HETEROCYCLIC COMPOUNDS WITH INDOLE AND CARBAZOLE SYSTEMS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*

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Preface

The chemistry of indole had its beginnings in the dye industry, and thus for a number of years was intimately associated with dye chemistry. The intensely fertile research of this period produced a very diverse group of closely related compounds; today the scope of indole chemistry is indeed multiform, extending from the rather simple parent material, through the condensed systems such as carbazole, the oxygenated indole derivatives, to the highly complex materials which occur naturally.

In undertaking the preparation of a monograph on compounds containing the indole and carbazole rings our purpose has been to present a thorough and comprehensive treatment of the methods of preparation, the properties and the reactions of these compounds without attempting to duplicate the coverage of Beilstein (or of Elsevier's Encyclopedia when completed) by listing every compound. We have, however, attempted to go beyond a simple listing of basic generalities by including a sufficiently large number of compounds to indicate exceptions and trends away from the general principles. The literature coverage extends through 1952, and includes several important papers of 1953.

In the preparation of this volume, the responsibility for Chapter I (Indole), II (Carbazole), V (Isatogens), VI (Indoxyl), and VII (Indigo) was assumed by W. C. S., while Chapters III (Isatin) and IV (Oxindole) were rewritten by F. M. M. from earlier reviews on these topics by W. C. S. Chapter VIII was entirely the responsibility of F. M. M.

We desire to acknowledge our indebtedness to Miss Josephine Williams and Mr. Phil Wilken for assistance in making the literature survey and for critically reading certain chapters, and to Mrs. Joseph Stewart for typing a large portion of the manuscript.

One of us (F. M. M.) is indebted to the National Institutes of Health for a postdoctoral fellowship held at Harvard University in 1948–1949, during which time much of the work on Chapter VIII was done.

We are grateful to Drs. C. F. H. Allen and Bernhard Witkop for reading the manuscript and for making helpful suggestions for its improvement.

Bowling Green, Kentucky W. C. S.
Baltimore, Maryland F. M. M.

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III. **Isatin** *(continued)*

VII. **Indigo** *(continued)*

VIII. Natural Products Containing the Indole Nucleus *(continued)*

CHAPTER I

Indole

Introduction

In 1866 and 1868 Baeyer[1] published the results of his researches on the reduction of isatin. In addition to isatide,[2] Baeyer obtained dioxindole, $C_8H_7NO_2$, by the further reduction of which oxindole, C_8H_7NO, was prepared. The constitution of oxindole as the lactam of 2-aminophenylacetic acid was established[3] through its synthesis by the reduction of 2-nitrophenylacetic acid with tin and hydrochloric acid.

Indole itself was first prepared[4] by heating oxindole with zinc dust. In addition to being the first synthesis of indole this was also the first application of the zinc dust pyrolytic technique. Subsequently indole was prepared by reduction of 2,3-dichloroindole.[5] Indole (1-benzo[*b*]pyrrole, 1-benzazole, 1-azaindene, ketole) (*R.I.* 821) is a nonbasic nitrogenous compound in which a benzene ring and a pyrrole nucleus are fused together in the 2,3-positions of the pyrrole ring. Indole and skatole (β-methylindole) both possess unpleasant (fecal) odors when impure; the pure materials have a pleasant fragrance and are found in both natural and synthetic perfumes. Indole is a colorless, crystalline solid, melting at 52°, and boiling at 254°. It is volatile with steam and soluble in alcohol, benzene, ether, and ligroin and many be recrystallized from water. The formula which is generally accepted for indole was proposed by Baeyer and Emmerling.[6] This structure was suggested

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[1] Baeyer, *Ber.*, **1**, 17 (1868). Baeyer and Knop, *Ann.*, **140**, 1 (1866).

[2] Laurent, *Rev. sci. ind.* (September, 1842); *J. prakt. Chem.*, [1] **47**, 166 (1849). Erdmann, *J. prakt. Chem.*, [1] **22**, 257 (1841).

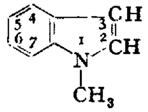
[3] Baeyer, *Ber.*, **11**, 582, 1228 (1878).

[4] Baeyer, *Ann.*, **140**, 296 (1866); *Ann., Suppl. Bd.*, **7**, 56 (1870). For a recent reduction of oxindole derivatives to the corresponding indole through the agency of $LiAlH_4$ see Julian and Printy, *J. Am. Chem. Soc.*, **71**, 3206 (1949).

[5] Baeyer, *Ber.*, **12**, 459 (1879).

[6] Baeyer and Emmerling, *ibid.*, **2**, 679 (1869). Compare also Baeyer, *ibid.*, **3**, 517 (1870).

largely as a result of synthetic methods of preparation of the compound by fusion of a mixture of *o*-nitrocinnamic acid, iron filings, and sodium hydroxide, and by the action of lead peroxide upon azocinnamic acid.



A system of nomenclature devised by Baeyer[7] and subsequently employed by Fischer[8] was cumbersome in that it employed independent numerical designations for each ring. Current practice in indole nomenclature is to number the positions as shown in the formula above. The 2- and 3-positions are also referred to as the α- and β-positions, respectively.

Indole derivatives are found in many natural products. Indole itself has been obtained from many naturally occurring materials by methods which suggest that the indole is in many cases the product of decomposition of its derivatives. Indole has been found in *Robinia pseudacacia*,[9] the jasmines[10], and certain citrus plants,[11] in the perfume of the *Hevea braziliensis*[12] and in orange blossoms.[13] Indole is also found in the wood of *Celtis reticulosa*.[14] The indole is usually obtained by repeated extraction of the blossoms with a suitable solvent with subsequent removal of the solvent by distillation.

Alkaline hydrolysis[15] and putrefaction[16] of proteins result in the formation of indole. Its formation in the putrefaction of proteins is presumed to be the result of the decomposition of tryptophan. The formation of indole from albumin may be stopped by the addition of lactose while other sugars have varying effects on its production.[17] Indole frequently accompanies pus

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[7] Baeyer, *ibid.*, **17**, 960 (1884).

[8] Fischer, *Ann.*, **236**, 116 (1886).

[9] Elze, *Chem.-Ztg.*, **34**, 814 (1910).

[10] Cerighelli, *Compt. rend.*, **179**, 1193 (1924). Hesse, *Ber.*, **37**, 1457 (1904). Soden, *J. prakt. Chem.*, [2] **69**, 256 (1904).

[11] Sack, *Pharm. Weekblad*, **48**, 307 (1911).

[12] Sack, *ibid.*, **48**, 775 (1911).

