INDOLES

PART THREE

This is the twenty-fifth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

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INDOLES
PART THREE

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The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

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INDOLES

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CHAPTER VIII

Hydroxyindoles, Indole Alcohols, and Indolethiols

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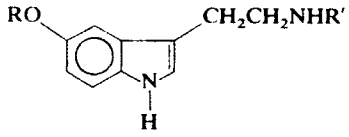
I. Introduction

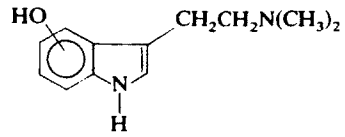
Sections II–VII of this chapter review the synthesis and reactions of indoles substituted in the benzene ring (positions 4, 5, 6, or 7) with one or more hydroxyl or alkoxyl groups. Section VIII treats the synthesis and reactions of the formally related but otherwise distinct class of 1-hydroxyindoles, and Sections IX and X cover the synthesis and reactions of the indole alcohols and thiols, respectively. The literature is covered thoroughly through 1973 with some additions (see addenda) through 1977.

The hydroxyindoles and their methyl or benzyl ethers have assumed great importance as synthetic precursors of such physiologically active hydroxytryptamines as the hormones serotonin (**1**) and melatonin (**2**), and the naturally occurring hallucinogens psilocin (**3**), bufotenine (**4**) and psilocybin (**5**). The hydroxy- and alkoxytryptamines are themselves important intermediates in the synthesis of the alkaloids physostigmine,[304] reserpine,[61,87,231,321a] harmaline,[553,280,302] or harmaline analogues.[88,301,554]

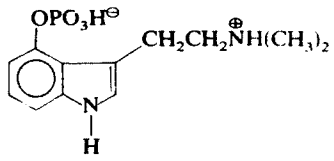
Hydroxyindoles are of added importance in alkaloid chemistry as frequently encountered degradation products, for example, physostigmol



1; R = H; R' = H
2; R = CH_3; R' = $COCH_3$



3; 4-isomer
4; 5-isomer



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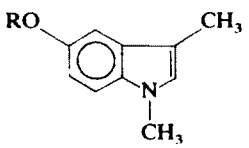
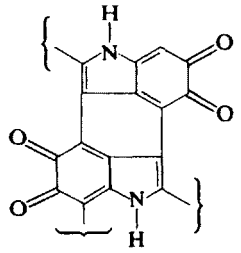


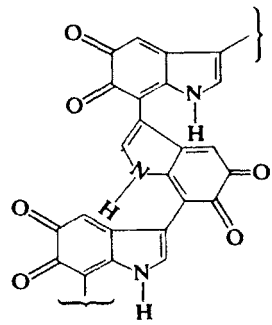
6; R = CH_3, C_2H_5

ethers (**6**)[1a,b,20,54] from eseroline (**325a**) ethers, 3-ethyl-5-methoxyindole from aricine,[2] 1,2-dimethyl-3-ethyl-5-hydroxyindole from ibogaine,[3] and 5-hydroxyindole from violacein[353] or sarpagine.[371] A number of alkoxyindolines have been synthesized for study as physostigmine analogues[38,50]; some are reported to have appreciable activity.[38] Hydroxyindoles are also employed as models in the interpretation of the uv spectra of hydroxylated indole alkaloids.[4,5,28,445]

Furthermore, hydroxyindoles have been used as laboratory models for the study of the melanization process, either in furnishing substrate analogues (e.g., *C*-methylated 5,6-dihydroxyindoles) or modified melatonins.[286,495] It has been primarily through studies using the former that investigators have been able to propose partial structures for melanin (e.g., **7a**[6] or **7b**[7]) (see Section VII.B.2). Most syntheses of the hydroxytryptophans—important intermediates in the metabolism of tryptophan—rely on simple hydroxyindole intermediates.



