

INDOLE

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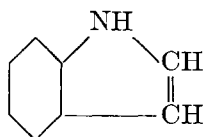
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I. INTRODUCTION

In 1866, Baeyer and Knop (26), in the course of a study of the structure of indigo, reduced isatin and obtained two products, $C_8H_7NO_2$ and C_8HN_7O (dioxindole and oxindole), which they regarded as hydroxy derivatives of C_8H_7N ; they named the latter "indole". The work was continued by Baeyer and Emmerling (24), who proposed in 1869 the formula which is generally accepted:



Indole

This structure was suggested largely as a result of synthetic methods of preparation of the compound by fusion of a mixture of nitrocinnamic acid, iron filings, and sodium hydroxide, and by the action of lead peroxide upon azocinnamic acid.

A system of nomenclature was devised by Baeyer (20), and used by Fischer (121), in order to differentiate the derivatives of indole. This system was cumbersome, involving independent numerical designations for each ring. Current practice is to use numbers, with the nitrogen atom as 1, and with clockwise assignment of numbers to the positions in the formula shown above. The 2- and 3-positions are occasionally referred to as the α - and β -positions, respectively.

Indole derivatives occur widespread in many natural products. Indole itself has been obtained, usually in small amounts, by extraction from naturally occurring materials by methods which suggest that the indole so obtained is in many cases the result of breakdown of its derivatives. Various plants have yielded indole, among them the following: *Robinia pseudacacia* (107), the jasmines (68, 170, 363), certain citrus plants (344), and orange blossoms (171). The usual procedure is to extract the blossoms repeatedly with a suitable solvent, followed by distillation of the extract. In this way, Hesse and Zeitschel (171) obtained about 0.1 per cent of indole from orange-blossom oil, while Hesse (170) isolated 2.5 per cent from jasmine. Herter (167) also found indole in the wood of *Celtis reticulosa*.

Indole is also found after putrefactive processes have taken place. It is found in the animal body wherever pus formation occurs (321) and in the liver and pancreas (278), the brain (371), and bile (111). It is formed in the putrefaction of milk (408), of blood fibrin (284, 347, 394), of albumin (36), and possibly of vegetable protein (170). Formation of indole from albumin may be stopped by the addition of lactose, while other sugars have varying effects upon its production (173, 355). The formation of indole is presumably the result of the decomposition of tryptophan in these cases of putrefaction of protein material.

Indole has also been found to be present in coal tar in the fraction boiling between 240° and 260°C. (396), from which it may be isolated as its solid sodium or potassium derivative after treatment with sodium amide, sodium, or potassium hydroxide. Homologous indole derivatives can also be obtained from coal tar (240). Molasses tar has also yielded some of the base (50).

II. SYNTHESSES OF INDOLE

Indole was first prepared synthetically by Baeyer (15); he oxidized indigo to obtain isatin, reduced the isatin to dioxindole and oxindole using zinc dust, and further reduced oxindole to indole by passing its vapors over hot zinc oxide. Also, Baeyer (17) reduced 2,3-dichloroindole to indole.

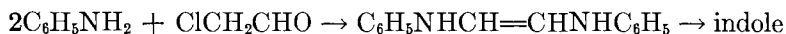
Indoxyl, reduced by sodium amalgam, by zinc dust and alkali (387), or catalytically (187), yields indole. Dihydroindole can be obtained by the electrolytic reduction of the sulfur analog of oxindole; this in turn yields indole upon being dehydrogenated (376).

In the preparation of synthetic indigo by the method involving the fusion of phenylglycine or its *o*-carboxylic acid with sodium hydroxide, if the melt is "over-melted" a small amount of indole is obtained (89). This melt also yields indole when a metal such as sodium or iron is added at 300°C. (90). By adding

sodium amalgam or zinc dust to the alkaline melt of indoxylic acid at 60–70°C. a fairly good yield of indole was obtained by Vorländer and Apelt (387).

More generally applicable methods of synthesis of indole and its derivatives involve ring closures to form the pyrrole side ring. Among these various methods, the Fischer procedure (see section IV B) is the most versatile for the preparation of derivatives. This method, discovered by E. Fischer and Jourdan (126) in 1883, involves in general the loss of ammonia from phenylhydrazones. Thus, the phenylhydrazone of pyruvic acid yields indole-2-carboxylic acid (91) and this upon decarboxylation gives indole (*vide infra*). It would be expected that acetaldehyde phenylhydrazone would form indole; this is not realized.

Other syntheses, which like the Fischer synthesis involve ring closure by the reaction of a carbon group with the ortho position, follow. Berlinerblau (42, 43, 283) employed aniline and α, β -dichloroethyl ether according to the following scheme:



Also, Prud'homme (323) used a somewhat analogous procedure with aniline and ethylene dibromide as the initial reactants:

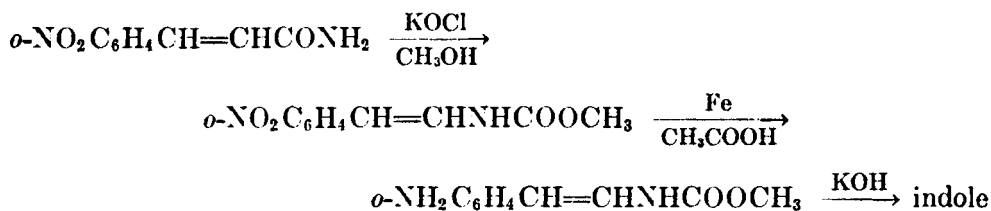


Polikier (317) heated the dianilide of tartaric acid with zinc chloride to obtain indole; dianilinosuccinanilide was an intermediate. The calcium salt of phenylglycine when heated with excess of calcium formate gave indole in very small yield (264); the product was isolated as the picrate. Distilling *o*-chloro- ω -chloro-acetanilide with zinc dust yielded small amounts of indole (352). Baeyer found that indole was formed when vapors of ethylaniline were led through hot tubes (22).

A rather large number of methods have been described in which ring closure is accomplished by reaction of a carbon group, attached to the benzene ring, with a nitro group, an amino group, or a substituted amino group at the ortho position. Gluud (144, 146) synthesized *o*-aldehydophenylglycine and effected ring closure (and decarboxylation of the intermediate indole-2-carboxylic acid) by heating the compound in acetic anhydride containing sodium acetate. A similar procedure (145) also gave indole. Verley (385) treated *N*-aldehydo-*o*-toluidine with sodium amide and obtained indole. The distillation of oxal-*o*-toluic acid with zinc dust, or dry distillation of the barium salt, gives indole (263). Also, *N*-methyl-*o*-toluidine, dropped on reduced nickel at 300–330°C., produces small yields of indole (65, 66, 67); other alkyltoluidines (23) also yield indoles.