[13] Hesse and Zeitschel, *J. prakt. Chem.*, [2] **66**, 481 (1902).

[14] Herter, *J. Biol. Chem.*, **5**, 489 (1909).

[15] Kühne, *Ber.*, **8**, 208 (1875). Nencki, *J. prakt. Chem.* [2] **17**, 97 (1878). Herzfeld, *Biol. Z.*, **56**, 82 (1913).

[16] Nencki, *Ber.*, **7**, 1596 (1874); **8**, 336, 725 (1875); **28**, 561 (1895). Brieger, *J. prakt. Chem.*, [2] **17**, 135 (1878). Salkowski and Salkowski, *Ber.*, **12**, 648 (1879). Brieger *Z. physiol. Chem.*, **3**, 134 (1879). Salkowski, *ibid.*, **8**, 417 (1884); **9**, 8 (1885). v. Moraczewski, *Biol. Z.*, **51**, 340 (1913).

[17] Hirschler, *Z. physiol. Chem.*, **10**, 306 (1886). Simnitzki, *ibid.*, **39**, 113 (1903).

formation[18] and is found in the liver and pancreas,[19] the brain,[20] and bile.[21] Indole, accompanied by its β-methyl homolog, skatole, is found in the feces of men and of animals[22] and in the contents of the intestines.[23]

Indole[24] and homologs of indole[25] have been found in coal tar. Indole has also been found in molasses tar.[26] Indole is present in "practical" α-methylnaphthalene.[27] Its presence was demonstrated by reaction with oxalyl chloride to give the acid chloride of 3-indoleglyoxylic acid. Indole can be prepared by the reduction of indoxyl by sodium amalgam, by zinc dust and alkali, or catalytically.[28] Indole can also be prepared by the dehydrogenation of dihydroindole.[29] In the preparation of indoxyl or of indoxylic acid in the synthesis of indigo a small amount of indole is obtained when the melt is overheated.[30] Indole has been prepared in fair yields by adding sodium amalgam or zinc dust to the alkaline melt[31] of indoxylic acid.

Synthesis of Indole

A number of more general methods for the synthesis of indole and indole derivatives involve procedures which form the pyrrole ring through ring closure. Among these the synthesis developed by Emil Fischer has proved to be the most versatile for the synthesis of indole derivatives although the reaction fails for the synthesis of indole itself. It would be expected that

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[18] Porcher, *Compt. rend.*, **147**, 214 (1908).

[19] Nencki, *Ber.*, **7**, 1593 (1874).

[20] Stöckley, *J. prakt. Chem.*, [2] **24**, 17 (1881).

[21] Ernst, *Z. physiol. Chem.*, **16**, 208 (1892).

[22] Brieger, *Ber.*, **10**, 1030 (1877); *J. prakt. Chem.*, [2] **17**, 129 (1878). v. Moraczewski, *Z. physiol. Chem.*, **55**, 42 (1908).

[23] Tappeiner, *Ber.*, **14**, 2383 (1881). Ellinger, *Z. physiol. Chem.*, **39**, 44 (1903). Rosenfeld, *Beitr. zur Chem. Physiol. und Path.*, **5**, 83 (1904). Blumenthal and Jacoby, *Biol. Z.*, **29**, 472 (1910).

[24] Weissgerber, *Ber.*, **43**, 3520 (1910).

[25] Kruber, *ibid.*, **B 59**, 2752 (1926); **B 62**, 2877 (1929). Kruber, German patent 515, 543.

[26] Boes, *Pharm. Ztg.*, **47**, 131 (1902).

[27] Kharasch, Kane, and Brown, *J. Am. Chem. Soc.*, **62**, 2242 (1940).

[28] Vorländer and Apelt, *Ber.*, **37**, 1134 (1904). U.S. patent 1,891,057; *Chem. Abstr.* **27**, 1892 (1933).

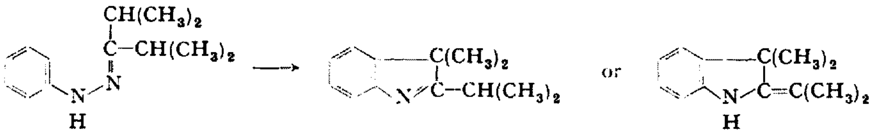
[29] Sugasawa, Saloda, and Yamagisawa, *J. Pharm. Soc. Japan*, **58**, 139 (1938); *Chem. Abstr.*, **32**, 4161 (1938).

[30] German patent 260,437; *Chem. Abstracts*, **7**, 3236 (1913).

[31] Vorländer and Apelt, *Ber.*, **37**, 1134 (1904).

acetaldehyde phenylhydrazone would yield indole through the Fischer synthesis but in reality none is obtained.

In 1883 Fischer and Jourdan[32] found that, when the methylphenylhydrazone of pyruvic acid was heated with alcoholic hydrogen chloride, a small yield of a compound, $C_{10}H_9NO_2$, was obtained. This compound proved to be 1-methylindole-2-carboxylic acid.[33] In subsequent studies of the reaction, it was found that zinc chloride was a better catalyst for the reaction than hydrogen chloride. Utilizing this procedure, Fischer[34] prepared 2-methylindole (methylketole) in 60% yields from acetone phenylhydrazone, and skatole in 35% yield from propionaldehyde phenylhydrazone. The Fischer synthesis has been utilized for the synthesis of many indole derivatives from ketone phenylhydrazones.



Since the early work by Fischer, a number of changes have been made in the procedure with material improvement in the yields. Thus, by employing an inert solvent such as methylnaphthalene[35] and by operating at temperatures below 150°, 2-methylindole was prepared in 75% yield from acetone phenylhydrazone, skatole in 80% yield from propionaldehyde phenylhydrazone, and indole-2-carboxylic acid in 60% yield from the phenylhydrazone of pyruvic acid. More recently it has been found[36] that the large amounts of zinc chloride used by early workers were not necessary. The reaction takes place in the presence of 1% of zinc chloride, while cuprous chloride, cuprous bromide, and platinum chloride may also be used as catalysts. Concentrated sulfuric acid has been employed as the catalyst,[37]

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[32] Fischer and Jourdan, *ibid.*, **16**, 2241 (1883).

[33] Fischer and Hess, *ibid.*, **17**, 559 (1884). Compare Hegel, *Ann.*, **232**, 214 (1882)

[34] Fischer, *Ann.*, **236**, 116, 126 (1886); *Ber.*, **19**, 1563 (1886).

