (1963).



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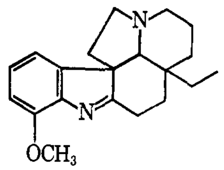

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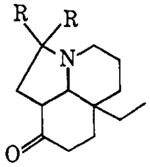

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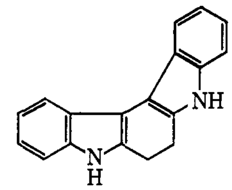

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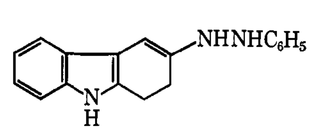

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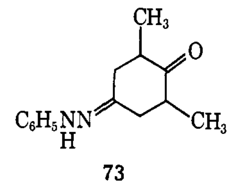

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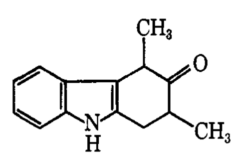

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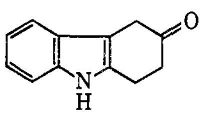
E. INDOLIZATION OF CYCLOHEXANE-1,4-DIONE BISPHENYLHYDRAZONE

A variety of products have been isolated from this indolization, the nature of the products depending upon the catalyst and reaction conditions used.

With 50% sulfuric acid at 100°, both 1,2,3,4-tetrahydro-3-oxocarbazole (**68**) and indolo[3,2-*b*]carbazole (**69**) were isolated[93] by fractional vacuum sublimation of the reaction product. With glacial acetic acid–concentrated sulfuric acid, **69** and 3-phenylhydrazinocarbazole (**70**) were formed;[94] dilute ethanolic sulfuric acid at 80° afforded **70**, 3-hydroxycarbazole, and a compound $C_{20}H_{17}N_3$ of unknown structure;[95] and more concentrated aqueous sulfuric acid gave[95] **69**.



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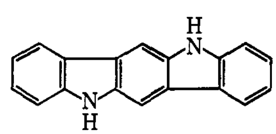

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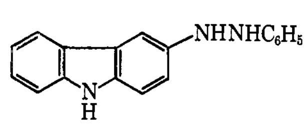

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In no case was indolo[2,3-*b*]carbazole or its dihydro precursor **71**, which would result from the direction of bisindolization alternative to that which led to **69**, formed in these reactions, probably owing to the steric interaction of the two terminal benzenoid nuclei in **71**, the intermediate **72** necessary for its formation preferentially undergoing aromatization to **70**.[94] Compound **68** and 3-hydroxycarbazole obviously result from indolization of one hydrazone moiety and hydrolytic cleavage of the other, with subsequent dehydrogenation in the latter case.

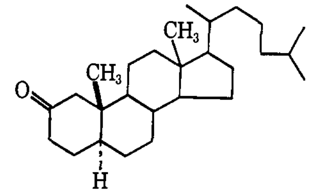
All attempts[93] to prepare cyclohexane-1,4-dione monophenylhydrazone, in which there is only one possible direction of indolization, failed. However, the 3,5-dimethylcyclohexane-1,4-dione monophenylhydrazone (**73**) has been[95] prepared and successfully indolized to the expected 1,2,3,4-tetrahydro-2,4-dimethyl-3-oxocarbazole (**74**).

(93) J. Harley-Mason and E. H. Pavri, *J. Chem. Soc.*, 2504 (1963).
(94) B. Robinson, *ibid.*, 3097 (1963).
(95) H. J. Teuber, D. Cornelius, and U. Wolcke, *Ann. Chem.*, **696**, 116 (1966).

F. INDOLIZATION OF KETOSTEROID ARYLHYDRAZONES

1. 2-Ketosteroid Arylhydrazones

Indolization of a mixture of 5α-cholestan-2-one (**75**) and N-methylphenylhydrazine gave a product, which was formulated[96] as **76**, and not the alternative angular isomer, since **75** was known[97] to form exclusively a Δ^2-enol, and by analogy enehydrazine formation, the initial stage of the indolization, would occur in the same direction. Similarly, indolization of



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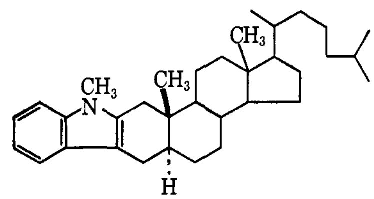

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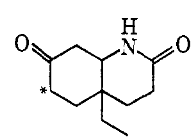
the phenylhydrazones of the *cis* and *trans* isomers of ketone **77** afforded[92] only the linear isomeric indolic products formed by indolization at C* as shown by mass spectral investigation. This result is as expected by analogy with the known direction



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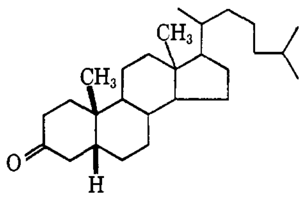
enolization of 10-methyl-*cis*-2-decalone toward C_3.[91]

2. 3-Ketosteroid Arylhydrazones

A 3-ketosteroid was first allowed to react with phenylhydrazine under Fischer indolization conditions in 1908[66] when 5β-cholestan-3-one (**78**) and phenylhydrazine were allowed to react in boiling glacial acetic acid, but it was not until the

(96) E. W. Warnhoff and P. NaNonggai, *J. Org. Chem.*, 27, 1186 (1962).
(97) C. Djerassi and T. Nakano, *Chem. Ind.* (London), 1385 (1960).

following year[98] that the indolic nature of the reaction product was recognized. Later,[67] the synthesis was repeated using 5α-cholestan-3-one (**79**), and the indolic reaction product was formulated as **80** rather than the linear isomer **81**. Structure **80**



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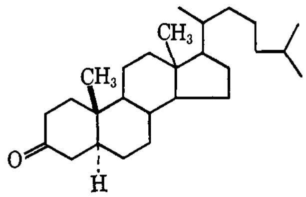

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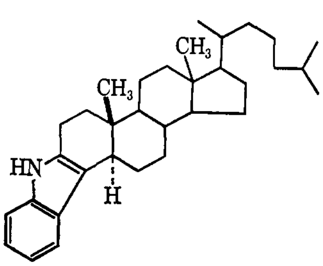

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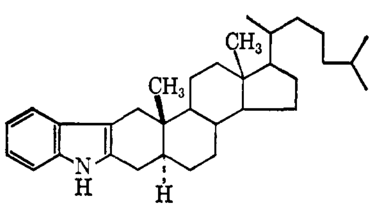
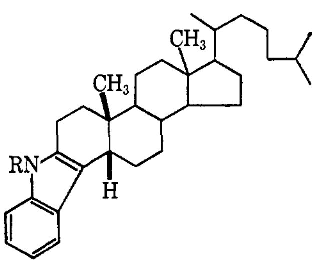


81

was supported by surface-film measurements, and the linear isomer was thought to be unlikely from chemical analogies available at the time.[67] Later,[99] however, but without any further reasons or evidence, this product was reformulated as **81**, structure **82** (R = H) (*i.e.*, **80** with H-5 β instead of α) being assigned to the product resulting from the reaction of 5β-cholestan-3-one (**78**) with phenylhydrazine in glacial acetic acid.[66,98]



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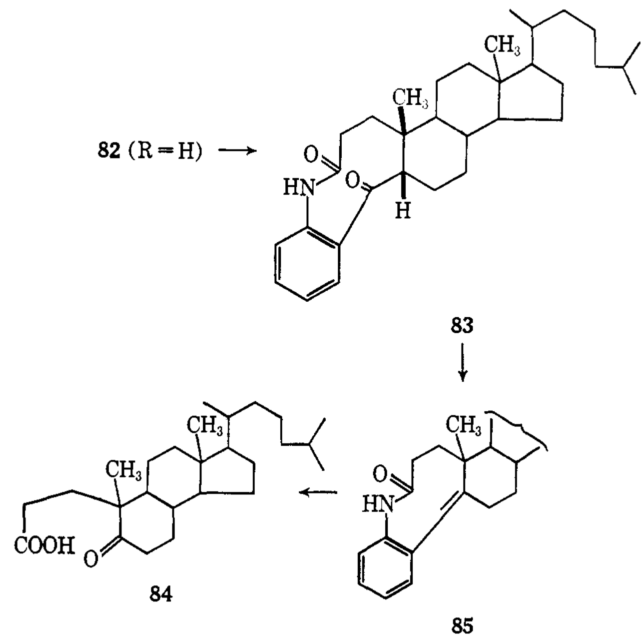
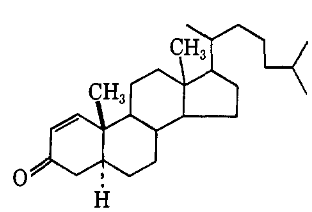
Structure **82** (R = H) has now[90] been verified for the product resulting from indolization of 5β-cholestan-3-one (**78**) phenylhydrazone by subjecting it to ozonolysis to afford **83**, sodium borohydride reduction of which was followed by spontaneous dehydration to give **85**, which upon ozonolysis followed by alkaline hydrolysis gave **84**, a known compound. A similar conclusion had also been reached earlier[96] when the product obtained by indolization of 5β-cholestan-3-one (**78**) N-methylphenylhydrazone was shown to be **82** (R = CH_3)



since it was found to be the C-5 epimer of the compound obtained by catalytic hydrogenation of the product resulting from indolization (which can only occur on C_4 of the steroid nucleus) of 5α-Δ_1-cholesten-3-one (**86**) N-methylphenylhydrazone.



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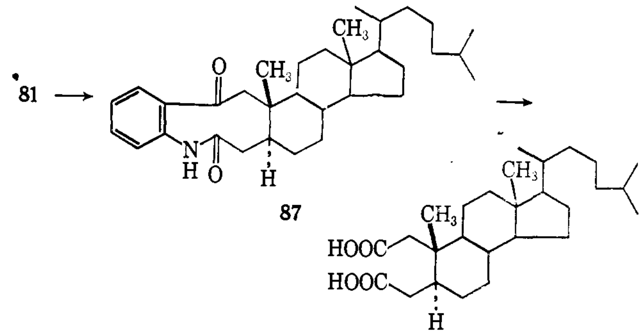
The product obtained by indolization of 5α-cholestan-3-one (**79**) phenylhydrazone has been shown[90] to have structure **81** by ozonolysis of it to **87** which upon oxidation with hydrogen peroxide followed by hydrolysis afforded the known dicarboxylic acid **88**. The above results conform with the mechanism of



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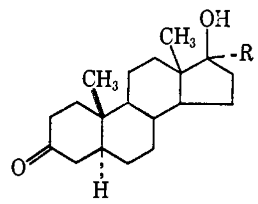
the Fischer indolization[1] and the known[100] direction of enolization of 5α- and 5β-cholestan-3-ones.

Androstan-17β-ol-3-one (**89**, R = H) 4-methoxy- and 4-nitrophenylhydrazones and 17α-methylandrostan-17β-ol-3-one (**89**, R = CH_3) 4-benzoyloxy- and 4-benzyloxyphenylhydrazones have all been indolized using acetic acid as catalyst

(98) C. Dorée, *J. Chem. Soc.*, **95**, 653 (1909).
(99) H. Antaki and V. Petrow, *ibid.*, 901 (1951).

(100) P. A. Hart, "Steroid Reactions. An Outline for Organic Chemists," C. Djerassi, Ed., Holden-Day Inc., San Francisco, Calif., 1963, p 182.