A series of methods involving substituted cinnamic acids, styrenes, stilbenes, and analogous compounds as starting materials are described in the literature; examples follow. Lipp's indole synthesis involves the heating of *o*-amino- ω -chlorostyrene with sodium ethylate; reduction of the nitro group and ring closure

result (249). Weermann (392, 393; also 93) has prepared indole by the use of *o*-nitrocinnamide as follows:



A quantitative yield of indole is reported when *o,o'*-diaminostilbene hydrochloride is heated under reduced pressure (94, 379). Baeyer and Emmerling (24) and Beilstein and Kuhlberg (39) prepared indole from *o*-nitrocinnamic acid. Reduction of *o*-nitrophenylacetaldehyde yields indole (392). Also, *o*-nitrophenylpyruvic acid has been converted into indole-2-carboxylic acid by Reissert (332), Kermack, Perkin, and Robinson (222), and Polyakov (320). Pschorr and Hoppe (324) prepared 2-aminoindole from *o*-nitrophenylacetic acid; this was converted into indole by reduction with sodium and alcohol. Indole may also be obtained from *o,o*-dinitrostyrene (266, 384). Walter (390) prepared it by treating acetylated *o*-aminocinnamic acid with fuming hydrochloric acid at high temperatures. Some indole is obtained from *o*-aminophenylpropionic acid (336).

A variety of miscellaneous methods have also been reported. In some of these cases rather strenuous treatment is involved, and for many the yields are not good. In summary, however, the following examples are cited: Morgan (274) provided one of the earliest syntheses of indole by his fusion of carbostyryl with alkali. Hofmann and Königs (175) obtained indole and quinoline as the products resulting from the high-temperature treatment of tetrahydroquinoline or methyltetrahydroquinoline. Fusion of albumin with potassium hydroxide yields indole, skatole, and other products (108, 243, 280); similarly strychnine yields indole (151, 250). Also, indole-2-carboxylic acid (75), and quinoline-2,3-dicarboxylic acid (153), when heated with calcium carbonate give indole. Ketodihydrobenzene-*p*-thiazine (383) with a red-hot mixture of zinc and copper powders yields some indole. Acetylene and aniline (257) passed over metallic or oxide catalysts form indole.

Also, Fileti (120) obtained indole by passing the vapor of cumidine over hot lead oxide, and by distilling skatole over hot porcelain chips. Widmann (399) distilled 3-nitro-4-isopropenylbenzoic acid with lime and obtained a small yield of indole.

Tripyrroline (85) and pyrrole (84) have been converted into indole.

III. PROPERTIES OF INDOLE

A. Miscellaneous

Indole is a colorless crystalline solid in the form of shining leaflets. It melts at 52°C. and boils at 253°C. (corr.) at 762 mm. It is volatile with steam. It is soluble in hot water and in hot alcohol, and is also soluble in ether and in benzene. The compound in the impure state has an unpleasant odor.

Indole is very feebly basic. Generally it tends to form resin-like materials when heated with acid; heating the hydrochloric acid solution of indole yields an orange resin, which upon precipitation with water from its alcohol solution is converted to a flocculent white precipitate (75).

Mild oxidation of indole leads in most instances to the formation of indigo. Thus, indigo is formed from indole by the action of air in the presence of sulfite or bisulfite (95, 279), by monopersulfuric acid (Caro's acid) (96), by hydrogen peroxide (322), and by ozone (279). On the other hand, chromic acid causes the precipitation of a dark violet-brown solid, which is dissolved by concentrated hydrochloric acid with a color change to green (109). Also, a gray-green powder is obtained as a result of the action of ferric chloride upon indole (244).

Indole yields 3-nitrosoindole through the action of sodium nitrite and acetic acid (279) or of amyl nitrite and sodium ethylate (5, 414, 418). Through migration of the hydrogen atom from position 1, this product exists largely as the isomeric 3-oxime.

Treatment of indole with acetic anhydride yields 1-acetyl- and 1,3-diacetyl-indoles (415). Chloroform and sodium ethylate, or alkali, produce a mixture of indole-3-aldehyde and 3-chloroquinoline (101).

Indole reacts to form a sodium derivative with metallic sodium or sodium amide and a potassium derivative with potassium hydroxide (396). This reaction is used in separating indole from the other constituents found in the portion of coal tar boiling at 240–260°C. (141).

Also, indole will condense with aldehydes in the molecular ratio of 2 to 1 (179) and similarly with acetone (350).

B. Reduction

Indole is readily converted to 2,3-dihydroindole by electrolytic reduction or by catalytic hydrogenation. Carraseo (64) and v. Braun and Sobeecki (55) have prepared the dihydroindole electrolytically. Catalytic reduction methods reported have made use most commonly of platinum, nickel, nickel salts, copper, or copper salts.

Catalytic hydrogenation under pressure produces first the dihydroindole, but absorption of hydrogen may continue, to form either octahydroindole or an aniline derivative if the pyrrole ring is fractured. The latter effect predominates if nickel is the catalyst. Thus, Willstätter, Seitz, and v. Braun (406) found that with a nickel catalyst at 225°C. no octahydroindole was formed, but that continued hydrogenation past the dihydro stage yielded 1-ethyl-2-aminocyclohexane, which v. Braun, Bayer, and Blessing (54) had erroneously thought to be octahydroindole. The true octahydroindole was obtained by Willstätter and Jaquet (405), who used platinum as the catalyst. The use of copper catalysts gives good yields of dihydroindole (188).

Treatment of molten indole at 200°C. with hydrogen in the presence of reduced nickel gives *o*-toluidine (65, 66).

C. Nitration

The simple nitro derivatives of indole are not obtained through direct nitration but are prepared by indirect methods such as those of Fischer (see section IV B)

by the use of the Japp and Klingemann reaction (210, 211, 259). Oxidation of the nitrosoindoles will yield the corresponding nitro derivatives (4, 6). 3-Nitroindole, which cannot be obtained from indole by the use of nitric acid, may be prepared by the action of ethyl nitrate and sodium ethylate upon indole (6).