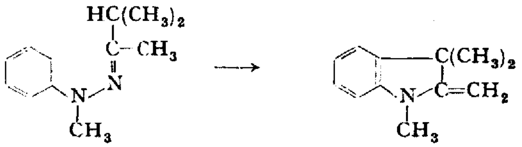
[35] German patent 238,138; *Chem. Abstr.*, **6**, 1659 (1912).

[36] Arbuzov and Tikhvinskii, *J. Russ. Phys.-Chem. Soc.*, **45**, 69, 649 (1915). Arbuzov and Tikhvinskii, *Ber.*, **43**, 2301 (1910).

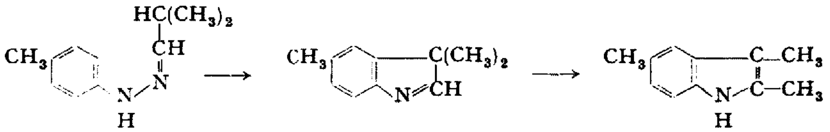
[37] Nef, *Ann.*, **266**, 72 (1891). Walker, *Am. Chem. J.*, **14**, 576 (1892). Reissert and Heller, *Ber.*, **37**, 4378 (1904).

while alcoholic sulfuric acid[38] and alcoholic zinc chloride[39] have also been used. Nickel, cobalt, and copper powder, cobalt chloride, and many other salts also catalyze the reaction.[40] The reaction has also been catalyzed by the use of Grignard reagents.[41] Boron fluoride is also effective as the condensing agent in the Fischer synthesis.[42] Recently, polyphosphoric acid has been employed effectively as a catalyst for the reaction.[42a]

The ease of indole formation varies irregularly with the various phenylhydrazones. In some cases the reaction takes place very readily. Thus cyclohexanone phenylhydrazone undergoes indole formation when warmed gently with aqueous hydrochloric acid, yielding tetrahydrocarbazole. The methylphenylhydrazone of isopropylmethyl ketone undergoes ring closure even at room temperature in the presence of alcoholic zinc chloride.[43]



3,3,7-Trimethyl-2-methyleneindoline has been prepared in similar fashion by heating the *o*-tolylhydrazone of isopropylmethyl ketone with alcoholic hydrogen iodide.[44] 3,3,5-Trimethylindolenine[45] was prepared by warming isobutyraldehyde *p*-tolylhydrazone at 60° with alcoholic zinc chloride. When heated with concentrated hydrochloric acid the 3,3,5-trimethylindolenine is converted into 2,3,5-trimethylindole.[45]



Although the Fischer synthesis is the most widely applicable of the indole syntheses, there are certain limitations and exceptions. Acetaldehyde

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[38] Wislicenus and Arnold, *Ann.*, **246**, 334 (1888).

[39] Plancher, *Gazz. chim. ital.*, **32**, 398 (1902); *Ber.*, **31**, 1496 (1898).

[40] Koraczynski and Kierzek, *Gazz. chim. ital.*, **55**, 361 (1925). Koraczynski, Brydowna, and Kierzek, *ibid.*, **56**, 903 (1926).

[41] Grammaticakis, *Compt. rend.*, **204**, 502 (1937).

[42] Snyder and Smith, *J. Am. Chem. Soc.*, **65**, 2452 (1943).

[42a] Kissman, Farnsworth, and Witkop, *ibid.*, **74**, 3948 (1952).

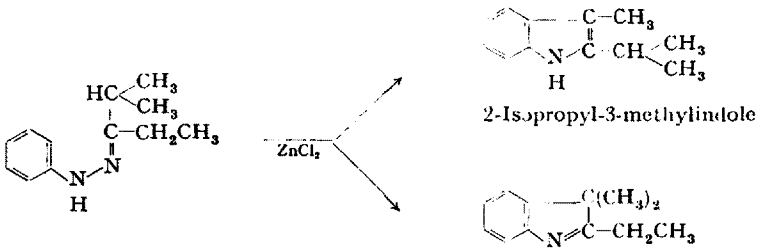
[43] Plancher, *Ber.*, **31**, 1496 (1898). Jenisch, *Monatsh.*, **27**, 1223 (1906).

[44] Plancher, *Monatsh.*, **26**, 833 (1905).

[45] Grgin, *ibid.*, **27**, 731 (1906).

phenylhydrazone should yield indole but this synthesis has not been accomplished. The phenylhydrazones of the β-ketone esters usually yield pyrazolones rather than indoles.

The catalytic decomposition of the arylhydrazones of unsymmetrical ketones can conceivably take place in two ways, yielding thereby a mixture of two products. While in many cases[46] only a single product of established structure has been obtained, in other cases the course of the reaction has not been determined.[47] In other cases two distinct products have been isolated.[48]



2-Isopropyl-3-methylindole

2-Ethyl-3,3-dimethylindolenine

The following rules governing the course of the reaction have been given by Plancher and Bonavia.[48] (*1*). Ketone phenylhydrazones containing the group $\text{-NH-N=CMe-CH}<\begin{smallmatrix}\text{R}\\ \text{R}\end{smallmatrix}$ yield only the corresponding indolenine. (*2*) Those with the grouping $\text{-NH-N=C}<\begin{smallmatrix}\text{CH}_2\text{R}\\ \text{CH}_2\text{R}\end{smallmatrix}$ give both the corresponding indole and the indolenine. (*3*) If the group $\text{-NH-N=C}<\begin{smallmatrix}\text{CH}_3\\ \text{CH}_2\text{R}\end{smallmatrix}$ is present the ketone phenylhydrazone is capable of yielding two indoles on condensation. Condensation by means of the $\text{-CH}_2\text{-}$ group preponderates.

The use of meta-substituted phenylhydrazones can lead to the formation of both the 4- and 6-derivatives. In a number of cases in the literature, the method of ring closure is not indicated.[49] The *m*-nitrophenylhydrazone of

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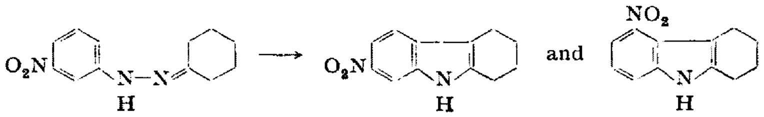
[46] Arbuzov and Tikhvinskii, *J. Russ. Phys.-Chem. Soc.*, **45**, 69, 694 (1915). Fischer, *Ann.*, **236**, 116 (1886). Jenisch, *Monatsh.*, **27**, 1223 (1906). Plancher, *Ber.*, **31**, 1496 (1898). Arbuzov, Zaitzev, and Razumov, *ibid.*, **B 68**, 1792 (1935).