(which in three cases also effected 17β-OH acetylation) to give in each case a corresponding product which, without reference to any experimental or theoretical verification, was formulated as the linear isomer resulting from indolization at C-2 of the steroid nucleus.[101] Similarly,[101] the product resulting from indolization of 2α,17α-dimethylandrostan-17β-ol-3-one phenylhydrazone was arbitrarily formulated as **90** (a 3H-indole) without the obvious support of ultraviolet spectral evidence which would have readily distinguished it from the possible corresponding angular isomer (an indole) formed by indolization at C-4 of the steroid nucleus. These structures,



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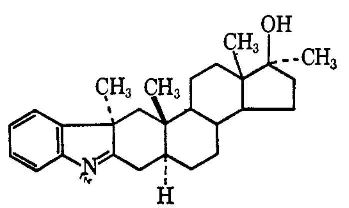

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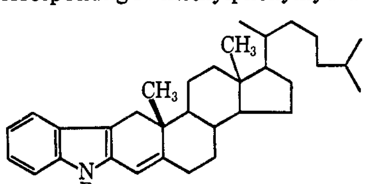
however, do receive support from the above-mentioned studies[90] on **78** and **79** phenylhydrazones and the known direction of enolization of 3-ketosteroids.[100]

3. Δ^4-3-Ketosteroid Arylhydrazones

Unlike simpler 1,2-unsaturated ketone arylhydrazones, attempted indolization of which failed,[1] Δ^4-cholesten-3-one phenylhydrazone afforded a product which was formulated,[102] without evidence, as **91** (R = H). However, similar indolization[96] of the correspondng N-methylphenylhydrazone afforded



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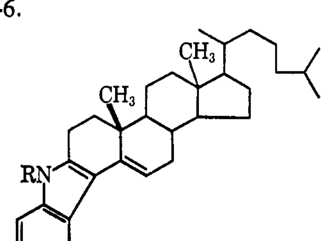
a compound which upon catalytic hydrogenation yielded a pair of C-5 epimers, one of which was identical with the product obtained by indolization of 5β-cholestan-3-one N-methylphenylhydrazone, which is known[90,96] to have structure **82** (R = CH_3). The structure of this compound therefore follows as **92** (R = CH_3) and not the possible alternative **91** (R = CH_3), and the structure **91** (R = H) assigned[102] to the product obtained from the corresponding phenylhydrazone must, by analogy, be revised to **92** (R = H).[96] The structures **92** (R = H and CH_3) established for the products from these indolizations are as expected[96] since Δ^4-cholesten-3-one enolizes toward C-6.



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(101) M. G. Lester, V. Petrow, and O. Stephenson, *Tetrahedron*, **21**, 1761 (1965).

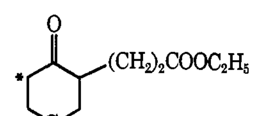
(102) W. Rossner, *Z. Physiol. Chem.*, **249**, 267 (1937).

G. INDOLIZATION OF 3-PYRIDYLHYDRAZONES

In agreement with previous results from indolizations involving 3-pyridylhydrazones,[1] piperidine-2,3-dione 3-(3-pyridylhydrazone) and 3-(3-pyridylhydrazone 1-oxide) afford[103] only 2,5-diaza-1,2,3,4-tetrahydro-1-oxocarbazole and its 5-oxide, respectively, the new C–C bond formation occurring exclusively at the 2 position of the pyridyl nucleus. The other theoretically possible isomeric product, 2,7-diaza-1,2,3,4-tetrahydro-1-oxocarbazole, from the former reaction was, however, prepared[103] by indolization of piperidine-2,3-dione 3-(2-chloro-3-pyridylhydrazone) followed by hydrogenolytic removal of the chloro substituent.

H. INFLUENCE OF ARYL SUBSTITUENT UPON DIRECTION OF INDOLIZATION ON THE KETONIC MOIETY

The phenylhydrazone and the 4-methyl-, 4-nitro-, and 4-carbethoxyphenylhydrazones of **93** have all been indolized under identical conditions.[104] In the former three compounds, indolization appeared to occur exclusively toward C* since the only reaction products isolated were **94** (R = H, CH_3, and NO_2, respectively), produced by intramolecular cyclization of the indoles initially produced (a similar result was also obtained using the corresponding 2-naphthylhydrazones) (see section VI.C.4). With the carbethoxyphenylhydrazone, however, indolization occurred in both directions since both the indole **94** (R = $COOC_2H_5$) and the 3H-indole **95** were formed.[104] It would be of interest to further investigate this ap-



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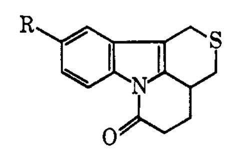

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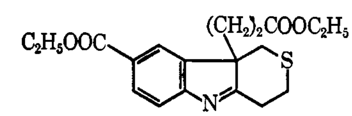

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parent effect of the aryl substituted upon the direction of indolization of *unsym*-ketone arylhydrazones.

I. INDOLIZATION OF *meta*-SUBSTITUTED PHENYLHYDRAZONES

Further examples of these indolizations have appeared, the orientation of the 4- and 6-substituted indoles obtained being in some cases postulated from theoretical considerations of relative yields[105–107] and in others being established by pmr[107,108] and ir (examination of the out-of-plane deformation

(103) G. Tacconi and S. Pietra, *Ann. Chim.* (Rome), **55**, 1223 (1965).

(104) L. N. Kakurina, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Obshch. Khim.*, **34**, 2805 (1964); *J. Gen. Chem. USSR*, **34**, 2829 (1964); *Zh. Org. Khim.*, **1**, 1108 (1965); *Chem. Abstr.*, **63**, 11525 (1965).

(105) R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.*, **23**, 435 (1958).

(106) R. C. Elderfield and S. L. Wythe, *ibid.*, **19**, 693 (1954).

(107) J. Symuszkovicz, E. M. Glenn, R. V. Heinzelman, J. B. Hester, Jr., and G. A. Youngdale, *J. Med. Chem.*, **9**, 527 (1966).

(108) J. B. McKay, R. M. Parkhurst, R. M. Silverstein, and W. A. Skinner, *Can. J. Chem.*, **41**, 2585 (1963).

of the aromatic C–H bonds)[107,109–111] spectral examination, by degradation,[109] and by unambiguous synthesis.[112] Isomer separations have been effected by chromatography[107,108] and fractional crystallization,[109–111] and indolization of ethyl levulinate 3-chlorophenylhydrazone has afforded a eutectic mixture consisting of 56% of the 6-chloro isomer and 44% of the 4-chloro isomer (as determined by ir spectral studies).[113]

In some cases[108] isomer ratios obtained in these reactions had no significance with regard to the mechanism of the formation of the new C–C bond, since product yields were low, but in others, with chloro[111–113] and methoxy[107] substituents, this ratio supports the intramolecular electrophilic nature of this rearrangement, as the many previous similar examples had done.[1] However, the ratio of 4:6 substituted indoles formed by indolization of both piperidine-2,3-dione 3-(3-acetyl- and 3-benzoylphenylhydrazones) is < 1,[110] which is contrary to what would have been predicted.[1]

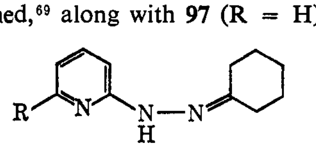
VI. Exceptions and Limitations to the Fischer Indole Synthesis

A. ATTEMPTED INDOLIZATIONS OF ACETALDEHYDE PHENYLHYDRAZONE

All earlier attempts to obtain indole from this reaction failed, as have the recent attempts[49,50] using polyphosphate ester as an acid catalyst and boiling diethylene glycol in a noncatalytic thermal attempt.[26] In the latter case,[26] however, ammonia evolution was detected during the reaction and aniline, N-ethylaniline, and an indolic product, which gave a positive Erhlich test and had a characteristic indolic NH stretching band at 3413 cm^{-1} in its ir spectrum, were isolated[26] from the reaction product.

B. INDOLIZATION OF PYRIDYLHYDRAZONES AND PYRIMIDYLHYDRAZONES

Cyclohexanone 2-pyridylhydrazone (**96**, R = H) affords 8-aza-1,2,3,4-tetrahydrocarbazole (**97**, R = H) when treated with polyphosphoric,[114] sulfosalicylic,[115] and 4-methylphenylsulfonic[115] acids and when boiled in diethylene glycol.[26] However, using hydrochloric acid as catalyst there was formed,[69] along with **97** (R = H), a further compound for



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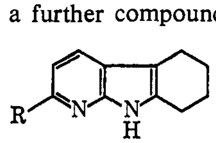


97

which structure **98** (R = H) was proposed on the basis of spectroscopic evidence. Similarly, **96** (R = CH_3) afforded[69] both **97** (R = CH_3) and **98** (R = CH_3).

(109) Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **11**, 1431 (1963).

(110) M. von Strandmann, M. P. Cohen, and J. Shavel, Jr., *J. Med. Chem.*, **6**, 719 (1963).

(111) L. H. Werner, D. C. Schroder, and S. Ricca, Jr., *J. Amer. Chem. Soc.*, **79**, 1675 (1957).

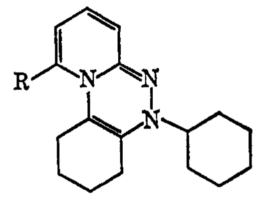
(112) J. R. Piper and F. J. Stevens, *J. Heterocycl. Chem.*, **3**, 95 (1966).

(113) F. J. Stevens, Auburn University, Auburn, Ala., personal communication, 1962.

(114) S. Okuda and M. M. Robison, *J. Amer. Chem. Soc.*, **81**, 740 (1959).

(115) M. V. Rubtsov, L. N. Yakhontov, and E. V. Pronina, *Byull. Izobret. i Tovarnykh Znakov*, [24] 22 (1965); *Chem. Abstr.*, **64**, 12679 (1966).

Using boron trifluoride etherate in acetic acid as catalyst, indolization of **96** (R = H) failed, the only product isolated[69] from this reaction being **99** (R = H), whereas similar catalytic treatment of **96** (R = CH_3) afforded[69] both **97** (R = CH_3) and **99** (R = CH_3).



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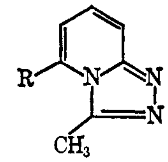

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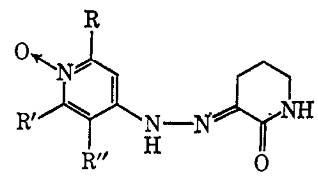
Usually, attempted indolization of pyridylhydrazones with acid catalysts either fails or affords only low yields of the corresponding indoles owing to deactivation of the pyridine nucleus toward electrophilic attack by both the inductive effect of the hetero nitrogen atom and by protonation of this atom under the acidic indolization conditions. Two methods have now been developed in which this latter deactivating effect has been prevented and indolizations successfully effected.

1. *Indolization of Pyridylhydrazone 1-Oxides*

Several piperidine-2,3-dione 3-(2,5-dialkyl- and 2- or 5-alkyl-4-pyridylhydrazone 1-oxides) (**100**, R = CH_3, R′ = H, R″ = C_2H_5; R = R′ = H, R″ = CH_3; R′ = R″ = H, R = CH_3) upon treatment with zinc chloride afford[116] the corresponding 2,6-diaza-1,2,3,4-tetrahydro-1-oxocarbazole 6-oxides (**101**, R = CH_3, R′ = H, R″ = C_2H_5; R = R′ = H, R″ = CH_3; R′ = R″ = H, R = CH_3; or R′ = CH_3, R = R″ = H, respectively) in reasonable yields, the orientation of the methyl group in the third product not being established. Similar



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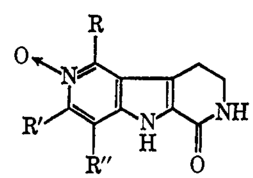

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treatment of cyclohexanone 4-pyridylhydrazone 1-oxide also effected indolization to 6-aza-1,2,3,4-tetrahydrocarbazole 6-oxide, although with other ketonic or aldehydic moieties the indolization was unsuccessful.[116] This reaction has been extended to 3-pyridylhydrazone 1-oxides, piperidine-2,3-dione 3-(3-pyridylhydrazone 1-oxide) with zinc chloride affording[103] 2,5-diaza-1,2,3,4-tetrahydro-1-oxocarbazole 5-oxide (see also section V.G).