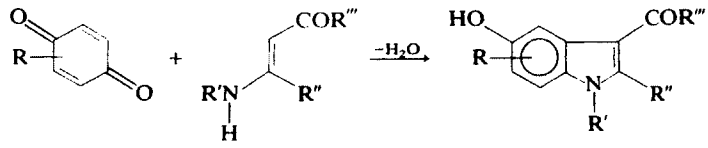
7a



7b

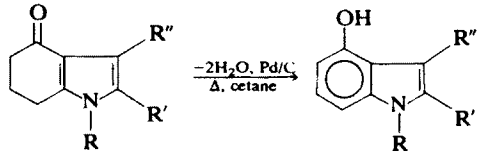
Synthetic schemes leading directly to hydroxyindoles are few in number and are restricted to the preparation of specific indole systems. Examples are the Nenitzescu synthesis of 5-hydroxyindoles (eq. 1), the dehydrogenation of 4-oxotetrahydroindoles to 4-hydroxyindoles (eq. 2), the synthesis of 6-hydroxyindoles by alkaline decomposition of adrenochrome semicarbazones (eq. 3), and the preparation of 5,6-dihydroxyindoles by reduction of adrenochromes (eq. 4), which result in turn from the oxidation of adrenaline derivatives.

Except for these cases, the hydroxyindoles have been traditionally obtained by demethylation of methoxyindoles with HBr or aluminum halides (see Section VII.D) or much more satisfactorily, in modern practice, by hydrogenolysis of benzyloxyindoles. Catalytic dehydrogenation of alkoxyindolines has recently been developed as a practical route to the alkoxyindoles (Section III.H.2.a).



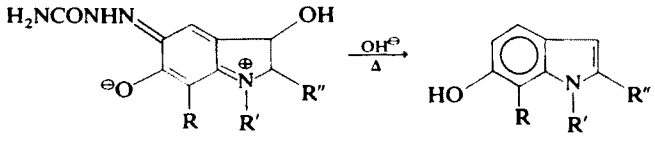
(1)

R or R′ = H, alkyl; R″ = alkyl; R‴ = OC_2H_5, CH_3



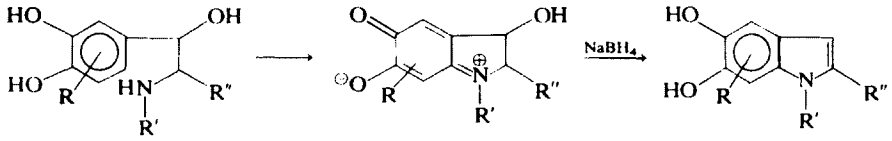
(2)

R, R′, R″ = H, alkyl



(3)

R, R′, R″ = H, CH_3



(4)

R, R′ = H, alkyl; R″ = H, CH_3

Most alkoxyindoles have been made by application of the venerable synthetic procedures of indole chemistry. Synthetic reactions that seem particularly suitable are the Fischer cyclization of alkoxyphenylhydrazones prepared either from alkoxyphenylhydrazines and carbonyl compounds or alkoxybenzenediazonium salts and acetoacetic ester derivatives (the Japp–Klingemann reaction); the Reissert reduction of alkoxy-2-nitrophenylpyruvates; the reduction of alkoxy-substituted 2,β-dinitrostyrenes, and lastly, the Bischler synthesis using alkoxyanilines.

Reactions that have been successfully employed but that have received less application are reduction of alkoxy-substituted 2-nitrobenzylnitriles

or 2-nitrophenylacetones; routes employing the dehydrogenation of 1-acylindolines; reduction of alkoxy-substituted oxindoles, dioxindoles, or isatins with complex metal hydrides; and procedures based on the ring contraction of quinoline derivatives and the ring closure of *m*-chloroalkoxyphenylethylamines to alkoxyindolines via "aryne" intermediates.

A recently introduced synthesis employing the reaction between alkoxyanilines and the chlorine complexes of appropriate α-methylthio aldehydes or ketones has a number of advantages over classical procedures and may in time supplant them as a route to 2-, 3-, or 2,3-substituted alkoxyindoles.[867]

One indole synthesis of general utility, the Madelung cyclization, is apparently not applicable to the synthesis of alkoxyindoles, presumably because of the strongly alkaline conditions required.[34,331]

The above syntheses all start from alkoxy-substituted non-indole precursors and generally involve several steps, very often including a decarboxylation. There do exist, however, scattered reports on the direct hydroxylation of the indole benzene ring in simple indoles, tryptamines, or tryptophan. This topic is considered first.