[47] Arbuzov, Zaitzev, and Razumov, *Ber.*, **B 68**, 1792 (1935). Arbuzov and Zaitzev, *Trans. Butlerov Inst. Chem. Technol. Kazan*, **No. 1**, 33-38 (1934); *Chem. Abstr.*, **29**, 4006 (1935).

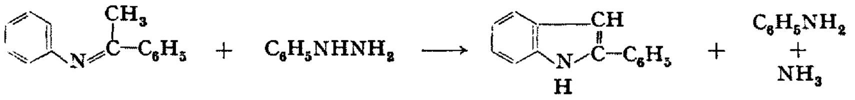
[48] Plancher and Bonavia, *Gazz. chim. ital.*, **32**, 414 (1902).

[49] Kermack, Perkin, and Robinson, *J. Chem. Soc.*, **119**, 1622 (1921); **121**, 1880 (1922). Roder, *Ann.*, **236**, 164 (1886). Tomicek, *Chem. Listy*, **16**, 1, 35 (1922).

cyclohexanone[50] has been found to undergo ring closure, yielding both possible isomers. Drechsel[51] was the first to prepare a tetrahydrocarbazole[52] in this way from phenylhydrazine and cyclohexanone.

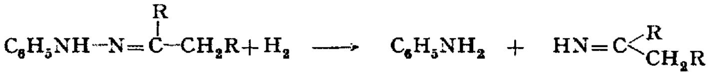


The study of the mechanism of the Fischer reaction has engaged the attention of a number of workers. Four distinct mechanisms have been proposed for the reaction. Reddelien[53] found that the anil of acetophenone is oxidized by phenylhydrazine or by phenylhydrazones to 2-phenylindole.



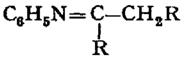
On the basis of this observation he proposed the following mechanism for the Fischer synthesis.

(I) Reduction of the phenylhydrazone during the simultaneous oxidation of stage III.



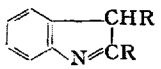
$$\mathrm{C_6H_5NH{-}N{=}\overset{R}{\overset{|}{C}}{-}CH_2R + H_2 \longrightarrow C_6H_5NH_2 + HN{=}C{<}^{R}_{CH_2R}}$$

(II) Condensation of the products of stage I with elimination of ammonia to yield



$$\mathrm{C_6H_5N{=}\underset{R}{\underset{|}{C}}{-}CH_2R}$$

(III) Ring closure by oxidation of the anil (accompanied by the reduction of stage I) to yield the indolenine.



(IV) Isomerization of the indolenine with migration of hydrogen from position 3 to position 1 yielding the indole.

This mechanism requires the assumption of an initial tautomeric

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[50] Borsche, Witte, and Bothe, *Ann.*, **359,** 49 (1908). Plant, *J. Chem. Soc.*, **1936,** 899. Barclay and Campbell, *ibid.*, **1945,** 530.

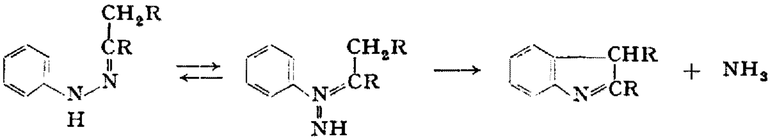
[51] Drechsel, *J. prakt. Chem.*, **38,** 65 (1888).

[52] Baeyer, *Ann.*, **278,** 88 (1894). Drechsel and Baeyer, *ibid.*, **278,** 105 (1894).

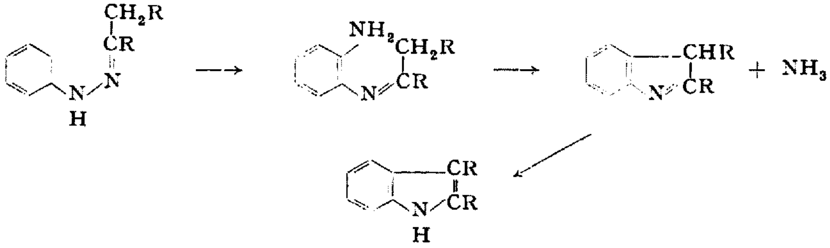
[53] Reddelien, *ibid.*, **388,** 179 (1912).

hydrogen in the original phenylhydrazone (or in the ketone imide of stage I) if it is to account for the preparation of 1-alkylindoles by the Fischer method.[54] The Reddelien mechanism has met with opposition from Robinson and Robinson,[55] Bodforss,[56] and Campbell and Cooper.[57] On the other hand, Hollins[54] has favored a modification of the Reddelien mechanism.

Bamberger and Landau,[58] basing their explanation on the formation of dimethylaniline oxide by methylation of phenylhydroxylamine with methyl sulfate, assume a mechanism based upon a tautomeric form of the hydrazones. The method of elimination of the ammonia is not explained and the hypothesis fails entirely to account for the formation of *N*-methylindoles from the phenyl methyl hydrazones of ketones.[59]



Cohn[60] suggested an ortho semidine rearrangement with subsequent loss of ammonia. This mechanism likewise fails to account for the formation of the *N*-alkylindoles and would require the formation of 6-substituted indoles from *p*-substituted phenylhydrazones, whereas 5-substituted indoles are actually obtained.



The fourth mechanism proposed for the Fischer synthesis and the one most generally accepted[61] is the one proposed by Robinson and Robinson.[55]

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[54] Hollins, *J. Am. Chem. Soc.*, **44**, 1598 (1922).

[55] Robinson and Robinson, *J. Chem. Soc.*, **113**, 639 (1918; **125**, 827 (1924).

[56] Bodforss, *Ber.*, **B 58**, 775 (1925).

[57] Campbell and Cooper, *J. Chem. Soc.*, **1935**, 1208.

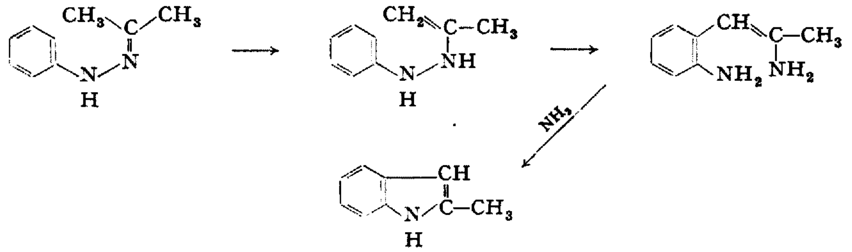
[58] Bamberger and Landau, *Ber.*, **52**, 1097 (footnote) (1919).