2. *Thermal Indolization of Pyridylhydrazones and Pyrimidylhydrazones*

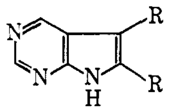
This second and more versatile method of preventing protonation of the hetero nitrogen atom during these indolizations employs[26,65,117] the noncatalytic thermal technique,[63] cyclohexanone 4-pyridylhydrazone,[26] several other 4-pyridylhydrazones,[65] and several 2-pyridylhydrazones[117] having been converted, mostly in good yields, into the corresponding

(116) G. Tacconi and S. Pietra, *Ann. Chim.* (Rome), **55**, 810 (1965).

(117) A. H. Kelly and J. Parrick, *Can. J. Chem.*, **44**, 2455 (1966).

5-aza- and 7-azaindoles, respectively, by boiling in di- or triethylene glycol. The application of this technique to the indolization of 3-pyridylhydrazones and an investigation of the direction of cyclization in these reactions are at present in progress.[118]

This method has also been[65] successfully applied to the indolization of 4-pyrimidylhydrazones, cyclohexanone, and ethyl methyl ketone 4-pyrimidylhydrazones having been converted into 6,8-diaza-1,2,3,4-tetrahydrocarbazole (**102**, R + R = $(CH_2)_4$) and 5,7-diaza-2,3-dimethylindole (**102**, R = CH_3), respectively. A similar reaction with isobutyraldehyde 4-pyrimidylhydrazone afforded none of the expected 5,7-diaza-3,3-dimethyl-3H-indole, but gave[65] only **102** (R = CH_3), presumably arising by a thermally induced noncatalytic Plancher rearrangement of the initially formed 3H-indole.[65] A



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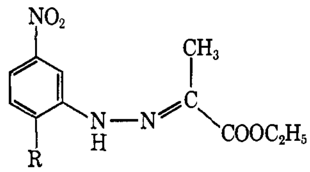
similar rearrangement occurred[65] upon thermal indolization of isobutyraldehyde 4-pyridylhydrazone which afforded exclusively 5-aza-2,3-dimethylindole. In view of these observations it was suggested[65] that the compound, prepared by thermal indolization of isobutyraldehyde 2-pyridylhydrazone and thought[117] to be 7-aza-3,3-dimethyl-3H-indole, should be reformulated as 7-aza-2,3-dimethylindole. this postulation later[118] being verified.

It is unfortunate that the noncatalytic thermal technique was not applied to the indolization of the arylhydrazones **103** (R = piperidyl) and **103** (R = morpholino) where acid-catalyzed indolization fails,[58] undoubtedly owing to protonation of the basic benz substituent which deactivates the ring toward electrophilic attack, since the corresponding 2-chloro-5-nitrophenylhydrazones **103** (R = Cl) undergo acid-catalyzed indolization in almost quantitative yield.[58]



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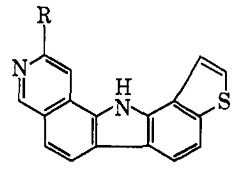
C. SUCCESSFUL INDOLIZATION WITH SUBSEQUENT FURTHER REACTIONS

1. *Indolization Followed by Spontaneous Dehydrogenation*

Further examples of this type of reaction have been discovered,[119–121] usually when zinc chloride at an elevated temperature is used to effect indolization. Under such conditions, 4,5,6,7-tetrahydro-4-oxobenzo[*b*]thiophen 5-isoquinolyl- and 3-methyl-5-isoquinolylhydrazones[120] and 3-, 5-, 6-, and 8-quinolylhydrazones,[119] and a series of 1- and 2-tetralone quinolylhydrazones[119] are converted directly into **104** (R = H and CH_3),[120] **105, 106, 107, 108,**[119] and a series of benzopyridocarbazoles,[119] respectively. Similarly, using sulfuric acid in acetic acid as catalyst, several 1,2,3,4-tetrahydro-4-oxoquinoline arylhydrazones are converted directly into the corresponding 1,2-benzo-3-carbolines[121] as are the corresponding 1- and 2-naphthylhydrazones and 6-quinolylhydrazone into **109, 110,** and **111**, respectively.[121] Sulfuric acid[94] or sulfuric–acetic acid[93,95] catalyzed indolization of cyclohexane-1,4-dione bisphenylhydrazone affords directly indolo[2,3-*b*]carbazole (**69**), along with other products (see section V.E). Usually, however,



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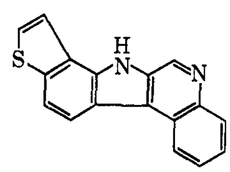

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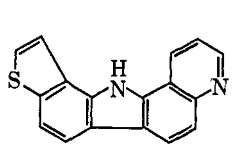

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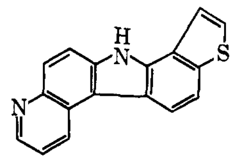

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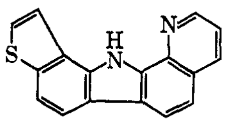

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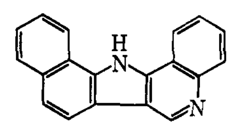

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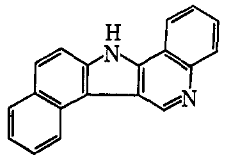

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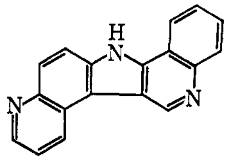


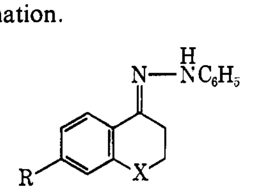
111

when a Brønsted acid catalyst is used in other similar indolizations, the subsequent dehydrogenations do not occur.[122–128]

Previous work has shown that indolization of **112** (X = NCH_3; R = H) was accompanied by spontaneous dehydrogenation to afford **113**, whereas the arsenic analog **112** (X = $AsCH_3$; R = OCH_3) afforded the normal indole **114** (X = $AsCH_3$; R = OCH_3) and not its dehydrogenation product corresponding to **113**. Compound **112** (X = PC_6H_5; R = H), the ketonic moiety of which occupies an intermediatory position between those of **112** (X = NCH_3, R = H, and X = $AsCH_3$, R = H), has now[129] been indolized under similar

(118) J. Parrick, Brunel College, London, personal communication, 1967.
(119) N. P. Buu-Hoï, P. Jacquignon, and J. P. Hoeffinger, *J. Chem. Soc.*, 4754 (1963).
(120) N. P. Buu-Hoï, P. Jacquignon, O. Roussel, and J. P. Hoeffinger, *ibid.*, 3924 (1964).
(121) O. Roussel, N. P. Buu-Hoï, and P. Jacquignon, *ibid.*, 5458 (1965).
(122) N. P. Buu-Hoï, P. Jacquignon, A. Croisy, and A. Ricci, *J. Chem. Soc., C*, 45 (1968).
(123) N. P. Buu-Hoï, M. Mangane, and P. Jacquignon, *ibid.*, 662 (1967).
(124) N. P. Buu-Hoï, A. Martani, A. Croisy, P. Jacquignon, and F. Périn, *ibid.*, 1787 (1966).
(125) N. P. Buu-Hoï, A. Martani, A. Ricci, M. Dufour, P. Jacquignon, and G. Saint-Ruf, *ibid.*, 1790 (1966).
(126) N. P. Buu-Hoï, F. Périn, and P. Jacquignon, *Bull. Soc. Chim. Fr.*, 33, 584 (1966).
(127) N. P. Buu-Hoï and G. Saint-Ruf, *J. Chem. Soc.*, 2642 (1965).
(128) N. P. Buu-Hoï and G. Saint-Ruf, *ibid.*, 5464 (1965).
(129) M. J. Gallagher and F. G. Mann, *ibid.*, 4855 (1963).

conditions (ethanolic hydrochloric acid) and affords **114** (X = PC_6H_5; R = H) and not the corresponding dehydrogenated product. This was as expected[129] since there was no evidence that the ketonic moiety existed, even in equilibrium, as the charge-separated species **115**. Differences between the steric, conformational, or inductive factors within this series of compounds may also be connected with the success or failure of the dehydrogenation.



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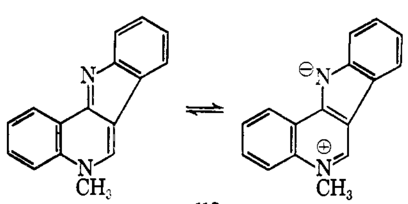

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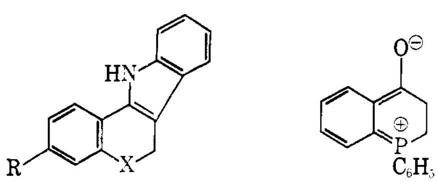
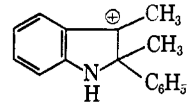


114 115

2. *Group Migrations on the Ketonic Moiety during Indolization*

Contrary to previous reports,[130,131] which claimed that indolization of 3-phenyl-2-butanone phenylhydrazone with zinc chloride, boron trifluoride, or hydrochloric acid afforded only 3,3-dimethyl-2-phenyl-3H-indole, it has been found[132] that this hydrazone or isobutyrophenone phenylhydrazone in the presence of polyphosphoric acid at an elevated temperature affords in each case an equilibrium mixture of 3,3-dimethyl-2-phenyl-3H-indole (30%) and 2,3-dimethyl-3-phenyl-3H-indole (70%) which can be separated by fractional crystallization of their picrates. The mixture is formed in each case by equilibration of the initially produced 2,3-dimethyl-3-phenyl-3H-indole and 3,3-dimethyl-2-phenyl-3H-indole, respectively, under the indolization conditions.[132,133] The rearrangement of the latter 3H-indole is unexpected, since it would be expected[132] to be thermodynamically more stable than the former isomer. This consideration, together with the failure to recognize the indolization product as a mixture and the difficulty in distinguishing the two 3H-indoles, led to the previous[130,131] erroneous conclusions. The above equilibrations, which can be prevented by effecting the indolizations with glacial acetic acid,[132] have been shown,[133] using ^{14}C tracers, to occur by a double Wagner–Meerwein shift *via* intermediate **116**. A related rearrangement observed when phenylacetaldehyde phenylhydrazone is indolized with zinc chloride to afford 2-phenylindole, presum-



116

ably by rearrangement of the initially formed 3-phenylindole has been shown[134] to be intramolecular in character and the rearrangement of 3-phenyl to 2-phenylindole under similar conditions is independent of the reaction solvent employed.[134]

3. *Group Eliminations during Indolization*

Indolization of 4-methyl-4-oxocapronitrile phenylhydrazone and 2-(2-cyanoethyl)cyclohexanone phenylhydrazone with zinc chloride at a elevated temperature affords only 2,3-dimethylindole and 1,2,3,4-tetrahydrocarbazole, respectively, these being formed by decyanoethylation of the initially produced 3H-indole and 1,2,3,4-tetrahydro-4aH-carbazole, respectively.[81] At a lower temperature the latter phenylhydrazone afforded 1,2,3,4-tetrahydrocarbazole together with 1-(2-cyanoethyl)-1,2,3,4-tetrahydrocarbazole, formed by indolization in the alternative direction, whereas with 20% sulfuric acid as catalyst the elimination is prevented and the normal expected indolic and 3H-indolic products result[81] (see sections V.A and V.B).