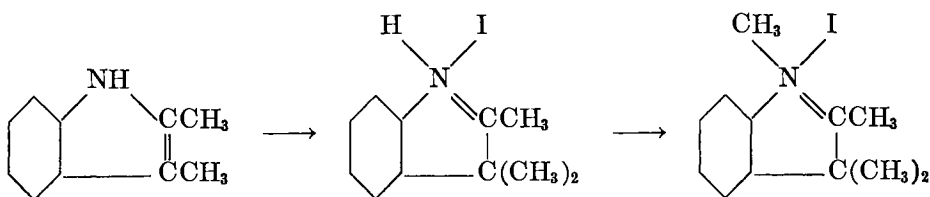
Nencki (279) treated a saturated aqueous solution of indole with fuming nitric acid and obtained a dark red solid which he designated as a "nitrosoindole nitrate" $C_{10}H_{13}(NO)N_2 \cdot HNO_3$. This product does not react like a true nitroso compound, nor does it give a positive Liebermann reaction (417).

D. Halogenation

Direct chlorination and bromination to yield indoles substituted in the benzene nucleus is not feasible; indirect methods of synthesis are necessary, as in the case of the nitro derivatives. Sulfuryl chloride, however, reacts to form 2-chloroindole (265). The addition of iodine in potassium iodide to the aqueous or alcoholic solution of indole causes the precipitation of 3-iodoindole (293, 295); in the presence of sodium bicarbonate this method yields indigo (295) also. Addition of bromine water to indole causes merely the appearance of a non-crystalline turbidity (35).

E. Alkylation

The alkylation of indole has been studied very thoroughly (71), the earliest investigations being those of E. Fischer (127, 130, 131). The difficulties encountered at first in ascribing structural formulas to the products were solved by the work of Brunner (56, 57, 58, 59) and of Plancher (73, 307, 311, 312, 313). It was assumed at first that methylation yielded a dihydroquinoline, but this conclusion was abandoned when it was shown that the 2,3-dimethylindole is first formed and that shifting of the hydrogen atom from the 1- to the 3-position allows further alkylation:



F. Chemical properties aiding in detection and identification

The pine-splinter test of Baeyer (16) consists in dipping a pine shaving into an alcoholic solution of indole which has been saturated with hydrogen chloride; the wood takes on a cherry-red coloration which changes to a brownish red. This effect is not given by indolecarboxylic acids or by 2- and 3-alkyl-substituted indoles (121). Ehrlich's sensitive test (98), which is suitable for the detection of indole in bacterial cultures and in plants, involves the addition of the solution being tested to a 2 per cent solution of *p*-dimethylaminobenzaldehyde; hydrochloric acid is added dropwise. The presence of indole is shown by the appear-

ance of a red coloration. Herter and Foster (168) have devised another color test: a 2 per cent solution of sodium β -naphthoquinonesulfonate is added to an alkaline solution of indole, whereupon a blue-green coloration results; concentration of the solution yields blue crystals. A quantitative determination of indole by color comparison with standard solutions is based upon this method. Further, a sodium nitroprusside test (345, 353) involves adding that reagent to an indole solution; addition of alkali then causes the appearance of a deep violet-blue, which in turn upon acidification produces a pure blue.

An indole-containing solution when treated with concentrated sulfuric acid and formaldehyde gives a violet-red coloration (233). Other aldehydes may be substituted for formaldehyde in this test with the production of various colors (see table 1). Other aliphatic aldehydes also may be used (156).

Oxalic acid melted with indole produces a crimson material which remains stable in aqueous solution and is changed only slightly by alkali (147). Sugars (136, 391) give color effects upon treatment with hydrochloric acid in the pres-

TABLE 1
Colors produced by the reaction of indole with aldehydes

ALDEHYDE	COLOR PRODUCED	REFERENCES
Glyoxylic acid.....	Red	(81, 135)
Vanillin.....	Orange	(277, 370)
Furfural.....	Orange	(135)
<i>p</i> -Nitrobenzaldehyde.....	Red	(48)
Protocatechuic aldehyde.....	Orange-red	(48)
Piperonal.....	Orange-red	(48)
Safrole.....	Greenish yellow	(48)
Cinnamaldehyde.....	Red	(48)

ence of indole. Many other color reactions have also been found to indicate the presence of indole (see, for example, references 75, 76, 149, 273).

The formation of a picrate is suitable for the identification of indole (170); the picrate was first described by Baeyer (18, 23) as consisting of long red glistening needles soluble to an extent in benzene. Compounds are formed by indole with *sym*-trinitrobenzene (341), with sodium bisulfite (170), and with sarcosine anhydride (298).

Pauly and Gundermann (295) have found that a determination of indole by iodimetry appears to be feasible for skatole-free solutions of indole.

IV. SIMPLE DERIVATIVES OF INDOLE

A. General description

All indole derivatives show certain family resemblances to indole (121), but striking changes can be brought about by substitution of groups in the pyrrole ring. Thus, the fecal-like odor of skatole is the most pronounced of all the methylindoles, less pronounced for the 2-methylindole and the 2,3-dimethyl-

indole; 1-methylindole, on the other hand, resembles methylaniline in odor. Introduction of carboxyl groups or phenolic hydroxyl groups causes elimination of the odor, and the naphthindoles are also without odor.

All the common indole derivatives, like indole, form well-defined crystalline picrates, yellow to red in color. Formation of picrates is usually a suitable procedure for identification and purification.

The pine-splinter test is given in varying degrees of sharpness and with the production of various colors by most indoles, failing, however, with indole-carboxylic acids and dialkylindoles having alkyl groups substituted in both the 2- and the 3-positions. Other alkyl derivatives give a cherry-red, while aryl-indoles, including both the phenyl- and naphthyl-indoles give a blue-violet coloration.

Nitrous acid has varying effects upon the different derivatives. 1-Methylindole reacts in a fashion similar to indole, forming a true nitroso compound. However, 2-methyl- and 2-phenyl-indoles give complex products which show no nitroso reactions. The 3-alkyl- and the 2,3-dialkyl-substituted indoles show the anticipated nitrosoamine formation at position 1.

Direct nitration of indole derivatives is generally impracticable, but some cases of successful nitration have been reported. Thus, by treating 2,3-dimethylindole with potassium nitrate and concentrated sulfuric acid at 0°C., Bauer and Strauss (34) obtained 5-nitro-2,3-dimethylindole, which proved to be identical with the product obtained by the Fischer method from the *p*-nitrophenylhydrazone of ethyl methyl ketone. Concentrated nitric acid gives a dinitro derivative with 2-methylindole (413); identical with this dinitroderivative is the compound obtained by direct nitration of 3-nitro-2-methylindole (6). Nitration of skatole gives no definite nitro derivative (34).