II. Direct Hydroxylation of the Indole Benzene Ring

A. The "Udenfriend" and Related Hydroxylating Systems

In 1954, Udenfriend and co-workers reported[8] that 5-hydroxytryptamine and an isomeric hydroxytryptamine, tentatively identified as 7-hydroxytryptamine, were produced in low yield when tryptamine was exposed to a hydroxylating system comprised of air (or oxygen), ferrous ion, EDTA, and ascorbic acid in a neutral phosphate buffer. This system has since become known as Udenfriend's model hydroxylating system.

Several groups have reported the hydroxylation of tryptophan with this system, but disagree about the identity of the resulting hydroxylated products. Dalgliesh[9a,b] claimed to have obtained 5-hydroxytryptophan and an isomer presumed to be 7-hydroxytryptophan on the basis of Udenfriend's results with tryptamine. No oxindoles or kynurenines could be detected. Wieland and co-workers, on the other hand, reported[10] that the major reaction product (25%) was oxindole-β-alanine with extremely low yields of 5-hydroxytryptophan (0.4%), 6-hydroxytryptophan (0.6%), and 6-hydroxyoxindole-β-alanine (0.6%). Similar results were noted with simple tryptophan-containing peptides. Eich and Rochelmeyer, in a careful but qualitative study, reported[11] that the Udenfriend system afforded

all four hydroxytryptophans. No mention was made of oxindoles, although it seems likely that these could have been missed in the work-up procedure.

Szara and Axelrod have described the 6-hydroxylation of N^{ω},N^{ω}-dimethyltryptamine,[14] and Kveder and McIsaac, the 6-hydroxylation of tryptamine using the Udenfriend system.[15] No mention of other isomers was made in either case. Melatonin failed[15] to undergo hydroxylation with the Udenfriend system. Acheson and King report that indole-3-carboxylic acid is hydroxylated to a mixture of 5- and 6-hydroxyindole-3-carboxylic acid and products of pyrrole ring cleavage.[362]

Indole was hydroxylated[11] to a mixture of the four possible hydroxyindoles in the following relative yields: 4-hydroxy- (35%), 5-hydroxy- (20%), 6-hydroxy- (35%), and 7-hydroxyindole (10%). Horning and co-workers have shown[12,13] that skatole gives a mixture of all four hydroxyskatoles when hydroxylated with the Udenfriend system in aqueous acetone. In addition, 3-methyloxindole and *o*-formamidoacetophenone were detected.

When hydrogen peroxide was used instead of oxygen in the Udenfriend system, Eich and Rochelmeyer reported achieving a *preparative* hydroxylation of indole.[11] The four hydroxyindoles were formed in 16% yield and were separated by preparative thin-layer chromatography to give 4-hydroxy- (25%), 5-hydroxy- (33%), 6-hydroxy- (25%), and 7-hydroxyindole (17%). The significantly different distribution of isomers with this system (a modified Fenton reagent) from that observed with the Udenfriend system implicates different hydroxylating species.[11]

Another system closely related to the Fenton reagent—ferrous ion chelated with polyphosphate and hydrogen peroxide in neutral phosphate buffer—has been employed by Nofre and co-workers in the hydroxylation of tryptophan and indoleacetic acid.[16] 5-Hydroxytryptophan and presumably 7-hydroxytryptophan are formed from the former and 5-hydroxyindole-3-acetic acid from the latter. 5-Hydroxyindole-3-acetic acid was also said to arise from the hydroxylation of tryptamine, although no other reaction products were mentioned. Employing another Fenton-type system (ferrous ion chelated with EDTA and hydrogen peroxide in a neutral phosphate buffer), Nofre and co-workers succeeded in identifying[17] eight products among the 13 or so produced. 5-Hydroxytryptophan, 3-hydroxy- and 5-hydroxykynurenine, and kynurenine were among the major products. In addition, fragments resulting from cleavage of the side chain (e.g., aspartic acid, alanine, and serine) were detected. Nofre and co-workers made the significant observation that greatly different results were obtained using the same hydroxylating system with the rigorous exclusion of air. The yield of 5-hydroxytryptophan increased, but the