Related to these studies are the observations that the 1,2,3,4-tetrahydro-4aH-carbazoles **57** [R = $C(CH_3)_3$, $C_6H_5CH_2$, and $CH(CH_3)_2$] upon treatment with acids afford in each case 1,2,3,4-tetrahydrocarbazole, elimination of the *t*-butyl group occurring under milder conditions than elimination of the other two groups.[135] Similarly, 3-*t*-butyl-2,3-dimethyl-3H-indole and 3-benzyl-2,3-dimethyl-3H-indole both afford 2,3-dimethylindole upon boiling with hydrochloric acid.[135] Acid-catalyzed elimination of the *t*-butyl group from 3-*t*-butylindole to afford indole has also been observed, although 2-*t*-butylindole is not affected to any great extent under similar conditions.[136]

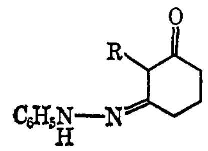
The above observations[135,136] must be considered in choosing the catalyst and reaction conditions when preparing 3H-indoles and 3-*t*-butylindoles by the Fischer method.

4. *Indolization with Subsequent Molecular Rearrangements*

Although the monoarylhydrazones of acyclic 1,3-diones are converted into pyrazoles under acidic conditions, cyclohexane-1,3-dione monophenylhydrazone affords 1,2,3,4-tetrahydro-4-oxocarbazole upon similar treatment.[1] Attempts have now been made[137] to effect the similar indolization of several 2-alkylcyclohexane-1,3-dione monophenylhydrazones **117** [R = CH_3, C_2H_5, and $(CH_2)_2CH_3$] to the corresponding 4a-alkyl-1,2,3,4-tetrahydro-4aH-carbazoles (**118**, R = CH_3, C_2H_5, and $(CH_2)_2CH_3$, respectively), but the reaction products formed were shown by ir spectral examination to have structures

(130) M. Nakazaki, *Bull. Chem. Soc. Jap.*, **33**, 472 (1960).
(131) M. Nakazaki, K. Yamamoto, and K. Yomagami, *ibid.*, **33**, 466 (1960).
(132) F. J. Evans, G. G. Lyle, J. Watkins, and R. E. Lyle, *J. Org. Chem.*, 27, 1553 (1962).
133) F. J. Evans and R. E. Lyle, *Chem. Ind.* (London), 986 (1963).
(134) N. P. Buu-Hoï and P. Jacquignon, *Bull. Soc. Chim. Fr.*, **34**, 1104 (1967).
(135) M. Nakazaki, S. Isoe, and K. Tanno, *Nippon Kagaku Zasshi*, **76**, 1262 (1955); *Chem. Abstr.*, **51**, 17878 (1957).
(136) S. David and P. Régent, *Bull. Soc. Chim. Fr.*, **31**, 101 (1964).
(137) H. J. Teuber, D. Cornelius, and E. Worbs, *Tetrahedron Lett.*, 331 (1964).

119 (R = CH_3, C_2H_5, and $(CH_2)_2CH_3$, respectively), presumably formed by cleavage of the C-4–C-4a bond in intermediates **118** to afford the corresponding 4-(3-alkylindol-2-yl)butyric acids which then cyclize into **119**. This postulation was



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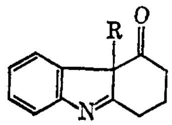

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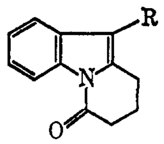
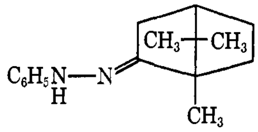


119

supported and structure **119** (R = CH_3) synthetically confirmed by indolization of 5-oxoheptanoic acid phenylhydrazone which afforded[137] a 23% yield of **119** (R = CH_3) and a 22% yield of 2-(2-ethyl-3-indolyl)propionic acid, formed by indolization in the alternative direction.[137] Similar ring closures subsequent to indolization have also been observed[104] using several ethyl 3-(tetrahydro-4-oxothiapyran-3-yl)propionate arylhydrazones (see section V.H).

The product resulting from the indolization of camphor phenylhydrazone (**120**) has previously[91,138,139] been formulated as **121**. Recently,[140] however, this structure has been corrected to **122** on the basis of uv and pmr spectral data of this product and its dihydro derivative **123**. It is suggested[140] that **122** arises by rearrangement of the initially produced **121**.



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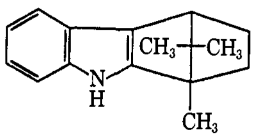

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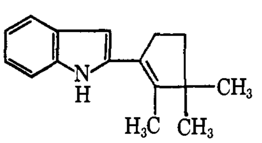

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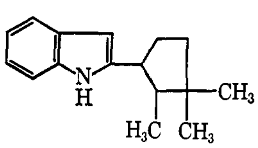

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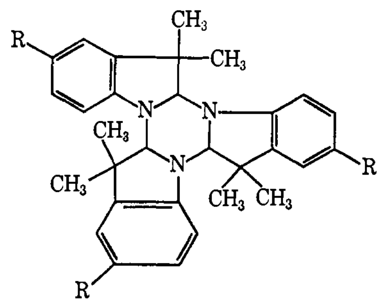
5. *Indolization with Subsequent Trimerization*

Indolization of isobutyraldehyde phenylhydrazone with a zinc chloride catalyst affords the expected 3,3-dimethyl-3H-indole combined with zinc chloride in a complex.[141] Attempts to isolate the free base from this complex led[141] to the formation of a trimer of molecular formula $C_{30}H_{33}N_3$, recent uv, ir, and pmr spectral investigations of which have led to the establishment[142,143] of its structure as **124** (R = H). Similarly, aqueous ethanolic acetic acid catalyzed indolization of isobutyraldehyde 4-methoxyphenylhydrazone affords[144] both 5-methoxy-3,3-dimethyl-3H-indole and its trimer **124** (R = CH_3O).



124

D. FORMATION OF INDAZOLES BY THE POLYPHOSPHORIC ACID CATALYZED CYCLIZATION OF 4-NITROPHENYLHYDRAZONES

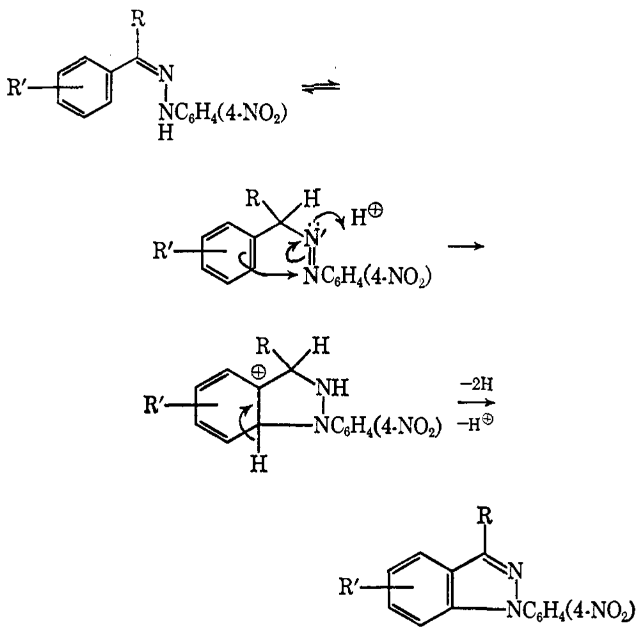
Attempted indolization of several aryl-substituted acetophenone 4-nitrophenylhydrazones using either sulfuric or hydrochloric acid as catalysts failed,[145,146] only starting materials being recovered from such reactions. With polyphosphoric acid as catalyst, however, 1-(4-nitrophenyl)indazoles **125** are the only products from such hydrazones[145,146] and from the 4-nitrophenylhydrazones of several benzophenones,[146] benzaldehydes,[146] and various acetylated polynuclear aromatic compounds.[147] Similar treatment of the 3-nitrophenylhydrazones of several acetophenones led to the simultaneous formation of both the corresponding indoles (resulting from Fischer indolization) and indazoles, whereas the corresponding 2-nitrophenylhydrazones afforded neither indoles nor indazoles.[146]

The above indazole formation appears to depend upon both the presence of a 4- (or 3-) nitro group on the phenylhydrazine moiety and the use of a methyl aryl ketone or benzaldehyde in which enehydrazine formation, the initial stage of the Fischer indolization, is difficult or impossible, respectively, since the corresponding methyl aryl ketone phenylhydrazones indolize normally with polyphosphoric acid,[148] as do the 2-, 3-, and 4-nitrophenylhydrazones of propiophenone,[149] in which enehydrazine formation involving the methylene group is facilitated by the terminal methyl group; no indazoles are formed in these reactions.

The cyclization step, which in the above reactions ultimately leads to indazole formation, has been postulated[145,146] to involve intramolecular nucleophilic attack by the p electrons of the N atom of the hydrazone group, after protonation of N′, on the 2 position of the aromatic ring of the ketone or aldehydic moiety. However, this postulation is invalidated[150] from experimental observations[145–147] upon the reaction which are consistent[150] with the cyclization stage involving an intramolecular electrophilic attack on the 2 position of the aro-

(138) S. Kuroda, *J. Pharm. Soc. Japan*, **493**, 131 (1923); *Chem Abstr.*, 17, 3031 (1923).
(139) F. Spartore, *Gazz. Chim. Ital.*, **92**, 596 (1962).
(140) D. Beck, K. Schenker, F. Stuber, and R. Zürcher, *Tetrahedron Lett.*, 2285 (1965).
(141) K. Brunner, *Monatsh. Chem.*, **16**, 849 (1895); **17**, 253 (1896).
(142) H. Fritz and P. Pfaender, *Chem. Ber.*, **98**, 989 (1965).
(143) A. H. Jackson and A. E. Smith, *Tetrahedron*, **21**, 989 (1965).
(144) M. Ahmed and B. Robinson, *J. Chem. Soc., C*, 411 (1967).
(145) E. B. Dennler and A. R. Frasca, *Tetrahedron*, **22**, 3131 (1966).
(146) A. R. Frasca, *Tetrahedron Lett.*, 1115 (1962).
(147) E. B. Dennler and A. R. Frasca, *Can. J. Chem.*, **45**, 697 (1967).
(148) E. B. Dennler, Doctoral Thesis, University of Buenos Aires, Buenos Aires, Argentina, 1965.
(149) A. R. Frasca, *An. Asoc. Quim. Argentina*, **50**, 162 (1962).
(150) B. Robinson, *Tetrahedron Lett.*, 5085 (1967).