[59] Degen, *Ann.*, **236**, 153 (1886).

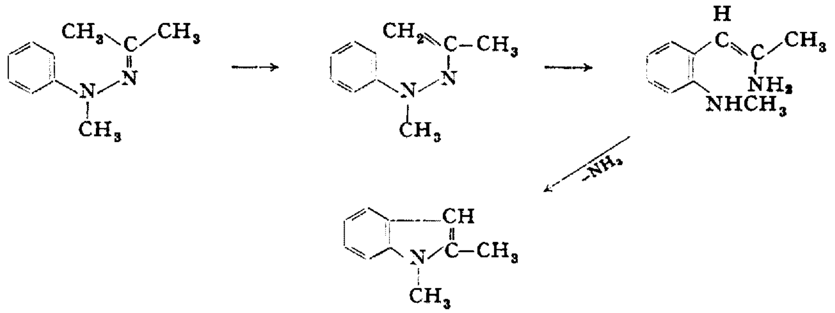
[60] Cohn, *Die Carbazolgruppe*. Thieme, Leipzig, 1919, p. 12.

[61] Neber, *Ann.*, **471**, 113 (1929). Campbell and Cooper, *J. Chem. Soc.*, **1935**, 1208. Plieninger, *Chem. Ber.*, **83**, 273 (1950).

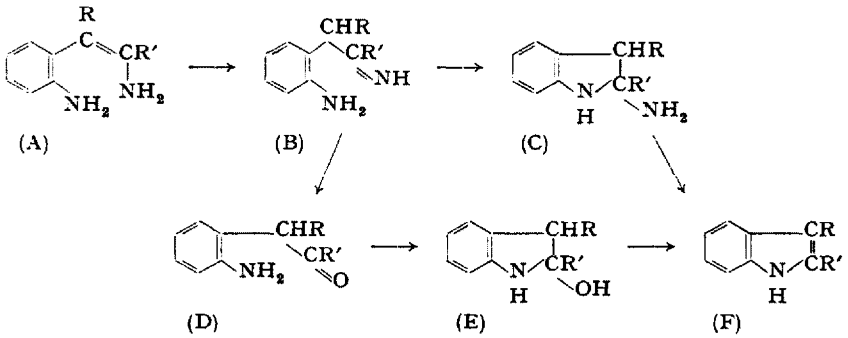
This mechanism involves tautomerization followed by rearrangement before ring closure as follows:



The preparation of *N*-alkylindoles from secondary hydrazines can be accounted for equally well under the Robinson mechanism. Evidence in support if the Robinson representation has been presented by Allen and



Wilson.[62] Through use of N^{15} isotope as a tracer element, these workers were able to show that the nitrogen farthest removed from the aromatic ring is the one eliminated as ammonia. They propose the following schemes for the elimination of ammonia:



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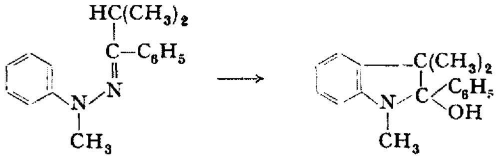
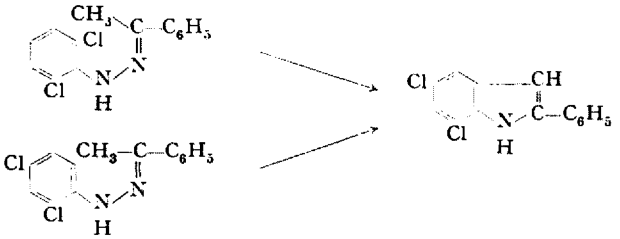
[62] Allen and Wilson, *J. Am. Chem. Soc.*, **65**, 611 (1943). Compare also Clausius and Weisser, *Helv. Chim. Acta*, **35**, 400 (1952).

This view assumes that A tautomerizes to B which may undergo ring closure to C which then eliminates ammonia to give the final indole F. The alternate hypothesis is that the ketimine B is hydrolyzed to the ketone D which through ring closure yields E which in turn loses water to give F. In support of the latter hypothesis (B → D → E → F) they cite the fact that the phenylmethylhydrazone of isopropylphenyl ketone yields 1,3,3-trimethyl-2-phenylindolin-2-ol in the Fischer synthesis.[63]



An interesting application of the Fischer synthesis in which halogen migration occurs has been reported recently.[64] The 2,6-dichlorophenylhydrazone of acetophenone on heating with zinc chloride gave 2-phenyl-5,7-dichloroindole in small yields. The same compound was also prepared (in better yields) from the 2,4-dichlorophenylhydrazone of acetophenone.



Halogen migration was not observed in the ring closure of any of the dichlorophenylhydrazones except the 2,6-dichloro derivative when displacement of a halogen atom is essential to ring closure. The 2,6-dichlorophenylhydrazones of four other ketones were converted into the corresponding 5,7-dichloroindoles by means of zinc chloride.

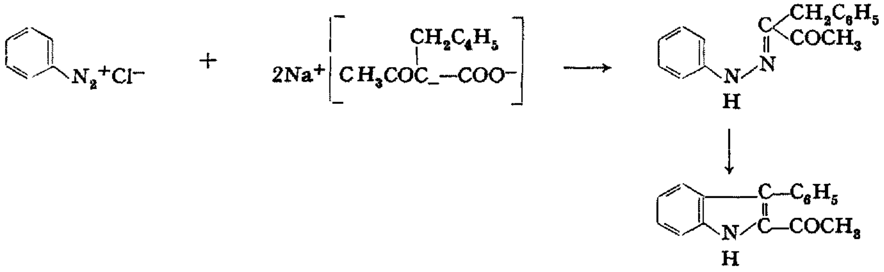
The hydrazones required for the synthesis of indoles by the Fischer synthesis may be prepared by means of the Japp-Klingemann reaction.[65]

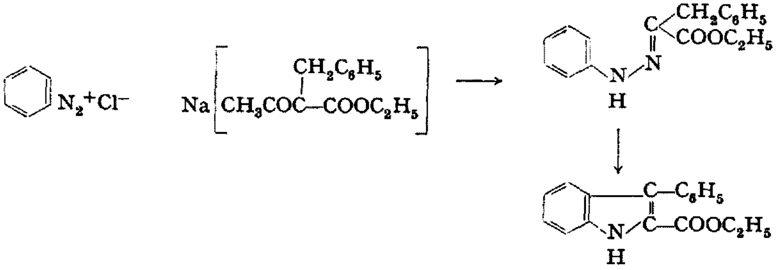
[63] Jenisch, *Monatsh.*, **27**, 1223 (1906).