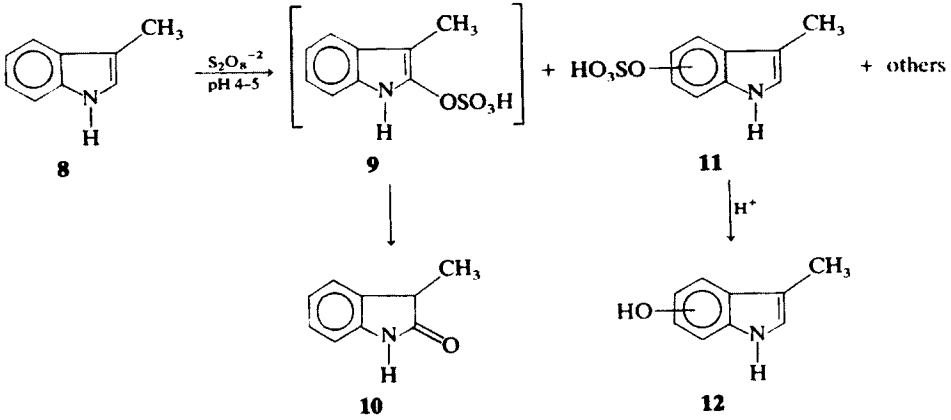
hydroxykynurenines were absent and kynurenine was formed in much lower yields.

Hydroxylation of tryptophan using ferrous ion chelated with polyphosphate and the oxidant, tetrahydropteridine, in a neutral phosphate buffer gave 5-hydroxytryptophan in 0.04–0.2% yield, along with an equivalent yield of melanin.[18a,b] Products of pyrrole ring cleavage, including kynurenine (0.5%) and 3-hydroxykynurenine (0.25%), were also isolated.

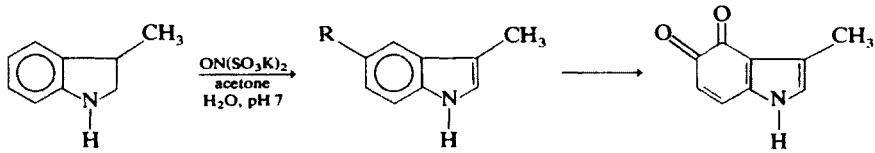
B. Persulfate and Other Oxidants

The action of alkaline potassium persulfate on tryptophan resulted only in products of pyrrole ring cleavage, for example, anthranilic acid, 3-hydroxyanthranilic acid sulfate (and probably the 5-hydroxy isomer), and *o*-aminophenol. Indole is converted to indoxyl sulfate.[19]

Under weakly acidic conditions, however, skatole (**8**) is reported[21] to give a 38% yield of 3-methyloxindole (**10**), probably via 2-hydroxyskatole-*O*-sulfate (**9**) and a mixture of hydroxyskatole-*O*-sulfates (**11**). The latter mixture is identical to the hydroxyindoles resulting from the Udenfriend hydroxylation of skatole,[12] subsequently shown to consist of all four hydroxyskatoles (**12**) (Scheme 1).[13] The same result was obtained by Heacock and Mahon[22] who identified the hydroxyskatoles after acid hydrolysis of the sulfates; a sulfatase assay had to be abandoned when it was discovered that 4-hydroxyskatole sulfate resisted hydrolysis. The yield of either 6- or 7-hydroxyskatole was estimated to be higher than that of 5-hydroxyskatole. In addition, the formation of



Scheme 1



13 **14a; R = OH** **15**
14b; R = H

Scheme 2

3-methyloxindole and of two products of pyrrole ring cleavage, *o*-formamidoacetophenone and *o*-aminoacetophenone, was reported.