Scheme III



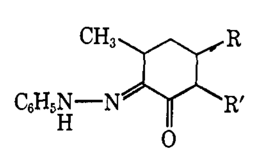
125

matic nucleus of the ketone or aldehyde moiety, probably initiated by protonation of N′ of the hydrazine moiety in the form of its azo tautomer[150] as shown in Scheme III. The hydrogen acceptor involved in the final step of this reaction is probably the C=N and/or nitro groups of other hydrazone molecules.[145]

E. CINNOLINE FORMATION FROM CYCLOHEXANE-1,2-DIONE MONOARYLHYDRAZONES

Cinnoline formation has been observed, sometimes exclusively and sometimes along with simultaneous indolization, when various cyclohexane-1,2-dione monophenylhydrazones are treated with concentrated sulfuric acid.[1,151,152]

Cinnoline formation by this reaction has now been extended[153,154] to the preparation of several polynuclear 5,6,7,8-tetrahydrocinnolines by treatment of cyclohexane-1,2-dione 1- and 2-naphthyl-,[154] 4-methyl-1-naphthyl-,[153] 3- and 5-acenaphthenyl-,[153,154] 9-phenanthryl-,[153] 1- and 2-anthryl-,[153] 6-chrysenyl-,[153] and 4-phenylazaphenylhydrazones[153] and 4-methylcyclohexane-1,2-dione 1-(1- and 2-naphthyl)hydrazones[153] with concentrated sulfuric acid at a low temperature, although cyclohexane-1,2-dione 5,6,7,8-tetrahydro-2-naphthyl-[154] and 3-acenaphthenyl hydrazones[153] and cyclopentane-1,2-dione monoarylhydrazones afforded neither cinnolines nor indoles under similar conditions.[155] At higher temperatures with the same catalyst, Fischer indolization occurs along with the above cinnoline formation, but only as a side reaction together with sulfonation and hydrolysis.[153,154] However, treatment of cyclohexane-1,2-dione 2- and 4-methyl- and 2- and 4-methoxyphenylhydrazones with dilute sulfuric acid[156] and 2-nitrophenylhydrazones with concentrated sulfuric acid[151] exclusively effects indolization; 4-methylcyclohexane-1,2-dione 1-(4-methoxyphenylhydrazone) is indolized to 1,2,3,4-tetrahydro-6-methoxy-3-methyl-1-oxocarbazole, but the catalyst is not specified,[157] and **126** (R = H; R′ = CH_3) is indolized in acetic acid–concentrated hydrochloric acid to **127**.[83] However, with **126** (R = CH_3; R′ = H), concentrated sulfuric acid favors cinnoline formation and affords **128**.[83]



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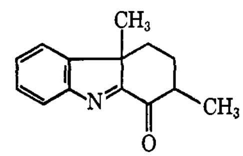

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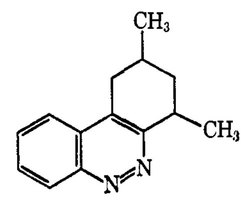

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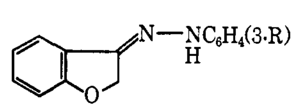
F. INDOLIZATION OF 3-(2H)-BENZOFURANONE ARYLHYDRAZONES

Although indolization of these compounds normally[52,157–159] affords the expected benzofuro[3,2-*b*]indoles, it has been found[159] that using large quantities of reactants and a higher reaction temperature, 3-(2H)-benzofuranone phenylhydrazone (**129**, R = H) affords, along with the expected benzofuro-[3,2-*b*]indole (**130**), three by-products, the structure of one of these being tentatively assigned as **131** (R = H), no structures



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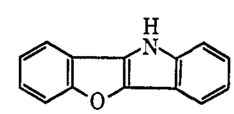

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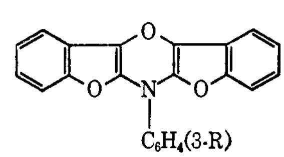
being postulated for the other two. Attempted indolization of 3(2H)-benzofuranone 3-chlorophenylhydrazone (**129**, R = Cl) failed[159] to afford any of the expected indole but gave a product which was formulated[159] as **131** (R = Cl) without verification.

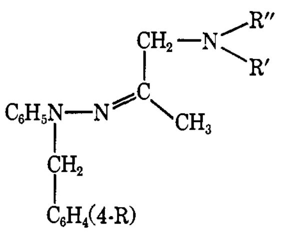


131

(151) P. B. Moore, *Nature*, **163**, 918 (1949).
(152) R. A. Soutter and M. Tomlinson, *J. Chem. Soc.*, 4256 (1961).
(153) A. H. Altiparmakian and R. S. W. Braithwaite, *ibid.*, *C*, 1973 (1967).
(154) R. S. W. Braithwaite and G. K. Robinson, *ibid.*, 3671 (1962).
(155) A. Allais, French Patent 1186258; *Chem. Abstr.*, **55**, 23562 (1961).
(156) V. I. Shvedov, L. B. Altukhova, E. K. Komissarova, and A. N. Grinev, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR*, 365 (1965); *Chem. Abstr.*, **63**, 14800 (1965).
(157) D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *Chem. Ind.* (London), 1684 (1966).
(158) D. A. Kinsley and S. G. P. Plant, *J. Chem. Soc.*, 4814 (1956).
(159) D. C. Schroeder, P. O. Corcoran, C. A. Holden, and M. C. Mulligan, *J. Org. Chem.*, **27**, 586 (1962).

G. INDOLIZATION OF AMINOACETONE ARYLHYDRAZONES

A series of N-substituted aminoacetone N-benzyl- and N-(4-chlorobenzyl)phenylhydrazones (**132**, R = H and Cl, respectively) (or a mixture of the corresponding ketonic and hydrazine moieties) have been[80] successfully indolized, using glacial acetic acid as catalyst, to the corresponding 3-(substituted amino)-2-methylindoles **133** (R = H and Cl, respectively) (see also section V.A). Small quantities of by-products from these reactions were shown[80] to have structures **134** (R = H and Cl, respectively), such compounds being the only reaction products if indolization was attempted with or without the same catalyst but using the ketonic and hydrazine moieties in methanolic or ethanolic solution instead of the hydrazone.



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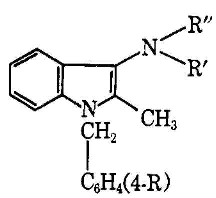

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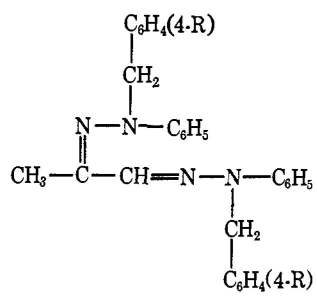

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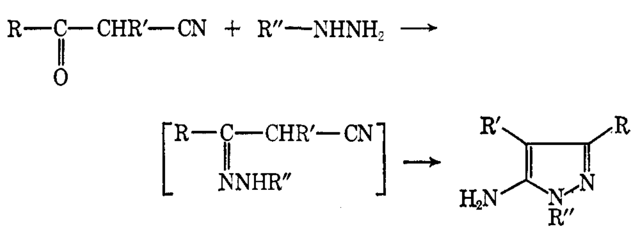
H. 2-CYANO KETONE ARYLHYDRAZONES

2-Cyano ketones react with hydrazines, including arylhydrazines, in dilute hydrochloric acid to afford the corresponding 3-aminopyrazoles **135**, presumably *via* formation of the



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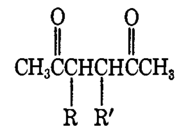
hydrazones.[160] These reactions are analogous to the cyclization of 1,3-diketone monoarylhydrazones to pyrazoles.[1]

I. REACTION OF 1,4-DIKETONES WITH 2,4-DINITROPHENYLHYDRAZINE

Hexane-2,5-dione (**136**, R = R′ = H) forms a diphenylhydrazone which undergoes noncatalytic thermal indolization to 2,2′-dimethyl-3,3′-diindolyl[79] (see section V.A), although under acidic conditions it is converted into 1-anilino-2,5-dimethylpyrrole (**137**, R = R′ = R′′ = R′′′ = H). Although a



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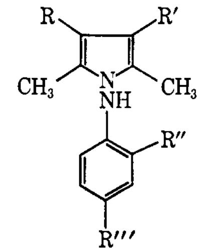

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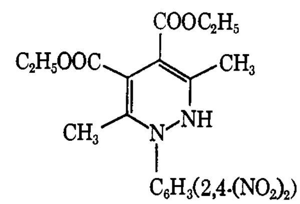
low yield of the corresponding bis(2,4-dinitrophenylhydrazone) is obtained by treating **136** (R = R′ = $COOC_2H_5$) with Brady's reagent (a solution of 2,4-dinitrophenylhydrazine in acidified ethanol), the major product from this reaction has been shown[161] to be the N-anilinopyrrole **137** (R = R′ = $COOC_2H_5$; R′′ = R′′′ = NO_2) and not the N-aryl-1,2-dihydropyridazine **138** as had previously been supposed. Similarly, the structure of the product obtained using 4-nitro-



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phenylhydrazine was shown[161] to be **137** (R = R′ = $COOC_2H_5$; R′′ = H; R′′′ = NO_2), and a product of structure **137** (R = H; R′ = $COOC_2H_5$; R′′ = R′′′ = NO_2) resulted from the reaction of **136** (R = H; R′ = $COOC_2H_5$) with Brady's reagent, although this latter product was only obtained in equal yield with the corresponding bis(2,4-dinitrophenylhydrazone)[161] which is converted into **137** (R = H; R′ = $COOC_2H_5$) under acidic conditions. Hexane-2,5-dione affords mainly the bis(2,4-dinitrophenylhydrazone), along with a small yield of **137** (R = R′ = H; R′′ = R′′′ = NO_2) upon reaction with Brady's reagent.

The above results suggested[161] that the N-anilinopyrroles are formed through the diarylhydrazones, and that their formation is facilitated by increasing the number of ester groups on the 2- and 3-carbon atoms of the 1,4-diketone unit.

J. ACYLCLIC 1,3-DIKETONE MONOARYLHYDRAZONES

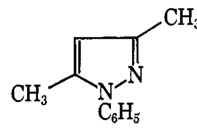
Arylhydrazones of 3-keto esters, 4-keto acids, and acyclic 1,3-diketones undergo cyclization to pyrazol-3-ones, 1,4,5,6-tetrahydropyridazin-6-ones, and pyrazoles, respectively, rather than indole formation, under Fischer indolization conditions.[1] In the former two groups, however, these reactions have been prevented, and good yields of the corresponding 1-alkylindoles have been obtained, using the N-alkylarylhydrazones.[1] This technique has now[162] been successfully applied to pentane-2,4-dione, the simplest acyclic 1,3-diketone, which with phenylhydrazine affords only 3,5-dimethyl-1-phenylpyrazole (**139**), but with N-methylphenylhydrazine affords the corresponding

(160) I. I. Grandberg, D. Wei-pi, and A. N. Kost, *Zh. Obshch. Khim.*, 31, 2311 (1961); *J. Gen. Chem. USSR*, 31, 2153 (1961).

(161) T. D. Binns and R. Brettle, *J. Chem. Soc., C*, 341 (1966).

(162) B. Robinson, University of Manchester, Manchester, England, unpublished observations.

hydrazone which is clearly indolized to 3-acetyl-1,2-dimethylindole.[162]



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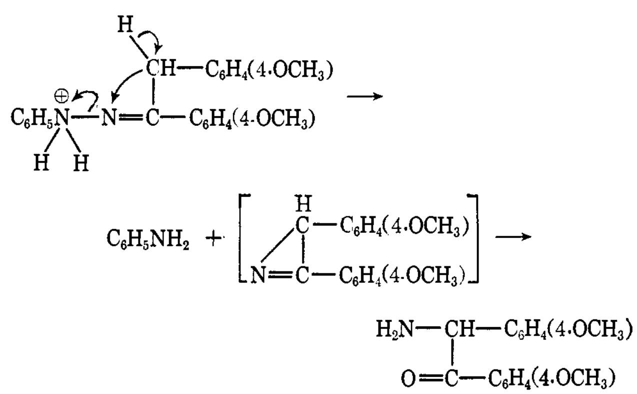
K. INDOLIZATION WITH SIMULTANEOUS NEBER REARRANGEMENT

Two by-products, shown to be aniline and compound **140**, have been isolated,[107] along with 2,3-bis(4-methoxyphenyl)-indole, the expected major product, from the indolization of desoxyanisoin 4-methoxyphenylhydrazone with ethanolic hydrochloride acid. The formation of the two by-products is postulated[107] to occur by a Neber rearrangement[163] of the hydrazone as shown in Scheme IV, simultaneous with Fischer indolization.

Scheme IV



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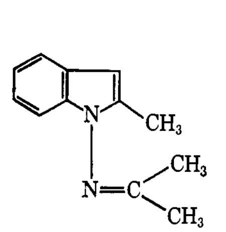
L. ALTERNATIVE DECOMPOSITION OF ARYLHYDRAZONES WITH CUPROUS CHLORIDE, SULFANILIC ACID, AND OTHER CATALYSTS

Previous studies which showed that cuprous chloride or sulfanilic acid catalyzed decomposition of acetone and isopropyl methyl ketone phenylhydrazones affords ammonia, aniline, and compounds having structures **141** and **142**, respectively, have now[164] been extended.