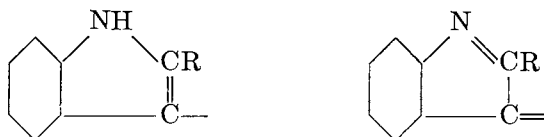
Indole-3-aldehydes can be prepared from indoles having a replaceable hydrogen at the 3-position and also with or without an alkyl or aryl group at the 2-position, by reaction with *N*-methylformanilide in the presence of condensing agents similar to phosphorus oxychloride (191). Certain indoles will also undergo the Gattermann and Hoesch aldehyde synthesis (354).

Indole-3-aldehyde was first obtained, along with harman, by Hopkins and Cole (178) as a result of treatment of tryptophan with ferric chloride. Later, Ellinger (102, 103) prepared it by treatment of indole with chloroform and potassium hydroxide; 3-chloroquinoline was also obtained in this reaction. Boyd and Robson (52) effected its preparation through the action of zinc cyanide upon 2-carbethoxyindole.

The usual condensation reactions are shown by indole-3-aldehyde. Thus, it will condense with hippuric acid to yield the azlactone which can be converted to the indoleacrylic acid (333) or to the amino acid tryptophan (104, 106). Hydantoin will also condense with the aldehyde (53, 235).

Reduction of derivatives, with the exception of the carboxylic acids, yields the dihydroindoles, and may be accomplished by electrolytic reduction, by catalytic hydrogenation, or by the use of acids and metals. The ease of reduction varies: 2,3-dimethylindole is more easily reduced than 2-methylindole, and that more easily than 1-methylindole.

Aldehydes (1 mole) will condense with 2-methylindole (2 moles), as was discovered by Fischer (123), with elimination of water to form leuco bases which yield dyes of the rosaniline type. Condensation with aldehydes may also take place in equimolecular proportions (138) to yield products in which the indole nucleus is contained in either of the following forms:



2-Methylindole has been condensed with various aldehydes (60, 123, 159, 179, 351, 386) and with ketones (350). Skatole will condense with benzaldehyde (159, 397) under rather strenuous conditions, e.g., when zinc chloride is used.

Derivatives of indole, like indole, give completely normal values for their molecular weights in benzene. In naphthalene there are anomalies, as in the cases of indole, skatole, and 2,3-dimethylindole (117).

Acids generally have less effect upon homologs of indole than upon indole itself, and fusion with potash oxidizes them to the respective carboxylic acids.

Indoles having no substituent group in the 1-position react with Grignard reagents to form the indolylmagnesium halides, in a fashion reminiscent of the pyrroles. The indolylmagnesium halides are, in turn, useful in further synthesis; with reagents common in Grignard syntheses, substitution in the 3-position results. In general, other substitution reactions commonly occur, with introduction of groups preferentially at the 3-position.

Of the simple alkyl-substituted indoles, skatole (3-methylindole) and "methylketole" (2-methylindole) deserve special mention. Of these, skatole is found in nature usually where indole is found, and is produced in bacterial cultures under conditions similar to those under which indole is formed. Methylketole, on the other hand, is essentially a synthetic product.

Skatole in the pure form is a white solid, melting at 95°C. and boiling at 266.2°C. at 760 mm.; it has a persistent fecal odor. When crystallized from water or ligroin, it is obtained as glistening leaflets. At 16°C. its solubility in water is 0.45 g. per liter.

Fusion of skatole with alkali gives indole-3-carboxylic acid (72). With sodium in a stream of carbon dioxide, skatole undergoes a Kolbe reaction with the formation of 3-methylindole-2-carboxylic acid (72). With chloroform and alcoholic alkali (103, 254, 316), or with chloroform and sodium ethylate (253, 254), 4-methyl-3-chloroquinoline is formed. Hydrochloric acid (286, 348) or sulfuric acid and acetic acid (349) will polymerize skatole to diskatole. Skatole will condense with benzaldehyde (397) and with cinnamaldehyde (87). It will form a hydrochloride (122). *sym*-Trinitrobenzene (341) and picric acid (281) will form compounds with it. Reduction of skatole with zinc dust and hydrochloric acid yields dihydroskatole (397).

Skatole may be synthesized easily by the Fischer method from the phenylhydrazone of propionaldehyde (8, 121, 122, 261) (*vide infra*); it may also be obtained from 3-nitrocumic acid (119), indigo (19), aniline and glycerol (134),

and *o*-acetylanilidoacetic acid ethyl ester (63), as well as from other sources (28, 39, 218).

Methylketole (2-methylindole) is a solid, melting at 60°C. and boiling at 272°C. at 750 mm.; it has an odor like that of indole. It is soluble in alcohol, but difficultly soluble in water. It gives the pine-splinter test in the presence of hydrochloric acid. Methylketole forms 2-methyl-3-nitrosoindole with isoamyl nitrite (367); this substance can be oxidized to the corresponding nitro compound (4). It gives colored solutions with aldehydes in the presence of hydrochloric acid (156). With chloroform and sodium ethylate, 2-methyl-3-chloroquinoline is obtained, while with bromoform the corresponding bromo compound is formed (254, 255). Reduction with tin and hydrochloric acid converts methylketole to 2-methyldihydroindole (397). Chloroplatinic acid and also picric acid yield crystalline products (25).

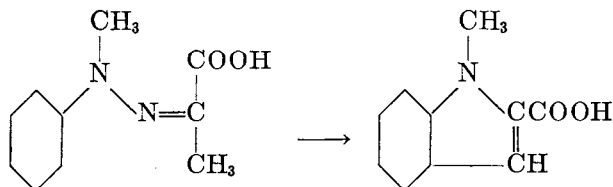
The Fischer method (*vide infra*) may be used for the preparation of 2-methylindole, employing the phenylhydrazone of acetone (121). Other methods of preparation involve aniline and monochloroacetone (283), dihydromethylketole (218), *o*-amidophenylacetone (25), and acetylated *o*-toluidine (192).

For a further summary of the properties of the simpler indole derivatives, see *Biochemisches Handlexikon*, Vol. IV, page 859.

B. The Fischer synthesis of indole derivatives

While the Fischer method may be applied somewhat indirectly to the preparation of indole (*vide supra*), it finds its chief usefulness in the preparation of many and varied indole derivatives. It is in itself very versatile, but it is made even more general by the preparation of otherwise unattainable phenylhydrazones from diazonium salts by the method of Japp and Klingemann (210, 211). In general, Fischer's synthesis may be described as involving the elimination of ammonia from phenylhydrazones, and may be accomplished with the phenylhydrazones of most carbonyl compounds the structures of which allow ring closures to occur.