The only report of anything approaching the selective introduction of an oxygen function into the benzene ring of an indole is that by Teuber and Staiger[23a,b] who found that the action of potassium nitrosodisulfonate (Fremy's salt) on 2,3-dihydroskatole (**13**) in aqueous acetone at pH 7 gave 5-hydroxyskatole (**14a**) and skatole (**14b**), each in about 25% yield (Scheme 2). Similarly, 2-phenyl-2,3-dihydroindole gave 2-phenyl-5-hydroxyindole (68%) and 2-phenylindole (10%). Treatment of the hydroxyindoles with excess reagent afforded 4,5-indolequinones (e.g., **15**) in good yields.

III. Synthesis of Hydroxyindoles

A. Fischer Cyclization

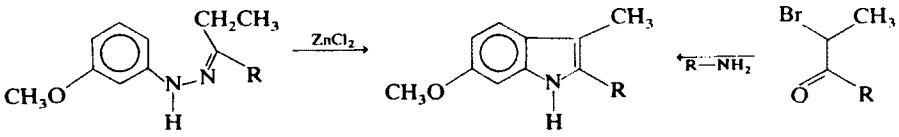
1. *Ketones and Aldehydes*

The Fischer cyclization of the *p*-methoxyphenylhydrazone of acetone proceeds poorly under the usual catalysis with $ZnCl_2$. Chapman and co-workers obtained[24] only a 1% yield of 2-methyl-5-methoxyindole and Bell and Lindwall reported[25] their failure to isolate indoles using acetone *o*- or *p*-methoxyphenylhydrazone. The former phenylhydrazone with $ZnCl_2$ in acetic acid afforded only a 9% yield of 2-methyl-7-methoxyindole.[26] Späth and Brunner modified[27] the usual Fischer procedure and used $ZnCl_2$ without a solvent at 110°, distilling the indole under vacuum as it formed. This procedure gave 2-methyl-5-methoxyindole in 43% yield from the acetone *p*-methoxyphenylhydrazone.[27] Bell and Lindwall reported a 20% yield of the same indole using this procedure.[25]

When applied to propionaldehyde *p*-methoxyphenylhydrazone or *N*-methyl-*N*-*p*-methoxyphenylhydrazone, this procedure afforded 3-methyl-5-methoxyindole[27] and 1,3-dimethyl-5-methoxyindole[20] (54%).[27] Using $ZnCl_2$ in acetic acid, Cook and co-workers reported[26] a 30% yield of

product in the former reaction and King and Robinson have described[20] the successful cyclization of the latter phenylhydrazone with 15% sulfuric acid in ethanol.

Späth and Brunner reported that acetone *m*-methoxyphenylhydrazone afforded a product assumed to be 2-methyl-6-methoxyindole in 36% yield.[27] They considered cyclization *para* to the methoxy group—affording the 6-methoxyindole—more likely than cyclization *ortho* to this group—giving the 4-methoxy isomer—although no structural proof was offered. The assumption that *para* substitution predominates in the Fischer cyclization of *m*-methoxyphenylhydrazones has been accepted by most workers and has received some experimental[29] and theoretical[30] support. Ockenden and Schofield treated[29] the *m*-methoxyphenylhydrazones of butanone and of deoxybenzoin with HCl and acetic acid and obtained products in 25% and 32% yield, respectively. Ozonolysis of these products was carried out in an attempted structure proof but the results were ambiguous and structural assignments were finally made on the basis of their experience with other *m*-substituted phenylhydrazones. They concluded that the major products were 6-methoxyindoles and the minor product, isolated in the butanone reaction, was 2,3-dimethyl-4-methoxyindole.[29] Vejdělek also showed that a mixture of 6- and 4-methoxy-2,3-dialkylindoles was formed when the *m*-methoxyphenylhydrazones of butanone or 2-pentanone were cyclized with HCl in acetic acid.[31] In the former reaction, an 82% overall yield of indoles was obtained, and in the latter reaction the two isomeric methoxy-2-methyl-3-ethylindoles were obtained in 19 and 27% yields. No attempt was made to assign structures. Mentzer observed[32] that the propiophenone *m*-methoxyphenylhydrazone **16** on treatment with $ZnCl_2$ gave the same product, presumably the 6-methoxyindole derivative **17**, as was obtained from the Bischler cyclization of *m*-anisidine and the bromoketone **18**.