Acetone, ethyl methyl ketone, and methyl isopropyl ketone phenylhydrazones, acetone 2-, 3-, and 4-methylphenylhydrazones, methyl isopropyl ketone 2- and 3-methylphenylhydrazones, and acetone 1- and 2-naphthylhydrazones were subjected to reaction with a sulfanilic acid catalyst. In all these reactions the ratio of anilines and products corresponding to compounds **141** and **142**, formed in the "abnormal" reaction (also formed were traces of benzene or toluene, aliphatic imines and amines, azo compounds, and gaseous products other than ammonia), to products resulting from Fischer indolization were determined. This ratio decreased in the order acetone phenylhydrazone > acetone 2-methylphenylhydrazone > methyl isopropyl ketone 2-methylphenylhydrazone > acetone 3-methylphenylhydrazone > methyl isopropyl ketone 3-methylphenylhydrazone > methyl ethyl ketone phenylhydrazone.[164] It can be seen that the "abnormal" reaction is favored for acetone arylhydrazones more than for the corresponding arylhydrazones of methyl isopropyl and methyl ethyl ketones, and methyl substituents in the 2 and more so in the 3 positions of the phenyl nucleus of the hydrazine moiety tend to favor Fischer indolization.[164] It is unfortunate that no recognizable products were isolated from the reactions with acetone 1- and 2-naphthylhydrazones. Cadmium chloride has also been investigated[164] as a catalyst in these reactions and, with the exception of methyl isopropyl ketone phenylhydrazone, has been found to favor Fischer indolization rather than formation of "abnormal" products when compared with sulfanilic acid. It is interesting that an unstable complex of cadmium chloride with acetone phenylhydrazone has been isolated, this presumably being an intermediate in the above reactions.[165]

Cuprous cyanide too has been[164] studied as a catalyst of the above type, although investigation of its catalytic action has been limited to its effect upon acetone and ethyl methyl ketone phenylhydrazones which are extreme cases favoring formation of "abnormal" and Fischer indolization products, respectively. Although a small yield of 2,3-dimethylindole was isolated from the latter reaction, no other reaction products could be recognized, and further work upon this problem is required.

More recent studies[166] upon the decomposition of various ketone arylhydrazones using the above catalysts have resulted in the formation of the expected indoles, along with aromatic and aliphatic amines, ketimines, ketone anils, and aromatic hydrocarbons, and similar catalytic treatment of acetone phenylhydrazone has afforded[167] a mixture containing 3,5-dimethyl-1-phenylpyrazole, 2-methylindole, and unchanged starting material.



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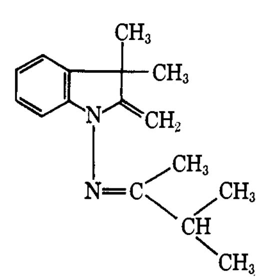

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VII. Extensions to the Fischer Indole Synthesis

A. THE ACID-CATALYZED CYCLIZATION OF O-ARYLOXIMES TO BENZOFURANS

Treatment of acetone, acetophenone, and cyclohexanone O-phenyloximes (prepared by boiling equimolar quantities of the ketones with O-phenylhydroxylamine) with boron trifluoride etherate in acetic acid at 100° gives high yields of 2-

(163) C. O'Brien, *Chem. Rev.*, 64, 81 (1964).

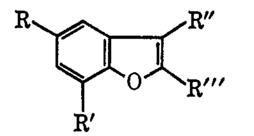
(164) Y. P. Kitaev, T. V. Troepol'skaya, and A. E. Arbuzov, *Zh. Obshch. Khim.*, 34, 1835 (1964); *J. Gen. Chem. USSR*, 34, 1848 (1964).

(165) G. Kempter, M. Schwalba, W. Stoss, and K. Walter, *J. Prakt. Chem.*, 18, 39 (1962).

(166) Y. P. Kitaev, T. V. Troepol'skaya, and A. E. Arbuzov, *Zh. Org. Khim.*, 2, 340 (1966); *Chem. Abstr.*, 65, 2202 (1966).

(167) Y. P. Kitaev, T. V. Troepol'skaya, and A. E. Arbuzov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 946 (1966); *Chem. Abstr.*, 65, 10577 (1966).

methylbenzofuran (**143**, R = R′ = R″ = H; R‴ = CH_3), 2-phenylbenzofuran (**143**, R = R′ = R″ = H; R‴ = C_6H_5), and 1,2,3,4-tetrahydrodibenzofuran (**143**, R = R′ = H; R″ + R‴ = $(CH_2)_4$), respectively.[168]



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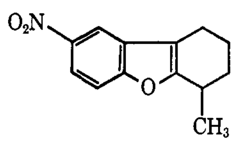
Similar cyclization of acetone, ethyl methyl ketone, and cyclohexanone O-(2- and 4-nitrophenyl) oximes (prepared by reaction of the sodium salts of the ketone oximes with 2- and 4-halonitrobenzenes) with ethanolic hydrochloric acid affords good yields of the corresponding nitrobenzofurans **143** (R = H, R′ = NO_2 and R = NO_2, R′ = H; R″ = H, R‴ = CH_3, R″ = R‴ = CH_3; and R″ + R‴ = $(CH_2)_4$, respectively).[169,170] The nitro substituent of the oximes can be replaced by other electron-withdrawing groups (*e.g.*, trifluoromethyl) without having any adverse effect upon the subsequent cyclizations.[170] The reaction also occurs, although in a comparatively lower yield, with acetone O-(2,4-dinitrophenyl)-oxime to afford 2-methyl-5,7-dinitrobenzofuran (**143**, R = R′ = NO_2; R″ = H; R‴ = CH_3),[170] a result which, in spite of the presence of two electron-withdrawing nitro groups, is not unexpected since several ketone 2,4-dinitrophenylhydrazones have been[171] successfully indolized to the corresponding 5,7-dinitroindoles.

Similar cyclization of ethyl methyl ketone O-(4-nitrophenyl)-oxime affords both 2,3-dimethyl-5-nitrobenzofuran (**143**, R = NO_2; R′ = H; R″ = R‴ = CH_3) and 2- (incorrectly quoted as 3- in the original paper[170]) ethyl-5-nitrobenzofuran (**143**, R = NO_2; R′ = R″ = H; R‴ = C_2H_5) in the ratio 3:1, although the presence of the latter product was only detected by pmr spectral examination of the total reaction mixture.[170] However, cyclization of 2-methylcyclohexanone O-(4-nitrophenyl)oxime affords a nearly quantitative yield of 1,2,3,4-tetrahydro-1-methyl-6-nitrobenzofuran (**144**), none of the other possible isomeric product, **145**, being formed[169] (*cf.* ref 172).



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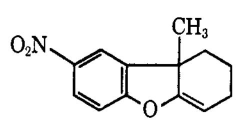

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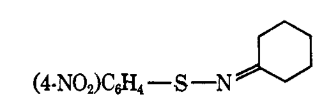
Attempts[169] to extend this synthesis to the preparation of benzothiophenes by cyclization of ketone arylsulfenamides failed, although it was found[169] that under acidic conditions the sulfenamide **146** affords both 4-nitrophenyl disulfide and 2-(4-nitrophenylthio)cyclohexanone, and the sulfenamide **147** affords 1-methyl-3-(2-pyridylthio)-4-piperidone, the mechanism of these reactions being presently investigated.[169]



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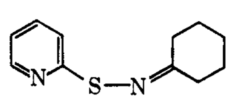

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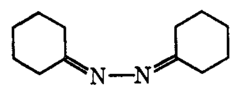
B. THE PILOTY PYRROLE SYNTHESIS

The hydrogen chloride catalyzed cyclization of biscyclohexanone azine (**148**) afforded a product which was formulated as **149**.[173] However, other studies[174–176] led to several reformulations of this product as double-bond isomers of **149**. However, structure **149** has now[177] been shown to be correct by analysis of the uv, ir, and pmr spectral properties of the compound.



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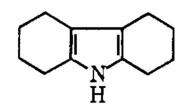
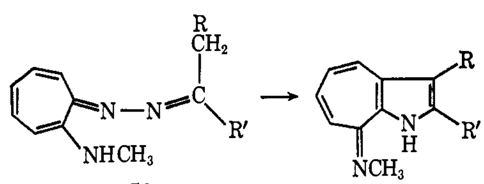


149

C. SYNTHESIS OF CYCLOHEPTA[*b*]PYRROLE DERIVATIVES

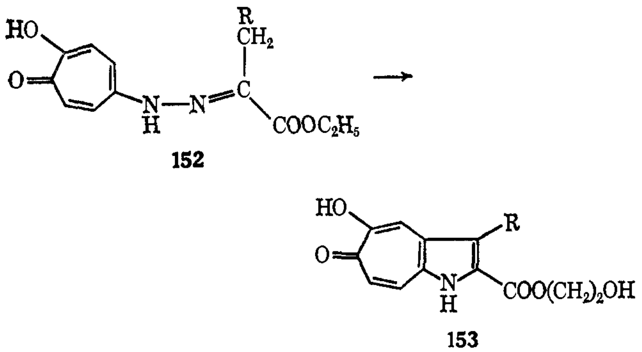
The 8-methylimino-1, 8-dihydrocyclohepta[*b*]pyrroles **151** (R = CH_3, C_2H_5, and C_6H_5, R′ = H; R = CH_3, R′ = CH_3; R + R′ = $(CH_2)_3$, $(CH_2)_4$, and $(CH_2)_5$) have been prepared[178] from the corresponding azines **150** (R = CH_3, C_2H_5, and C_6H_5, R′ = H; R = CH_3, R′ = CH_3; R + R′ = $(CH_2)_3$, $(CH_2)_4$, and $(CH_2)_5$, respectively) using polyphosphoric acid as catalyst. However, similar attempts to cyclize acetaldehyde and acetone 2-methylaminotropone azines (**150**, R = R′ = H, and R = H, R′ = CH_3, respectively) failed,[178] but the cyclization could[178] be extended to the direct synthesis of tryptamine analogs containing the cyclohepta[*b*]pyrrole system.



150 **151**

Whereas the above cyclizations are Piloty reactions (see previous section), the 5-hydroxycyclohepta[*b*]pyrrol-6-(1H)-ones **153** (R = H, CH_3,[179] C_6H_5,[109] 4-ClC_6H_4,[109] and $(CH_2)_2$-N-1,2$(CO)_2C_6H_4$[180]) were prepared by indolization of the corresponding 2-hydroxy-5-tropolonylhydrazones **152** (R = H, CH_3, C_6H_5, 4-ClC_6H_4, and $(CH_2)_2$N-1,2$(CO)_2C_6H_4$, respectively) with concentrated sulfuric acid in monoethylene glycol, which also effected an ester interchange reaction, but attempts[180] to indolize **152** (R = $CO_2C_2H_5$, CH_2CN, and $CH_2N(C_2H_5)_2$) with either this catalyst or polyphosphoric acid were unsuccessful, although polyphosphoric acid-catalyzed indolization of 1-methyl-4-piperidone 2-troponylhydrazone

(168) T. Sheradsky, *Tetrahedron Lett.*, 5225 (1966).
(169) D. Kaminsky, J. Shavel, Jr., and R. I. Meltzer, *ibid.*, 859 (1967).
(170) A. Mooradian, *ibid.*, 407 (1967).
(171) D. S. Deorha and S. S. Joshi, *J. Org. Chem.*, 26, 3527 (1961).
(172) K. H. Pausacker, *J. Chem. Soc.*, 621 (1950), and references therein.
(173) W. H. Perkin, Jr., and S. G. P. Plant, *ibid.*, 125, 1503 (1924).
(174) J. von Braun and O. Bayer, *Chem. Ber.*, 58, 387 (1925).
(175) J. von Braun and H. Ritter, *ibid.*, 55, 3792 (1922).
(176) J. von Braun and L. Schörnig, *ibid.*, 58, 2156 (1925).
(177) B. Robinson, *Tetrahedron*, 20, 515 (1964).
(178) Y. Sato and G. Sunagawa, *Chem. Pharm. Bull.* (Tokyo), 15, 634 (1967).
(179) Y. Sato and G. Sunagawa, *Yakugaku Zasshi*, 82, 414 (1962); *Chem. Abstr.*, 58, 6773 (1963).
(180) Y. Sato, *Chem. Pharm. Bull.* (Tokyo), 11, 1440 (1963).