In 1883, E. Fischer and Jourdan (126) found that when they boiled the methylphenylhydrazone of pyruvic acid with alcoholic hydrogen chloride, they obtained $C_{10}H_9O_2N$ in about 5 per cent yield. Fischer and Hess (125) investigated this compound further and found it to be an indole derivative:

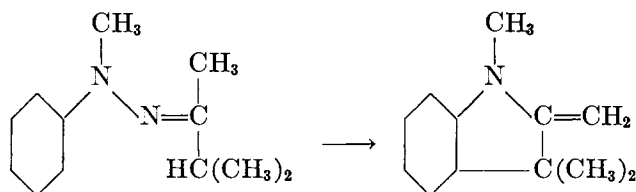


This work was continued by Fischer, who found that zinc chloride was a better catalyst for the reaction, since this catalyst allowed a wider range of applicability (122). The procedure employed by Fischer may be described by citing his preparation of 2-methylindole; this he accomplished by mixing acetone phenyl-

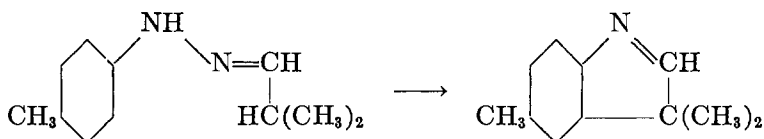
hydrazone with five times its weight of anhydrous zinc chloride, and by heating the mixture to about 200°C. A yield of 60 per cent of 2-methylindole was obtained. Similarly, Fischer obtained in this way a 35 per cent yield of skatole from propionaldehyde phenylhydrazone (121).

Since the time of this early work a number of changes have been introduced into the method, with improvement in the yields. Thus it was found (91) that by the use of an inert solvent such as methylnaphthalene, and by keeping the temperature below 150°C., acetone phenylhydrazone gave a 75 per cent yield of 2-methylindole, propionaldehyde phenylhydrazone an 80 per cent yield of skatole, and the phenylhydrazone of pyruvic acid gave a 60 per cent yield of indole-2-carboxylic acid. Also, the large amounts of zinc chloride used by Fischer were shown to be unnecessary (9). The reaction was found to proceed in the presence of 1 per cent of zinc chloride; cuprous chloride, cuprous bromide, or platinum chloride may also be used. Besides these, a number of other catalysts have been employed: concentrated sulfuric acid by Nef (276), Walker (388), and Reissert and Heller (332); alcoholic sulfuric acid by Wislicenus and Arnold (409); alcoholic zinc chloride by Plancher (306). It has also been found that nickel, cobalt, and copper powder, cobalt chloride, nickel chloride and many other salts catalyze the reaction (234). Grignard reagents have also been used (154).

The ease of indole formation from the various phenylhydrazones varies irregularly; with some, the reaction occurs extremely readily. For example, the cyclohexanone phenylhydrazone undergoes indole formation as a result of gentle warming with aqueous hydrochloric acid. Also Plancher (306) and Jenisch (212) found that the methylphenylhydrazones of isopropyl methyl ketone and isopropyl phenyl ketone undergo ring closure even at room temperature in the presence of alcoholic zinc chloride.

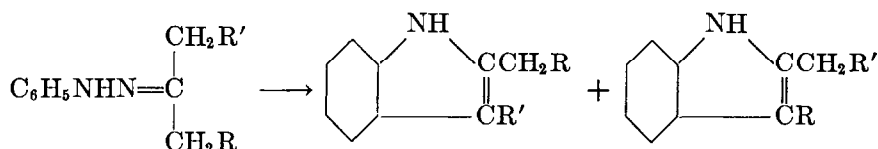


Grgin (158) obtained 3,3,5-trimethylindolenine by warming the *p*-tolylhydrazone of isobutyraldehyde at 60°C. with alcoholic zinc chloride:



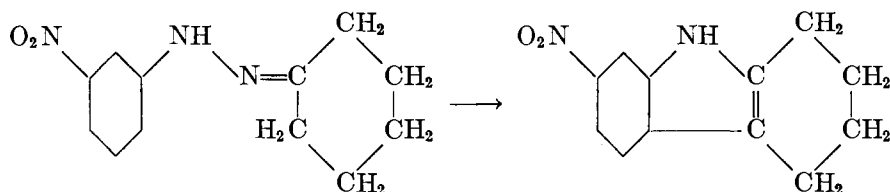
While the Fischer method is extremely varied in its applications, occasional exceptions and limitations should be noted. Acetaldehyde phenylhydrazone would be expected to yield indole, but this has not been realized. Also, phenylhydrazones of β -keto esters more commonly produce pyrazolones. The catalytic

decomposition of arylhydrazones of unsymmetrical ketones would be expected in many instances to lead to a mixture of two products:



This possibility has not been investigated very extensively, but isolated reports indicate only one product in each case. For example: the phenylhydrazone of methyl propyl ketone (9, 121) gives only 2-propylindole; the phenylhydrazone of isopropyl methyl ketone gives only 2,3,3-trimethylindolenine (212, 306); when butyl methyl ketone is used, 2-methyl-3-propylindole is formed (10).

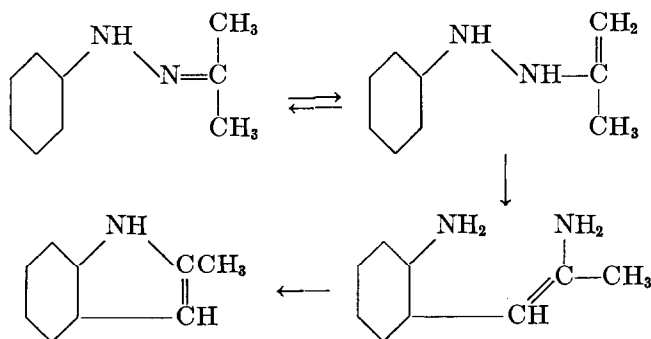
When meta-substituted phenylhydrazines are used as reagents, the possibility of two products being obtained is apparent. In some instances of such indole syntheses the mode of ring closure is not specified (92, 221, 224, 340, 381). However, Borsche found that the *m*-nitrophenylhydrazone of cyclohexanone (51) underwent ring closure to the position para to the nitro group:



The preparation of a tetrahydrocarbazole in the fashion indicated above was first accomplished by Drechsel (88), who used phenylhydrazine and cyclohexanone; Baeyer (21) identified the product as tetrahydrocarbazole. This method of synthesis has been used to quite an extent, but applies most generally to the use of the simpler cyclohexanones. A number of ketones of the terpene group will not give the reaction.

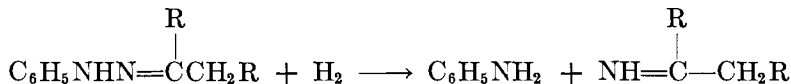
The elucidation of the mechanism of the Fischer synthesis has occupied the attention of many workers in the field. No very critical evaluation of the various postulates that have been advanced will be attempted here, but a statement of some of the suggestions will be of interest.