16 **17**; R = 4-$CH_3OC_6H_4$ **18**

Neuss and co-workers have claimed[28] without any evidence that cyclization of butanone *m*-methoxyphenylhydrazone (neat, with HCl) afforded 2,3-dimethyl-6-methoxyindole in 58% yield. Related to the question of the preferred direction of ring closure of *m*-methoxyphenylhydrazones is the observation by Tomlinson and coworkers[33] that deoxybenzoin and 2-chloro-5-methoxyphenylhydrazones

failed to cyclize in an attempted synthesis of 2,3-diphenyl-4-methoxy-7-chloroindole.

The most widely used procedure for the cyclization of alkoxyphenylhydrazones would appear to be HCl in anhydrous or aqueous acetic acid, although Keglevic and co-workers have recently reported[34] the formation of 3-methyl- and 3-ethyl-5-benzyloxyindole in 54 and 53% yields, respectively, using 25% acetic acid with *no* added mineral acid. Boron trifluoride etherate was found to be unsatisfactory for the cyclization of methoxyphenylhydrazones.[29] According to an early report, $NiCl_2$ is a good catalyst for the synthesis of 2-phenyl-5-methoxyindole.[35]

On treatment with HCl in acetic acid, butanone *p*-methoxyphenylhydrazone cyclizes to 2,3-dimethyl-5-methoxyindole in 60%[29] and 52%[31] yields. The corresponding phenylhydrazone of deoxybenzoin gave[29] 2,3-diphenyl-5-methoxyindole in 21% yield.

Vejdělek has described[31] the cyclization of butanone and 2-pentanone *o*-methoxyphenylhydrazones to the 2,3-dialkyl-7-methoxyindoles in 47 and 51% yields. In the hands of Borsche and Groth, the former compound with HCl in 10% aqueous acetic acid gave 2,3-dimethyl-7-methoxyindole in 57% yield.[36]

The closely related catalyst, H_2SO_4 in acetic acid, has been used in the cyclization of butanone *N*-methyl-*N*-*p*-methoxyphenylhydrazone to 1,2,3-trimethyl-5-methoxyindole with a 64% yield.[38] Robertson and co-workers have reported the synthesis of the 2-phenyl-3-methyl, 2-methyl-3-phenyl, and 2,3-diphenyl derivatives of 5-methoxyindole in 25, 24, and 68% yields, respectively, on cyclization of the *p*-methoxyphenylhydrazones of propiophenone, phenylacetone, and deoxybenzoin with HCl in ethanol.[37] The same catalyst produced 1,2-dimethyl-5-methoxyindole in 37% yield from acetone *N*-methyl-*N*-*p*-methoxyphenylhydrazone.[39] The same phenylhydrazine derivative of 2-pentanone was cyclized by Schlittler and co-workers using $ZnCl_2$ under reduced pressure to prepare 1,2-dimethyl-3-ethyl-5-methoxyindole in 34% yield.[3] Likewise, acetophenone *N*-ethyl-*N*-*p*-ethoxyphenylhydrazone on treatment with $ZnCl_2$ in acetic acid gave 1-ethyl-2-phenyl-5-ethoxyindole in 30% yield.[40]

In an early investigation of melanin formation, Clemo and Weiss prepared 2,3-dimethyl-5,6-methylenedioxyindole as the precursor of the 5,6-dihydroxyindole derivative.[41] Fischer cyclization of butanone 3,4-methylenedioxyphenylhydrazone with HCl in acetic acid afforded the indole in 62% yield. Removal of the methylene group was effected with 75% H_2SO_4. Robertson and co-workers applied the same procedure to butanone 3,4-dimethoxyphenylhydrazone and obtained 2,3-dimethyl-5,6-dimethoxyindole in 33% yield.[42] Here as in the previous case, cyclization

para, rather than *ortho*, to the 3-methoxy group is observed. The dimethoxyindole could be demethylated in 78% yield with $AlBr_3$ in benzene.[42]