[64] Carlin and Fisher, *J. Am. Chem. Soc.*, **70**, 3422 (1948) Carlin, Wallace, and Fisher, *ibid.*, **74**, 990 (1952). Carlin, *ibid.*, **74**, 1077 (1952).

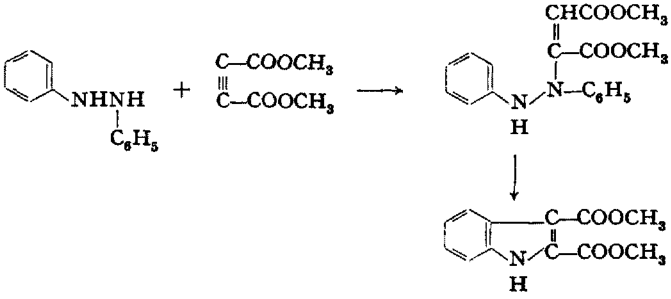
[65] Japp and Klingemann, *Ber.*, **21**, 549 (1888); *Ann.*, **237**, 218 (1888). Lions, *J. Proc. Soc. N.S. Wales*, **66**, 516 (1933); *Chem. Abstr.*, **27**, 2954 (1933). Hughes, Lions, *et al.*, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 475 (1938); *Chem. Abstr.*, **33**, 587 (1939). Hughes and Lions, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 494 (1938); *Chem. Abstr.*, **33**, 588 (1939). Hughes, Lions, and Ritchie, *J. Proc. Roy. Soc. N.S. Wales*, **72**, 209 (1939); *Chem. Abstr.*, **33**, 6837 (1939). Sempronj. *Gazz. chim. ital.*, **68**, 263 (1938).

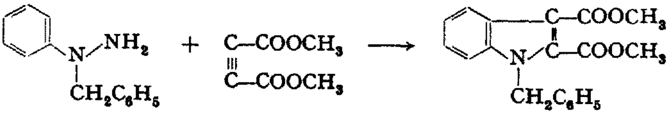
In this reaction, benzenediazonium chloride couples with the sodium salt of a β-keto acid yielding a phenylhydrazone through elimination of the carboxyl group. If the carboxyl group is protected by esterification the acetyl group is eliminated rather then the carboxyl.[65,66]





In a synthesis resembling the Fischer synthesis, Diels and Reese[67] found that acetylenedicarboxylic esters react with hydrazobenzene as well as with unsymmetrical hydrazines to give intermediates which on heating give indole





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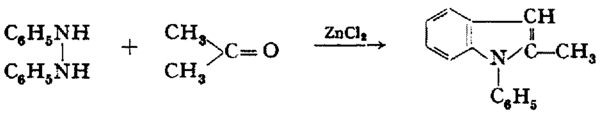
[66] Manske, Perkin, and Robinson, *J. Chem. Soc.*, **1927**, 1.

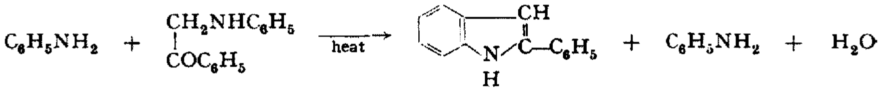
[67] Diels and Reese, *Ann.*, **511**, 168 (1934); **519**, 147 (1935). Huntress and Hearon, *J. Am. Chem. Soc.*, **63**, 2762 (1941).

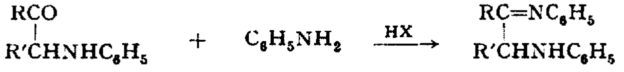
derivatives. Hydrazobenzene and acetone condense similarly in the presence of acetic acid and zinc chloride to give 1-phenyl-2-methylindole (m.p. 58–58.5°).[68]



Another general method for the synthesis of indoles makes use of the reaction of arylamines with α-halogenated ketones or α-hydroxyketones.[69] The first product, isolable at low temperatures but not usually separated, is a phenacylaniline. Reaction with a second molecule of aniline completes the synthesis. It has been suggested by Bischler[69] that the arylamino ketone (I) formed in the first step shown above then condenses with a second molecule of arylamine to yield the "aniline anil" (II). Julian and Pikl[70] were able to show that in addition to III an isomer IV was also obtained in some instances. The formation of IV as well as of III in this reaction is

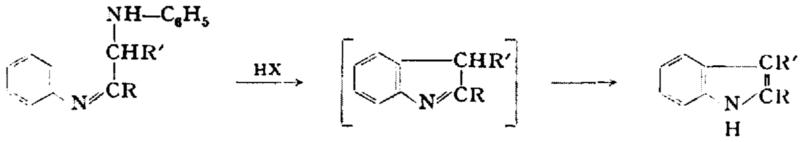
$C_6H_5NH_2 + BrCH_2COC_6H_5 \longrightarrow C_6H_5NHCH_2COC_6H_5$ (I)



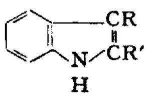


$$\begin{matrix}RCO\\ |\\ R'CHNHC_6H_5\end{matrix} + C_6H_5NH_2 \xrightarrow{HX} \begin{matrix}RC{=}NC_6H_5\\ |\\ R'CHNHC_6H_5\end{matrix}$$

(II)



(III)



(IV)

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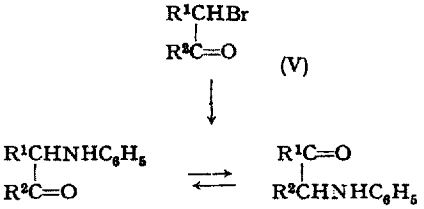
[68] Mann and Haworth, *J. Chem. Soc.*, **1944**, 670.

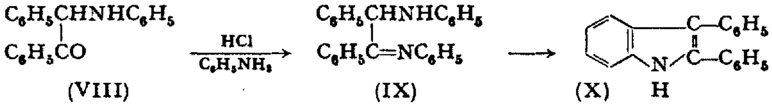
[69] Mohlau, *Ber.*, **15**, 2480 (1882); **21**, 510 (1888). Bischler, *ibid.*, **25**, 2860 (1892). Nencki and Berlinerblau, German patent 40,889 (1884); *Friedl.*, I, 150 (1886). Bischler and Fireman, *Ber.*, **26**, 1336 (1893). Ritchie, *J. Proc. Roy. Soc. N.S. Wales*, **80**, 33–40 (1946); *Chem. Abstr.*, **41**, 3094 (1947). Cowper and Stevens, *J. Chem. Soc.*, **1947**, 1041. Mentzer, Molho, and Berguer, *Bull. soc. chim. France*, **1950**, 555.