The mechanism proposed by R. Robinson and G. M. Robinson (337, 338) involves rearrangement before ring closure, and adapts itself quite generally to various specific cases. Its essentials follow:

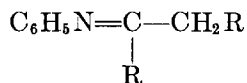


Reddelien (328), on the basis originally of his discovery of the oxidation of acetophenone phenylhydrazone by the action of phenylhydrazine to yield 2-phenylindole, proposed a mechanism which may be described as involving three separate stages:

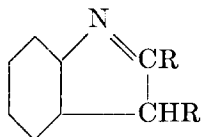
I. Reduction of the phenylhydrazone during the simultaneous oxidation of stage III.



II. Elimination of ammonia from the products of stage I to yield:



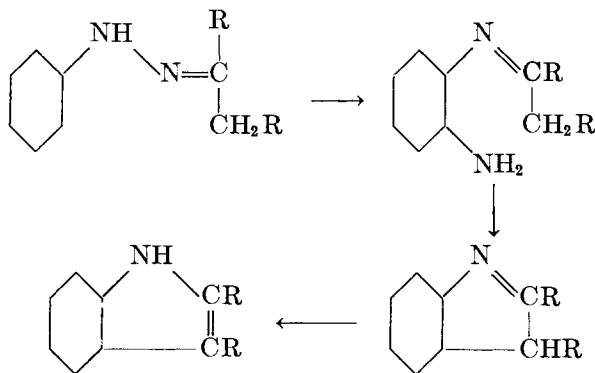
III. Oxidation of the anil of stage II by the action of the original phenylhydrazone to yield the indolenine,



which undergoes a tautomeric shift of hydrogen from position 3 to position 1, producing the indole.

This mechanism requires the assumption of an initial tautomeric shift of hydrogen in the original phenylhydrazone to yield an unsaturated substituted hydrazine, prior to stage I, if it is to explain the formation of 1-alkylindoles by the Fischer method. The Reddelien mechanism has met with considerable criticism; Robinson and Robinson (338), Bodforss (49), and Campbell and Cooper (62) have advanced substantial arguments against it.

The Cohn mechanism (77) fails to explain the fact of formation of 1-alkylindoles, and furthermore would require the formation of 6-substituted indoles from *p*-substituted phenylhydrazones:



Another mechanism, set forth by Bamberger and Landau (29), also fails to explain the formation of 1-alkyl-substituted indoles.

TABLE 2
Alkyl- and aryl-substituted indoles

INDOLES	REFERENCES*
1-Methylindole.....	(249, 148, 124)
2-Methylindole.....	(See section IV ⁷ A)
3-Methylindole.....	(See section IV ⁷ A)
5-Methylindole.....	(326)
6-Methylindole.....	(331)
7-Methylindole.....	(52)
1-Ethylindole.....	(125, 268)
2-Ethylindole.....	(121)
3-Ethylindole.....	(305, 41)
1,2-Dimethylindole.....	(82)
1,2-Dimethyl-5-chloroindole.....	(37)
1,3-Dimethylindole.....	(302, 82)
2,3-Dimethylindole.....	(121, 411, 8, 314, 219, 285)
2,5-Dimethylindole.....	(326, 389)
3,5-Dimethylindole.....	(8)
5,6-Dimethylindole.....	(294)
1,2,3-Trimethylindole.....	(82)
1,2,5-Trimethylindole.....	(37)
2,3,5-Trimethylindole.....	(412)
2,3,7-Trimethylindole.....	(412)
2,3,5,6-Tetramethylindole.....	(83)
2-Methyl-3-ethylindole.....	(121, 308, 285)
2-Ethyl-3-methylindole.....	(309)
1-Ethyl-2-methyl-5-chloroindole.....	(38)
1-Ethyl-2,3-dimethylindole.....	(412)
1-Ethyl-2,5-dimethylindole.....	(38)
1,3-Dimethyl-2-ethylindole.....	(313)
1-Propylindole.....	(268)
1-Isopropylindole.....	(268)
1-Allylindole.....	(270)
2-Isopropyl-3-methylindole.....	(310, 315)
2- <i>tert</i> -Butylindole.....	(313)
1-Benzylindole.....	(7, 86)
3-Triphenylmethylindole.....	(241)
1-Phenylindole.....	(125, 299)
2-Phenylindole.....	(121, 128, 304, 112, 80)
3-Phenylindole.....	(129)
1-Methyl-2-phenylindole.....	(82, 368, 80)
1-Methyl-3-phenylindole.....	(193)
2-Methyl-3-phenylindole.....	(382)
5-Methyl-2-phenylindole.....	(46)
7-Methyl-2-phenylindole.....	(46)
1,2-Diphenylindole.....	(299)
2,3-Diphenylindole.....	(121)
1,2,3-Triphenylindole.....	(335)
1-Methyl-2,3-diphenylindole.....	(47)
7-Methyl-2,3-diphenylindole.....	(47)
2-Anisyl-3-methylindole.....	(165)
2-Anisyl-3,5-dimethylindole.....	(165)
2-Anisyl-3,7-dimethylindole.....	(165)

*Where more than one reference appears, methods of synthesis are indicated first.