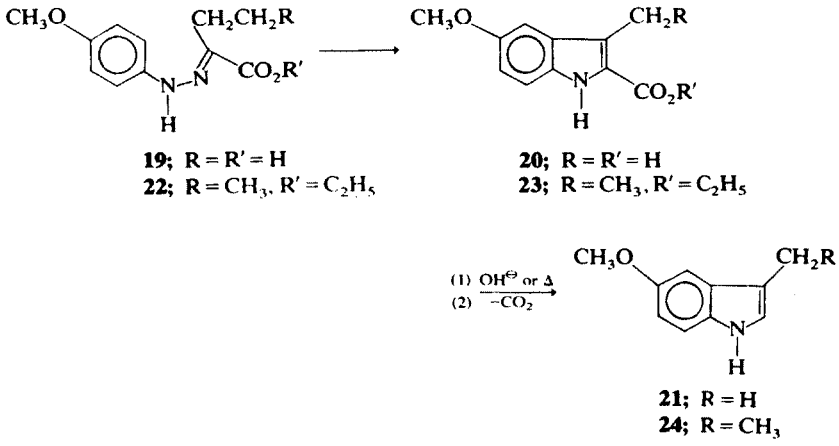
2. α-Ketoacids

Because indolecarboxylic acids are covered in a later chapter this and the following section deal only with the formation of alkoxyindolecarboxylic acids, produced by Fischer cyclization, that have been decarboxylated to alkoxyindoles. Many of the same compounds are obtainable also by the Reissert reaction and decarboxylation.

a. PYRUVATES. The *p*-methoxyphenylhydrazone of pyruvic acid has been cyclized to 5-methoxyindole-2-carboxylic acid (the ethyl ester is obtained when the reaction is carried out in ethanol) in yields of 20[43] and 30%[45] with H_2SO_4 in ethanol or 38% with HCl in acetic acid.[44] Decarboxylation with copper chromite in quinoline[45] or heating at 205–210°[44,45] gave 5-methoxyindole. Rydon and Siddappa reported[46] the formation of ethyl 5-ethoxyindole-2-carboxylate in 27% yield from the *p*-ethoxyphenylhydrazone of ethyl pyruvate. Saponification and decarboxylation by fusion afforded 5-ethoxyindole in 46% yield. It has been reported that the *p*-ethoxyphenylhydrazone of pyruvic acid can be cyclized with $ZnCl_2$, whereas the methoxy analogue fails.[47] The *N*-methyl-*N*-*p*-methoxyphenylhydrazone of pyruvic acid has been cyclized with HCl in acetic acid to give 1-methyl-5-methoxyindole-2-carboxylic acid in 21,[49] 32,[48] or 33%[25] yield. Decarboxylation at 200° was reported[25] to give 1-methyl-5-methoxyindole in 72% yield, whereas fusion at 220–225° gave a yield of 92%.[49] The ethoxy analogue was cyclized in acetic acid (41% yield) and decarboxylated at 205° to afford 1-methyl-5-ethoxyindole.[50]

The *o*-methoxyphenylhydrazone of pyruvic acid gave 7-methoxyindole-2-carboxylic acid in 40% yield on cyclization with ethanolic sulfuric acid,[43] although the analogous *N*-methylphenylhydrazone was reported to cyclize (HCl/HOAc) in very poor yield.[25] When the former reaction is conducted in HCl–ethanol, the expected product is produced in poor yields and the major products are the 6-chloro- and 6-ethoxyindole-2-carboxylic acid ethyl esters.[374,375] Pappalardo and Vitali attempted this reaction in HOAc–HCl, but failed to identify the resulting indole.[43] The *N*-methyl-*N*-*m*-methoxyphenylhydrazone of pyruvic acid has been cyclized with HCl in ethanol and decarboxylated to give, allegedly, 1-methyl-6-methoxyindole.[51]

b. OTHER α-KETOACIDS. Blaikie and Perkin in their pioneering study of hydroxyindoles[52] reported that 3-methyl-5-methoxyindole-2-carboxylic acid (**20**) was formed in 43% yield on cyclization of the *p*-methoxyphenylhydrazone of 2-ketobutanoic acid (**19**) in alcoholic sulfuric