[70] Julian and Pikl, *J. Am. Chem. Soc.*, **55**, 2105 (1933).

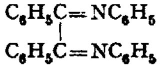
understandable since it has been shown[71] that two anilinoketones may be obtained in the reaction of the α-bromoketone (V) with aniline.



While the Bischler hypothesis of the intermediate formation of the "aniline anil" (II) has been rejected by some[72] in favor of a mechanism involving direct ring closure of the anilinoketone strong evidence in favor of the intermediate formation of II has been produced.[71] When desylaniline (VIII) was heated for several hours with one molecular proportion of aniline in the presence of a few drops of hydrochloric acid 2,3-diphenylindole was obtained in good yield.



Repetition of this experiment using dimethylaniline as a substitute for aniline gave a recovery of 98% of VIII unchanged. Failure to obtain X in this experiment constitutes strong evidence against a direct ring closure and in favor of a mechanism providing for the interaction of a second molecule of aniline. In further experiments[71] in which the reaction was interrupted at definite intervals IX was isolated from the reaction mixture. By dividing the product into two portions it was possible to convert part to X as shown and to oxidize the other part to the dianil XI.[73]



$$\begin{array}{l} C_6H_5C{=}NC_6H_5 \\ \quad | \\ C_6H_5C{=}NC_6H_5 \end{array}$$

(XI)

Support for the last step of the Bischler mechanism, that the indole formation takes place

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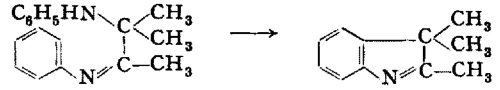
[71] Julian, Meyer, Magnani, and Cole, *ibid.*, **67**, 1203 (1945). Brown and Mann, *J. Chem. Soc.*, **1948**, 858. Catch, Elliott, Hey, and Jones, *ibid.*, **1948**, 272. Catch, Hey, Jones, and Wilson, *ibid.*, **1948**, 276.

[72] Crowther, Mann, and Purdie, *ibid.*, **1943**, 58. Brown and Mann, *ibid.*, **1948**, 847 Verkade and Janetsky, *Rec. trav. chim.*, **62**, 763, 775 (1943); **64**, 129 (1945); **65**, 193 (1946).

[73] For further conversion of IX to X see also Strain, *J. Am. Chem. Soc.*, **51**, 269 (1929).

through the indolenine, has come from the observation that "aniline anils" of the type of XII do in fact yield indolenines of the type of XIII when heated in the presence of HCl.[74] The work of Julian and his collaborators

(XII)



(XIII)

establishes definitely the intermediate formation of the "aniline anils" in the Möhlau-Bischler synthesis. These investigators are careful to state, however, that their work does not completely rule out the possibility of direct ring closure in some cases. Thus 3-phenylamino-2-butanone on heating with an equal weight of zinc chloride for thirty minutes gave a 56% yield of 2,3-dimethylindole,[75] showing that direct ring closure is possible. However, the same anilinoketone on heating with twice its weight of aniline hydrochloride gave the same indole in 65% yield. It seems probable that direct ring closure takes place when the compound is heated with zinc chloride but that the Julian mechanism is the correct one under the conditions of the Bischler reaction.

Benzoin has been used also in this synthesis in place of desyl bromide for the preparation of 2,3-diphenylindole.[76] The Möhlau-Bischler synthesis has been employed by a number of workers[77] for the synthesis of indole derivatives. A variation of the synthesis[78] gives indole from aniline and

$$\mathrm{ClCH_2CHClOC_2H_5} \longrightarrow \mathrm{ClCH_2CHO}$$

$$2\,\mathrm{C_6H_5NH_2} + \mathrm{ClCH_2CHO} \longrightarrow \mathrm{C_6H_5NH{-}CH{=}CH{-}NHC_6H_5} \longrightarrow \text{Indole}$$

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[74] Garry, *Compt. rend.*, **211**, 399 (1940); **212**, 401 (1941). Garry, *Ann. Chim.*, **17**, 5 (1942).

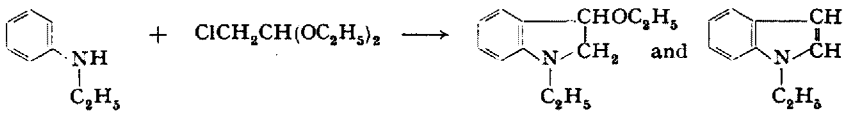
[75] Janetzky and Verkade, *Rec. trav. chim.*, **65**, 691 (1945). Brown and Mann, *J. Chem. Soc.*, **1948**, 847.

[76] Japp and Murray, *J. Chem. Soc.*, **65**, 889 (1894); *Ber.*, **26**, 2638 (1893). Lachowicz, *Monatsh.*, **15**, 402 (1894).

[77] Wolff, *Ber.*, **20**, 428 (1887); **21**, 133, 3360 (1888). German patent 533,471; *Chem. Abstr.*, **26**, 480 (1932). Richards, *J. Chem. Soc.*, **97**, 977 (1910); *Proc. Chem. Soc.*, **26**, 92 (1910). Pictet and Duparc, *Ber.*, **20**, 3415 (1887). British patent 354,392; *Chem. Anstr.*, **26**, 5431 (1932). Sircar and Guha, *J. Indian Chem. Soc.*, **13**, 704 (1936); *Chem. Abstr.*, **31**, 3911 (1937). Hell and Cohen, *Ber.*, **37**, 866 (1904). Hell and Bauer, *ibid.*, **37**, 872 (1904). Mentzer, *Compt. rend.*, **222**, 1176 (1946), Meisenheimer, Angermann, Finnand, and Vieweg, *Ber.*, **B 57**, 1774 (1924). Bauer and Bühler, *Arch. Pharm.*, **262**, 128 (1924). Emerson, Heimach, and Patrick, *J. Am. Chem. Soc.*, **75**, 2256 (1953).

[78] Berlinerblau, *Monatsh.*, **8**, 180 (1887). Berlinerblau and Poliker, *ibid.*, **8**, 187 (1887). Nencki and Berlinerblau, German patent 40,889 (1884).