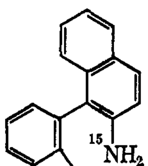


hydrochloride affords[181] 2,3,4,5-tetrahydro-2-methylcyclohepta[4,5]pyrrolo[3,2-*c*]pyridin-6(1H)-one. 1,2,3,4-Tetrahydro-1-oxoquinolizinium bromide 2-troponylhydrazone is also[181] indolized with ethanolic hydrogen bromide being used as catalyst.

D. THE USE OF PHENOLS AS THE CARBONYL MOIETIES OF ARYLHYDRAZONES (THE BUCHERER CARBAZOLE SYNTHESIS)

A review including the Bucherer carbazole synthesis has appeared[182] in which the isolation of intermediates in the reactions between 1- and 2-naphthol and 1- and 2-naphthylamine with phenylhydrazine and sodium bisulfite, which ultimately afford 1,2- and 3,4-benzocarbazoles, respectively, is summarized, and the previously mentioned mechanistic analogy between this reaction and the Fischer indole synthesis is pointed out.

The reaction of 2-naphthol with phenylhydrazine-2-^{15}N in the presence of sulfur dioxide at 100° results[183] in most of the ^{15}N being eliminated in the evolved ammonia and affords mainly unlabeled 3,4-benzocarbazole. Since 1-(1-aminophenyl)-2-[^{15}N]naphthylamine (**154**), isolated as an intermediate, exclusively eliminates the label upon treatment with



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sulfur dioxide and affords only unlabeled 3,4-benzocarbazole, it is suggested[183] that this is the intermediate in the formation of the unlabeled 3,4-benzocarbazole in the main reaction which must therefore in its later stages involve an analogous mechanism to the Fischer indolization. However, 6% of the 3,4-benzocarbazole produced in the main reaction retained the ^{15}N label, and it was suggested[183] that this might be produced by the occurrence of an *o*-semidine rearrangement, simultaneous to the Fischer indolization, of the common intermediate N′-(2-naphthyl)phenylhydrazine, although the formation of both the labeled and unlabeled 3,4-benzocarbazole could be[183] mechanistically interpreted in terms of the Fischer indolization.

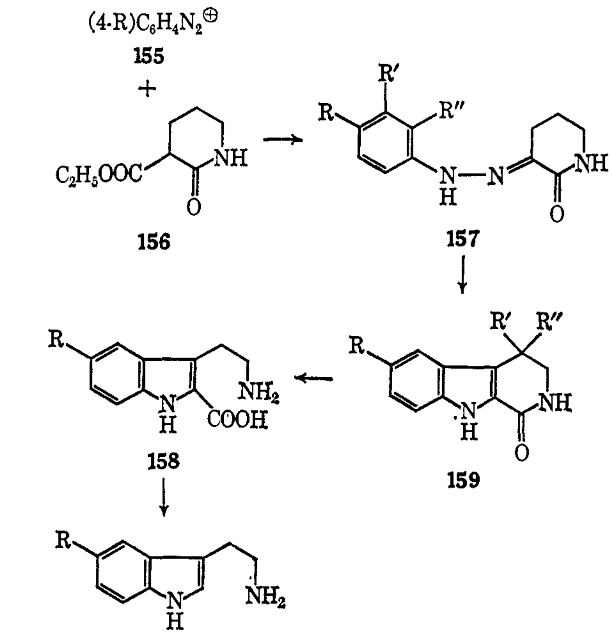
VIII. Selected Examples of Fischer Indolization

No attempt is to be made in this review to tabulate all known examples of the Fischer indole synthesis. However, the following selected examples given below, together with the many examples mentioned in previous sections of this review and in the previous review,[1] illustrate the scope, versatility, and synthetic utility of the reaction in indole synthesis.

A. SYNTHESIS OF TRYPTAMINES

1. From Piperidine-2,3-dione 3-Arylhydrazones

An elegant route to tryptamines, obviating the use of difficultly obtainable indoles as intermediates in such syntheses, was developed[184] when the piperidine-2,3-dione 3-arylhydrazones **157** (R′ = R″ = H; R = H, OCH_3, and $OCH_2C_6H_5$) [prepared by the Japp-Klingemann reaction (see section IV.A) in which the corresponding diazonium salts **155** (R = H, OCH_3, and $OCH_2C_6H_5$, respectively) were treated with 3-carbethoxypiperidine-2-one (**156**)] were indolized to the corresponding 1,2,3,4-tetrahydro-1-oxo-2-carbolines **159** (R′ = R″ = H; R = H, OCH_3, and $OCH_2C_6H_5$, respectively). Base-catalyzed hydrolysis of the amide group in these latter compounds afforded the amino acids **158** (R = H, OCH_3, and $OCH_2C_6H_5$, respectively) which upon decarboxylation by treatment with acid afforded the tryptamines **160** (R = H and OCH_3, respectively). When R = $OCH_2C_6H_5$, this decarboxylation could not be effected,[184] and the base-catalyzed hydrolysis

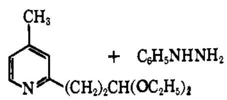
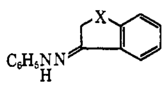
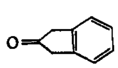
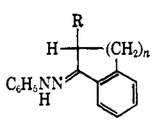
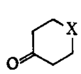
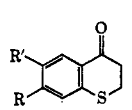


stage fails[185] with **159** (R = OCH_3 and SCH_3; R′ = R″ = CH_3). When R = halo, the stages **159** → **158** → **160** can be[185] effected in one step by prolonged boiling of **159** in a hydrochloric–acetic acid mixture.

The versatility of this synthetic route has been proven by

(181) G. Sunagawa and Y. Sato, *Yakugaku Zasshi*, 82, 408 (1962); *Chem. Abstr.*, 58, 6773 (1963).
(182) H. Seeboth, *Angew. Chem.*, 307 (1967).
(183) P. F. Holt and C. J. McNae, *J. Chem. Soc.*, 1759 (1964).
(184) R. A. Abramovitch and D. Shapiro, *ibid.*, 4589 (1956).
(185) J. I. DeGraw and W. A. Skinner, *Can. J. Chem.*, 45, 63 (1967).

Table I

Arylhydrazone	*Ref*
$(4\text{-R})C_6H_4NN{=}CR'(CH_2)_nR''$ H	
$R = R' = H$; $R'' = N{=}1,2\text{-}(CO)_2C_6H_4$; $n = 2$	*a*
$R = C_6H_5CH_2O$; $R' = COOC_2H_5$, $R'' = N{=}1,2\text{-}(CO)_2C_6H_4$; $n = 3$	*b*
$R = CH_3CO$; $R' = COOC_2H_5$; $R'' = N(CH_3)_2$; $n = 2$ and 3	*c*
$R = H$; $R' = COOC_2H_5$; $R'' = N(CH_3)_2$; $n = 2$	*d*
$R = R' = H$; $R'' = C(COOC_2H_5)_2\text{-}NCOCH_3$; $n = 2$	*e*
	*f*
	
$X = CH_2$	158, 165
$X = O$	52, 158, 159, *g*
$X = S$	111
Arylhydrazones of 	158
	
$R = CH_3$; $n = 2$, 3, and 4	*h*
$R = C_2H_5$; $n = 1$	*h*
$R = C_6H_5CH_2$; $n = 1$	*i–k*
Arylhydrazones of 	
X = N-alkyl	*l*, *m*
$X = O$	*n*
$X = S$	55, *o*
$X = AsCH_3$	129
$X = PC_6H_5$	129
Arylhydrazones of 	
$R = R' = H$	*p–s*
$R = H$; $R' = Cl, NO_2, CH_3$	*s*
$R + R' = (CH_2)_4$	*t*

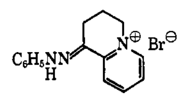
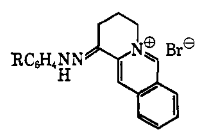
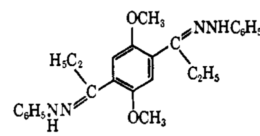
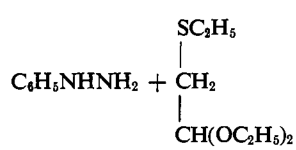
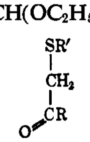
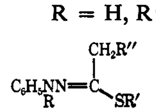
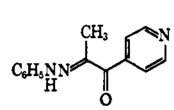
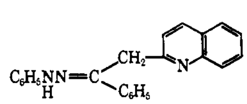
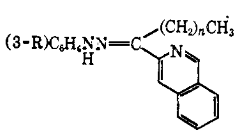
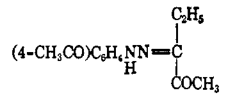
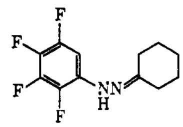
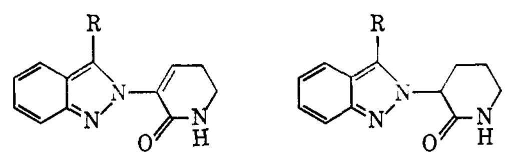
Arylhydrazone	*Ref*
Arylhydrazones of $O{=}C(CH_2)_n$	
$n = 4$	26, 165, *u*, *v*
$n = 6$	*w*
$n = 7, 8, 9, 10$	*w*, *x*
$n = 11$	*w–y*
$n = 12, 14$	59, *w* *x*
$n = 13$	*x*
$n = 15$	59, *x*
$n = 16$	*x*
	*z*
	105
$R = H$ and 3- and 4-OCH_3 and 3,4-$(OCH_3)_2$	
	*aa*
References to previous diindolizations of bisphenylhydrazones are given in ref 148	
	*bb*
Arylhydrazones of 	*cc*
$R = CH_3$, $R' = C_6H_5$ and $CH_2COOC_2H_5$;	
$R = H$, $R' = C_6H_5$ and $CH_2COOC_2H_5$	
	
$R = R' = CH_3$, $R'' = C_6H_5$ and $3\text{-}CH_3C_6H_4$; $R = CH_3$, $R' = C_6H_5$	*dd*
Arylhydrazones of $(4\text{-}OCH_3)C_6H_4COCH_2C_6H_4\text{-}(4\text{-}OCH_3)$ and related ketones	107
	75
	68

Table I (Continued)

Arylhydrazone	*Ref*	*Arylhydrazone*	*Ref*
			*ff*
R = H, n = 2, + 5,6,7,8-tetrahydro derivative	*ee*		*gg*
R = OCH_3, n = 1	106		