TABLE 3
Acid derivatives of indole

ACID DERIVATIVES	REFERENCES*
Indole-2-carboxylic acid.....	(330, 74, 251, 121, 126, 303, 155, 262)
1-Methyl-2-indolecarboxylic acid.....	(125, 40)
3-Methyl-2-indolecarboxylic acid.....	(410, 110)
3-Hydroxymethyl-2-indolecarboxylic acid (lactone).....	(163)
5-Methyl-2-indolecarboxylic acid.....	(326)
6-Methyl-2-indolecarboxylic acid.....	(330)
7-Methyl-2-indolecarboxylic acid.....	(326, 52)
5,6-Dimethyl-2-indolecarboxylic acid.....	(294)
1-Ethyl-2-indolecarboxylic acid.....	(125, 269)
1-Propyl-2-indolecarboxylic acid.....	(268)
1-Allyl-2-indolecarboxylic acid.....	(270)
1-Isopropyl-2-indolecarboxylic acid.....	(268)
1-Isobutyl-2-indolecarboxylic acid.....	(268)
1-Isoamyl-2-indolecarboxylic acid.....	(268)
1-Phenyl-2-indolecarboxylic acid.....	(125)
1-Benzyl-2-indolecarboxylic acid.....	(7)
Indole-3-carboxylic acid.....	(102, 416, 395)
1-Methyl-2-amino-3-indolecarboxylic acid.....	(329)
2-Methyl-3-indolecarboxylic acid.....	(72, 389)
1,2-Dimethyl-3-indolecarboxylic acid.....	(82, 226)
2,5-Dimethyl-3-indolecarboxylic acid (ethyl ester).....	(389)
2,7-Dimethyl-3-indolecarboxylic acid (ethyl ester).....	(389)
1-Allyl-2-methyl-3-indolecarboxylic acid.....	(270)
2,4-Indoledicarboxylic acid.....	(340)
1-Methyl-2,3-indoledicarboxylic acid.....	(329)
1-Benzyl-2,3-indoledicarboxylic acid.....	(86)
Indole-3-acetic acid.....	(See section V)
Indole-3-aminoacetic acid.....	(27)
1-Methylindole-3-acetic acid.....	(302, 226)
2-Methylindole-3-acetic acid.....	(121)
1,2-Dimethylindole-3-acetic acid.....	(282)
β -(Indole-1)propionic acid.....	(190)
β -(2-Methylindole-1)propionic acid.....	(190)
α -(Indole-2)propionic acid (ethyl ester).....	(389)
α -(Indole-3)propionic acid.....	(100)
β -(Indole-3)propionic acid.....	(100, 190, 217, 260, 174, 419, 262)
β -(Indole-3)- α -aminopropionic acid.....	(See section V)
γ -(Indole-3)butyric acid.....	(194, 275, 419)
δ -(Indole-3)valeric acid.....	(258)
Indole-3-glyoxylic acid.....	(27)
1-Methyl-2-(3',4'-dimethoxyphenyl)indole-3-acetic acid.....	(69)

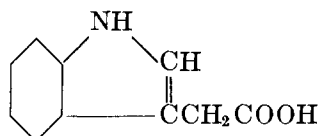
*Where more than one reference appears, methods of synthesis are indicated first.

C. Alkyl, aryl, and acid derivatives of indole

The alkyl and aryl derivatives of indole are listed in table 2, while the acid derivatives are given in table 3.

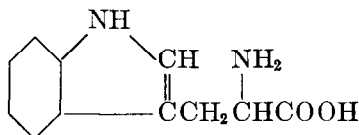
V. NATURAL PRODUCTS CONTAINING THE INDOLE NUCLEUS

The indole nucleus is found to be present in a varied group of products of natural occurrence in both the animal and the vegetable kingdoms. Most of these products show marked physiological activity, and some are extremely complex in structure.

A. *Heteroauxin* (*indole-3-acetic acid*)

This acid is important in plant physiology because of the part it plays as a promoter of the growth of seedlings. It has been isolated from urine by Kögl and his collaborators (230, 231, 232); other sources of the acid are yeast and moulds. The compound is soluble in alcohol, ether, benzene, and slightly soluble in cold water. Crystallized from water or benzene it is obtained as leaflets, melting at 165°C. When heated above its melting point, the compound loses carbon dioxide to form skatole. As a color test, the Adamkiewicz-Hopkins reaction can be used (407).

Heteroauxin can be obtained by bacterial action upon tryptophan (166), albumin (346), or milk (169). A convenient synthesis, however, is by the method of Majima and Hoshino (256), who treated indolylmagnesium iodide with chloroacetonitrile and hydrolyzed the resulting indole-3-acetonitrile. Another method of synthesis is that of King and L'Ecuier (226), who used as starting materials benzenediazonium chloride and α -acetoglutaric acid ethyl ester; the successive steps of hydrolysis, Fischer indole formation, and partial decarboxylation produce the product. The acid has also been synthesized by Tanaka (377, 378). Indole-3-acetic acids, in general, may be prepared from indoles having an unsubstituted 3-position through the reaction of formaldehyde and hydrocyanic acid and subsequent hydrolysis of the resulting nitrile (189).

B. *Tryptophan*

Tryptophan, one of the essential amino acids, as isolated from natural sources exists as the levo isomer in the form of colorless hexagonal leaflets. Various melting points have been reported for the levo form (273°C., 289°C., 293°C.), while for the racemic mixture melting points about 30° lower have been noted. Dry distillation of tryptophan results in decomposition, with the formation of both indole and skatole, although strong heating yields indole alone.

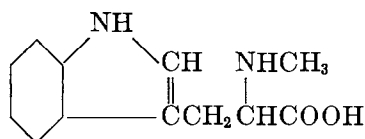
Oxidation with ferric chloride gives two products, C_8H_7NO (indole-3-aldehyde) and $C_{12}H_{10}N_2$ (harman), while ozone and chromic acid cause breakdown of the molecule. Ultraviolet light causes the formation of indole-3-acetic acid (45).

Tryptophan gives several well-defined color reactions. Thus, chlorine or bromine water produces a red-violet coloration (44, 380), while the Adamkiewicz reaction (1, 2), Ehrlich's reaction (99), and the pine-splinter test also apply.

Tryptophan as the levo isomer may be isolated from certain proteins, but such hydrolytic procedure requires care in the choice of agents. For example, acid agents yield condensation products (60), and barium hydroxide gives the racemic mixture. Enzymatic hydrolysis using trypsin (288) yields *l*-tryptophan, and it can also be obtained from casein (78). In both of these latter cases use is made of the formation of an insoluble compound with mercuric sulfate. There are many sources from which tryptophan may be obtained (177, 247, 248, 290, 291, 292, 334).

The first synthesis of *dl*-tryptophan was accomplished by Ellinger and Flamand (104, 106), who carried out an Erlenmeyer synthesis on indole-3-aldehyde. This was condensed with hippuric acid in the presence of acetic anhydride and sodium acetate to yield the azlactone, which upon subsequent hydrolysis and reduction gave the racemic mixture. A similar synthesis by Kotake (235) employed indole-3-aldehyde and hydantoin; this method was improved by modifications introduced by Boyd and Robson (53).

C. "Abrine"¹ (*d*- α -methylamino- β -(indolyl-3)propionic acid)



This compound was first encountered as a result of its isolation from the seeds of *Abrus precatorius* Linn (398). Later, in 1932, it was isolated in pure state from the same source and investigated by Ghatak and Kaul (142, 143). Its structure was assigned by Hoshino (180) after he had accomplished decarboxylation of the compound and identified the resultant as monomethyltryptamine, which he had previously synthesized (182, 183). "Abrine" and tryptophan upon complete methylation both yield the same product (343).

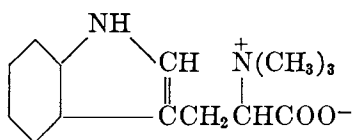
"Abrine" in the *d*-form after crystallization from water as colorless prisms melts with decomposition at 295°C.; the *dl*-form melts at 245°C. with decomposition (271).