α,β-dichloroethyl ether according to the preceding scheme. A modification employs the diethylacetal of chloroacetaldehyde to obtain *N*-alkylindoles.[79]

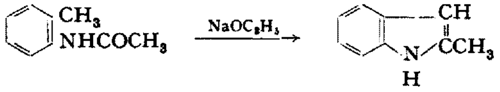


The procedure does not yield indole with aniline but has been reported to give satisfactory results with secondary amines.[80] In the hands of other workers the procedure has been less satisfactory.[81]

Indole has also been prepared through a scheme in which aniline and ethylene bromide are the initial reactants.[82]

$$C_6H_5NHCH_2CH_2NHC_6H_5 \xrightarrow{CrO_3} C_6H_5NHCH{=}CHNHC_6H_5 \xrightarrow{Zn} \text{Indole}$$

An indole synthesis[83] which has found considerable use consists of an intramolecular Claisen condensation of an acyl derivative of an *o*-toluidine.



Sodium amide[84] and a variety of other condensing agents[85] have also been employed in this synthesis. Indole itself has been prepared by treating *N*-formyl-*o*-toluidine with sodium amide.

Indole has been prepared[86] by heating *o*-amino-ω-chlorostyrene with

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[79] Rath, *Ber.*, **B 57,** 715 (1924).

[80] Kiematsu and Inoue, *J. Pharm. Soc. Japan,* **No. 518,** 351 (1925); *Chem. Abstr.,* **19,** 2493 (1925).

[81] Koenig and Bucheim, *Ber.,* **B 58,** 2868 (1925). Janetzky, Verkade, and Meerburg, *Rec. trav. chim.,* **66,** 317 (1947); *Chem. Abstr.,* **42,** 558 (1948).

[82] Prud'homme, *Bull. soc. chim.,* [2] **28,** 558 (1877).

[83] Madelung, *Ber.,* **45,** 1128, 3521 (1912). Madelung, German patent 262,237; *Chem. Abstr.,* **7,** 3642 (1913). Verley, *Bull. soc. chim.,* [4] **35,** 1039 (1924). Verley and Beduive, *ibid.,* **37,** 189 (1925). Salway, *J. Chem. Soc.,* **103,** 351, 1988 (1913).

[84] Kiematsu and Sugasawa, *J. Pharm. Soc. Japan,* **48,** 755 (1928); *Chem. Abstr.* **23,** 834 (1929). British patent 303,478; *Chem. Abstr.,* **23,** 4484 (1929)

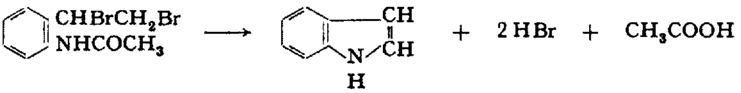
[85] British patent 330,332; *Chem. Abstr.,* **24,** 5770 (1930). Tyson, *J. Am. Chem. Soc.*), **63,** 2024 (1941); *Org. Synthesis,* **23,** 42 (1943). Marion and Ashford, *Can. J. Research,* **B 23,** 26 (1945). Galat and Friedman, *J. Am. Chem. Soc.,* **70,** 1280 (1948). U.S. patent 2,442,952; *Chem. Abstr.,* **42,** 6857 (1948). Tyson, *J. Am. Chem. Soc.,* **72,** 2801 (1950). Tyson and Shaw, *ibid.,* **74,** 2273 (1952).

[86] Lipp, *Ber.,* **17,** 1067, 2507 (1884).

sodium ethoxide. Indole has been prepared from *o*-nitrocinnamide[87] according to the scheme:

$$\begin{tikzcd}
o\text{-}O_2NC_6H_4CH{=}CHCONH_2 \arrow[r, "KOCl", "CH_3OH"'] & o\text{-}O_2NC_6H_4CH{=}CHNHCOOCH_3 \arrow[d, "Fe+CH_3COOH"] \\
\text{Indole} & H_2NC_6H_4CH{=}CHCOOCH_3 \arrow[l, "KOH"']
\end{tikzcd}$$

Heating the dianilide of tartaric acid with zinc chloride gives indole.[88] Small yields of indole are obtained when the calcium salt of phenylglycine is heated with excess calcium formate,[89] as well as when *o*-chloro-ω-chloroacetanilide is distilled with zinc dust.[90] Heating *o*-formylphenylglycine with acetic anhydride and sodium acetate yields indole-2-carboxylic acid[91] as an intermediate and through decarboxylation of this product indole is obtained. Indole has been prepared through the distillation of oxal-*o*-toluic acid with zinc dust or by dry distillation of its barium salt.[92] Small yields of indole were obtained by dropping *N*-methyl-*o*-toluidine on reduced nickel at 300–330°.[93] Other indole derivatives were prepared in similar fashion from alkyl toluidines.[94] Indole has been obtained through the pyrolysis of *N*-ethylaniline[95] as well as by catalytic dehydrogenation of *o*-ethylaniline.[96] Heating *o,o'*-diaminostilbene hydrochloride under reduced pressure gives a quantitative yield of indole.[97] Indole has been prepared by the action of alcoholic potash on the dibromide of *N*-acetyl-*o*-aminostyrene.[98]



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[87] Weermann, *Rec. trav. chim.*, **29**, 18 (1910); *Ann.*, **401**, 14 (1913); German patent 213,713 (1908).

[88] Poliker, *Ber.*, **24**, 2954 (1891).

[89] Mauthner and Suida, *Monatsh.*, **10**, 250 (1889).

[90] Schwalbe, Schulz, and Jockheim, *Ber.*, **41**, 3792 (1908).

[91] Gluud, *J. Chem. Soc.*, **103**, 1254 (1913); *Ber.*, **48**, 420 (1915); German patent 287,282 (1913).

[92] Mauthner and Suida, *Monatsh.*, **7**, 230 (1886).

[93] Carrasco and Padoa, *Gazz. chim. ital.*, **36**, ii, 512 (1906); **37**, ii, 49 (1907); *Atti accad. Lincei*, [5] **15**, i, 699 (1906); [5] **15**, ii, 729 (1906).

[94] Baeyer and Caro, *Ber.*, **10**, 1262 (1877).

[95] Baeyer and Caro, *ibid.*, **10**, 692 (1877).

[96] Gresham and Brunner, U.S. patent 2,409,676; *Chem. Abstr.*, **41**, 998 (1947). Hansch and Kelmkamp, *J. Am. Chem. Soc.*, **73**, 3080 (1951).

[97] Thiele and Dimroth, *Ber.*, **28**, 1411 (1895); German patent 84,578 (1895).

[98] Taylor and Hobson, *J. Chem. Soc.*, **1936**, 181.