[a] V. P. Mamaev and V. F. Sedova, *Izv. Sib. Otd. Akad. Nauk SSSR*, 142 (1961); *Chem. Abstr.*, **57**, 5872 (1962). [b] L. Bretherick, K. Gaimster, and W. R. Wragg, *J. Chem. Soc.*, 2919 (1961). [c] M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Med. Chem.*, **7**, 141 (1964). [d] B. Hegedüs, *Helv. Chim. Acta*, **29**, 1499 (1946). [e] S. Grudzinski and A. Kotelko, *Acta Polon. Pharm.*, **12**, 201 (1955); *Chem. Abstr.*, **50**, 12978 (1956). [f] G. C. Morrison, R. O. Waite, A. N. Caro, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 3691 (1967). [g] S. R. Cawley and S. G. P. Plant, *J. Chem. Soc.*, 1214 (1938). [h] M. Nakazaki and M. Maeda, *Bull. Chem. Soc. Jap.*, **35**, 1380 (1962). [i] H. Leuchs, C. D. Philpot, P. Sauder, A. Heller, and K. Köhler, *Ann. Chem.*, **461**, 27 (1928). [j] H. Leuchs and K. Winzer, *Chem. Ber.*, **58**, 1520 (1925). [k] H. Leuchs, J. Wutke, and E. Giesler, *ibid.*, **46**, 2200 (1913). [l] N. P. Buu-Hoï, O. Roussel, and P. Jacquignon, *J. Chem. Soc.*, **708** (1964). [m] R. G. W. Spickett, *J. Med. Chem.*, **9**, 436 (1966). [n] N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Obshch. Khim.*, **32**, 3640 (1962); *J. Gen. Chem. USSR*, **32**, 3572 (1962), and references therein. [o] N. F. Kucherova, M. I. Petruchenko, and V. A. Zagorevskii, *Zh. Obshch. Khim.*, **32**, 3645 (1962); *J. Gen. Chem. USSR*, **32**, 3576 (1962), and ref 1, therein. [p] L. A. Aksanova, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Obshch. Khim.*, **33**, 220 (1963); *J. Gen. Chem. USSR*, **33**, 213 (1963). [q] A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 1909 (1951). [r] N. F. Kucherova, L. A. Aksanova, N. M. Sharkova, and V. A. Zagorevskii, *Zh. Obshch. Khim.*, **33**, 3662 (1963); *J. Gen. Chem. USSR*, **33**, 3593 (1963). [s] T. E. Young and P. H. Scott, *J. Org. Chem.*, **30**, 3613 (1965). [t] T. E. Young and P. H. Scott, *ibid.*, **31**, 343 (1966). [u] W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 3242 (1923). [v] S. G. P. Plant, *ibid.*, 2493 (1929). [w] L. M. Rice, E. Hertz, and M. E. Freed, *J. Med. Chem.*, **7**, 313 (1964). [x] E. B. Dennler and A. R. Frasca, *An. Asoc. Quím. Argentina*, **54**, 3 (1966). [y] P. Jacquignon, N. P. Buu-Hoï, and M. Dufour, *Bull. Soc. Chim. Fr.*, 2765 (1966). [z] K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2024 (1958). [aa] W. E. Noland and F. J. Baude, *J. Org. Chem.*, **31**, 3321 (1966). [bb] R. V. Jardine and R. K. Brown, *Can. J. Chem.*, **43**, 1293 (1965). [cc] T. Wieland and K. Rühl, *Chem. Ber.*, **96**, 260 (1963). [dd] H. Wuyts and A. Lacourt, *Bull. Classe Sci. Acad. Roy. Belg.*, **21**, 736 (1935); *Chem. Abstr.*, **29**, 7952 (1935). [ee] P. L. Julian, W. J. Karpel, A. Magnani, and E. W. Meyer, *J. Amer. Chem. Soc.*, **70**, 180 (1948). [ff] K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 863 (1967). [gg] T. D. Petrova, V. P. Mamaev, and G. G. Yakobson, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1633 (1967).

several groups[110,155,186–194] who have applied it to the synthesis of various benz-substituted and side-chain alkylated tryptamines. Starting with 4-benzylmercapto-,[189] 3,4,5-trimethoxy-,[155] 4-fluoro-,[185,187,193] 4-chloro-,[185,193] 4-bromo-,[185,193] 3,4-dibenzyloxy-,[193] 4-methyl-,[187] 4-ethoxy-,[187] 2-[187] and 4-methylmercapto-,[187,188] 4-benzylmercapto-,[188] 3- and 4-acetyl,[109] 3- and 4-benzoyl-,[110] 4-propionyl-,[110] 4-isonicotinyl-,[110] 4-(4-chlorobenzoyl)-,[110] and 3-acetyl-6-chloro-[191] benzenediazonium salts, the corresponding benz-substituted tryptamines were prepared by this route. Starting with the 3-acetyl- and 3-benzoylbenzenediazonium salts, the intermediate hydrazones **157** (R = R'' = H; R' = $COCH_3$ and COC_6H_5, respectively) underwent indolization in both possible directions and ultimately afforded both 4- and 6-acetyl- and 4- and 6-benzoyltryptamines.[110] Starting with 2-acetyl- and 2-benzoylbenzenediazonium salts, the intermediate hydrazones **157** (R = R' = H; R'' = $COCH_3$ and COC_6H_5, respectively) under indolization conditions cyclized exclusively to the indazolyltetrahydropyridones **161** (R = CH_3 and C_6H_5, respectively).[110] Even the corresponding 1-hydroxyethyl and 1-hydroxybenzyl analogs **157** (R = R' = H; R'' = $CHOHCH_3$ and $CHOHC_6H_5$, respectively) under indolization conditions underwent a similar alternative cyclization to afford **162** (R = CH_3 and C_6H_5, respectively) exclusively.[110]



161 **162**

Indolization of various 3-arylhydrazones of 6-[188,192–194] and 5-methyl-,[185,186,188] 5,6-dimethyl-,[188,190] and 5,5-dimethylpiperidine-2,3-diones[185,188] has also been successfully effected and has led ultimately to the corresponding α- and β-methyl- and α,β- and β,β-dimethyltryptamines, respectively. However, 4-methylpiperidine-2,3-dione 3-phenylhydrazone could not be indolized to the corresponding 3H-indole, attempts[195] to effect such a reaction affording only a geometrically isomeric phenylhydrazone. This does not appear to be a general limitation of 4-alkylpiperidine-2,3-dione 3-phenylhydrazones toward indolization, since decahydroisoquinoline-3,4-dione

(186) R. A. Abramovitch and J. M. Muchowski, *Can. J. Chem.*, **38**, 554 (1960).

(187) E. Adlerová, I. Ernest, V. Hnevsova, J. O. Jílek, L. Novák, J. Pomykáček, M. Rasjner, J. Sova, Z. J. Vejdělek, and M. Protiva, *Collect. Czech. Chem. Commun.*, **25**, 784 (1960).

(188) J. K. Horner, J. I. DeGraw, and W. A. Skinner, *Can. J. Chem.*, **44**, 307 (1966).

189) J. K. Horner and W. A. Skinner, *ibid.*, **42**, 2904 (1964).

(190) A. V. Mkhitaryan, A. A. Kogodosskaya, A. G. Terzyan, and G. T. Tatevosyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauk*, **15**, 379 (1962); *Chem. Abstr.*, **59**, 2753 (1963).

(191) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Med. Chem.*, **8**, 200 (1965).

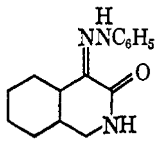
(192) N. N. Suvorov, M. N. Preobrazhenskaya, and N. V. Uvarova, *Zh. Obshch. Khim.*, **32**, 1567 (1962); *J. Gen. Chem. USSR*, **32**, 1552 (1962).

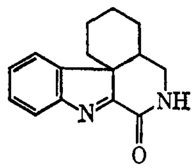
(193) N. N. Suvorov, M. N. Preobrazhenskaya, and N. V. Uvarova, *Zh. Obshch. Khim.*, **33**, 3738 (1963); *J. Gen. Chem. USSR*, **33**, 3672 (1963).

(194) A. G. Terzyan, R. R. Safrazbekyan, R. S. Sukasyan, and G. T. Tatevasyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauk*, **14**, 261 (1961); *Chem. Abstr.*, **57**, 8531 (1962); *Experientia*, **17**, 493 (1961).

(195) R. A. Abramovitch, *Can. J. Chem.*, **36**, 354 (1958).

4-phenylhydrazone (**163**) under indolization conditions affords a product which appears[196] to have structure **164**. Attempted base-catalyzed hydrolysis of this product, however, did not

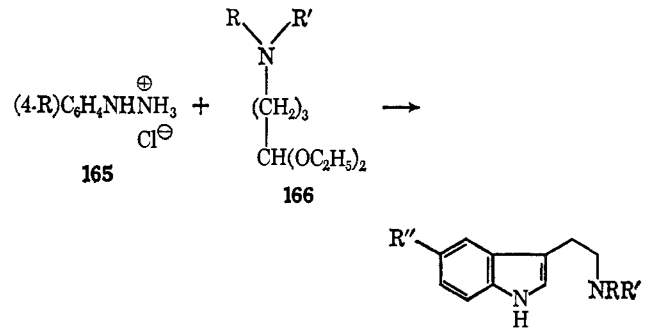

163


164

afford the expected amino acid but afforded[196] an isomeric product of unknown structure.

2. From Arylhydrazines and 4-Amino- (and Substituted Amino-) butanal Diethyl Acetals

A further synthesis of tryptamines, again obviating the use of 3-unsubstituted indoles as intermediates, was initially developed[197] when a mixture of 4-aminobutanal diethyl acetal and phenylhydrazine were, without isolation of the intermediate phenylhydrazone, indolized using a zinc chloride catalyst at 180° to afford tryptamine. A similar technique was used in subsequent[198,199] analogous reactions, and the use of xylene as an inert solvent in such reactions has also been investigated.[200] Later,[201,202] however, it was shown that substitution of the zinc chloride catalyst in such reactions by acetic acid or hydrochloric–acetic acid mixtures led to cleaner reaction products and improved yields. Using these modified catalysts, 4-aminobutanal diethyl acetal (**166**, R = R′ = H)[202] and its N-acetyl derivative (**166**, R = H; R′ = $COCH_3$)[203] and various 4-alkylaminobutanal diethylacetals (**166**, R = R′ = CH_3; R = R′ = C_2H_5; R = R′ = $CH(CH_3)_2$; R = CH_3, R′ = $CH_2C_6H_5$; R + R′ = $(CH_2)_4$; R + R′ = $(CH_2)_5$; and R + R′ = $(CH_2)_2O(CH_2)_2$)[201] were allowed to react with 4-methoxy- and 4-benzyloxyphenylhydrazine hydrochlorides (**165**, R = OCH_3 and $OCH_2C_6H_5$, respectively) to afford the corresponding tryptamines **167** (R″ = OCH_3 and $OCH_2C_6H_5$; R = R′ = H; R = H, R′ = $COCH_3$; R = R′ = CH_3; R = R′ = C_2H_5; R = R′ = $CH(CH_3)_2$; R = CH_3, R′ = $CH_2C_6H_5$; R + R′ = $(CH_2)_4$; R + R′ = $(CH_2)_5$; and R + R′ = $(CH_2)_2O(CH_2)_2$, respectively). However, no indolic



165 **166** **167**

product could be isolated[202] after reaction of 3-benzyloxyphenylhydrazine hydrochloride and 4-aminobutanal diethyl acetal under these modified catalytic conditions.

B. OTHER EXAMPLES

A selection of arylhydrazones and references to their successful indolization under Fischer conditions are given in Table I,

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(197) A. J. Ewins, *J. Chem. Soc.*, **99**, 270 (1911).
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(199) E. Späth and E. Lederer, *Chem. Ber.*, **63B**, 120 (1930).
(200) G. Bernini, *Ann. Chim.* (Rome), **43**, 559 (1953).
(201) D. Desaty and D. Keglević, *Croat. Chem. Acta*, **36**, 103 (1964).
(202) D. Keglević, N. Stojanac, and D. Desaty, *ibid.*, **33**, 83 (1961).
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