The compound has been synthesized by Gordon and Jackson (152) and by Miller and Robson (271), starting with indole-3-aldehyde and 1-methylhydantoin. These compounds condensed under the influence of piperidine to form

¹ It has been suggested (271) that the name abrine be dropped from use to avoid confusion with "abrin," which has been applied for years to a mixture of two poisonous proteins, a paraglobulin and a phytoalbuminose, obtained from *Abrus precatorius* Linn.

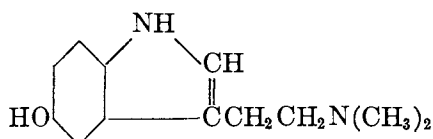
5-(indolal-3')-1-methylhydantoin. Reduction to the indolyl product and subsequent hydrolysis completed the synthesis of the *dl*-compound.

D. Hypaphorine



Hypaphorine was discovered by Greshoff (157) in the seeds of *Erythrina hypaphorus* Boerl. The name and molecular formula ($C_{14}H_{18}O_2N_2$) were assigned by Greshoff. The study of its constitution was undertaken by van Romburgh (343) who obtained, by the methylation of tryptophan, a compound resembling hypaphorine closely; later van Romburgh and Barger obtained complete proof of its identity (343). The racemic form has been synthesized by Cahill and Jackson (61).

E. Bufotenine

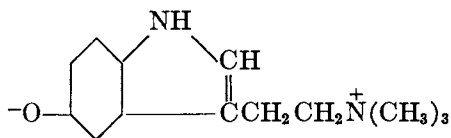


Phisalix and Bertrand in 1893 (300, 301) obtained an amorphous base from the secretions of *Bufo vulgaris* which they named bufotenine. Later, in 1920, Handovsky (162) obtained the base from the same source as a crystalline compound. Later methods of isolation made use of the formation of an insoluble flavianate (213).

The constitution of bufotenine was investigated and established by Wieland and coworkers (400, 402) through the synthesis, from 5-methoxyindolyl-3-acetonitrile, of the product of methylation of bufotenine. Hoshino and Shimodaira (183, 184) have synthesized bufotenine itself from the same acetonitrile derivative.

Bufotenine crystallizes from acetone-ether solutions; it melts at 146–147°C., and may be distilled without decomposition at 320°C. at 0.1 mm. Its picrate melts at 178°C. (402). Bufotenine has a pronounced effect upon the blood pressure (70).

F. Bufotenidine



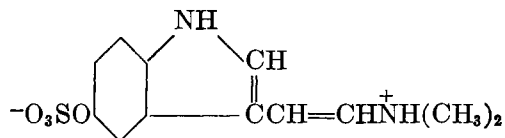
Bufotenidine was isolated as the flavianate in 1931 by Mittasch (400) from the extract of the Chinese toad. Its structural relationship to bufotenine was

shown by Wieland, Konz, and Mittasch (402); methylation of both compounds yielded the same product.

TABLE 4
Some complex natural products containing the indole or dihydroindole grouping

PRODUCTS	REFERENCES
Harmine.....	(259, 366, 3, 164, 296, 133, 132, 139)
Harman.....	(133, 178, 220, 259, 204, 366, 3, 364, 365, 296, 297)
Harmaline.....	(259, 366, 132, 223, 140, 133)
Harmalol.....	(150, 133)
Harmol.....	(133, 325)
Harmalan (dihydroharman).....	(259, 366)
Norharman.....	(220)
Physostigmine (eserine).....	(216, 215, 319, 185, 369, 172)
Eseroline.....	(216, 319)
Geneserine.....	(318)
Eserethole.....	(182, 215, 216, 227, 181, 369)
Desoxyeseroline.....	(215)
Noreserethole.....	(339)
Noresermethole.....	(228)
Methyleserethole.....	(229)
Ergotoxine.....	(30, 31, 357, 197, 198, 202, 79)
Ergotinine.....	(30, 31, 357, 197, 198, 79)
Ergotamine.....	(357, 198, 202, 79)
Ergotaminine.....	(357, 198, 79)
Ergonovine.....	(97, 225, 372, 373, 199, 374, 79, 375, 356)
Ergometrinine.....	(361, 79, 374)
Ergine.....	(358, 359, 196, 360, 79)
Isoergine.....	(362, 79)
Lysergic acid.....	(195, 196, 360, 200, 225, 201, 203, 206, 362, 208, 207, 209, 205)
Isolysergic acid.....	(362, 79)
Yohimbine.....	(161, 137, 32, 118, 327, 33, 160)
Evodiamine.....	(13, 14, 12)
Rutecarpine.....	(11, 12, 287)
Strychnine.....	(267, 246, 237, 238, 239, 236, 272, 176, 245)
Brucine.....	(267, 246, 176, 245)

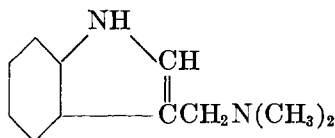
G. Bufothionine



In 1930, Wieland and Vocke (403) isolated a compound, containing both nitrogen and sulfur, from the extract of skins of Japanese toads and gave the substance the name bufothionine. It has also been isolated from the skin of the South American toad, *Bufo arenarum* (402), and from *Bufo marinus* (214).

Hydrolysis of the compound produces sulfuric acid with the formation of a compound having phenolic properties. Wieland (404) showed the relationship of the latter compound (dehydrobufotenine) to bufotenine by its hydrogenation to yield bufotenine. No synthesis of bufothionine has been reported.

H. Gramine (donaxine)



Von Euler and Hellström (114) in 1932 isolated a base from the germ of Swedish barley which they recognized as an indole derivative from the spectroscopic measurements of Hellström (115). Later, in 1935, the substance was named gramine (116); in the same year Orechhoff and Norkina (289) reported isolation of a similar substance from the Asiatic reed, *Arundo donax* L., and named their substance donaxine. Von Euler, Erdtman, and Hellström (113) showed the two compounds to be identical. The constitution of gramine was established, after several attempts at its degradation (252), by the synthesis of Wieland and Hsing (401), using indolyl-1-magnesium iodide. Kühn and Stein (242) prepared it by condensing indole with formaldehyde and dimethylamine.

I. More complex natural products

Among the more complex naturally occurring products of the alkaloid type, and compounds derived from them, there are many which include in their structures the indole or dihydroindole grouping. A detailed consideration of the chemistry of these compounds falls outside the scope of this review, but the names of a number of these products and references to principal articles concerning them are included in table 4.

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