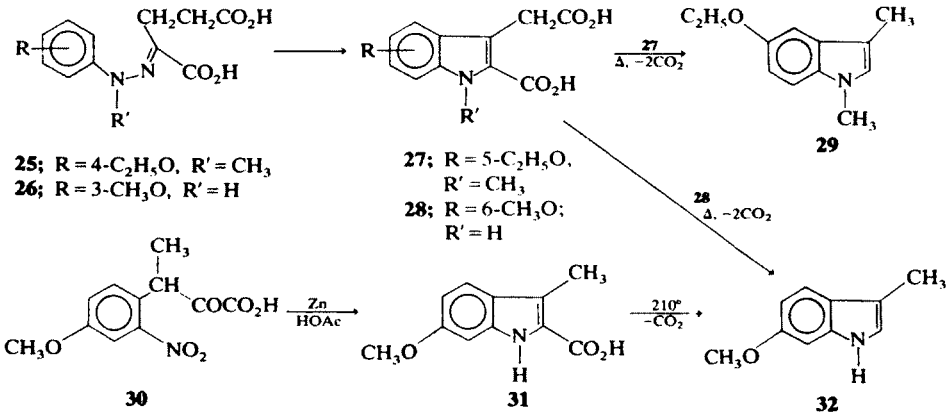
19; R = R' = H
22; R = CH_3, R' = C_2H_5

20; R = R' = H
23; R = CH_3, R' = C_2H_5

21; R = H
24; R = CH_3

acid. On decarboxylation at its melting point, **20** afforded a 75% yield of 3-methyl-5-methoxyindole (**21**). The isomeric *o*-methoxyphenylhydrazone was reported to cyclize slowly and only in 23% yield, to afford, after fusion, 7-methoxyskatole.[52]

Stedman cyclized[54] the *N*-methyl-*N*-*p*-ethoxyphenylhydrazone of 2-ketoglutaric acid (**25**) in 50% acetic acid to the dicarboxylic acid **27** in 27% yield, which was then decarboxylated at 250° to 1,3-dimethyl-5-ethoxyindole (physostigmol ethyl ether) (**29**) (Scheme 3). Robinson and co-workers established that the *m*-methoxyphenylhydrazone of the same acid (**26**) in alcoholic HCl gave the 6-methoxyindole diacid **28**[55] in low yield. The methoxyskatole **32** obtained on decarboxylation proved to be



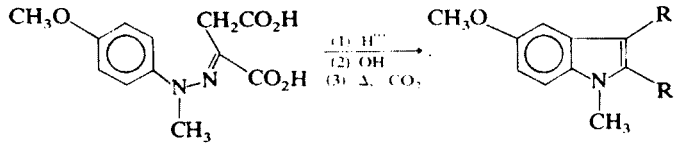
25; R = 4-C_2H_5O, R' = CH_3
26; R = 3-CH_3O, R' = H

27; R = 5-C_2H_5O, R' = CH_3
28; R = 6-CH_3O; R' = H

30 **31** **32**

Scheme 3

identical with the indole-2-carboxylic acid **31** which was obtained by reduction and decarboxylation of the 4-methoxy-2-nitrophenylpyruvate derivative **30**.



33 **34a**; R = CO_2H
34b; R = H

Bell and Lindwall, after cyclizing the *N*-methyl-*N*-*p*-methoxyphenylhydrazone of 2-ketosuccinic acid (**33**) with HCl in acetic acid, decarboxylated the resulting diacid **34a** at 200° to 1-methyl-5-methoxyindole (**34b**) in 72% yield.[25] The isomeric *o*-methoxyphenylhydrazone was reported as cyclizing in poor yield.[25]

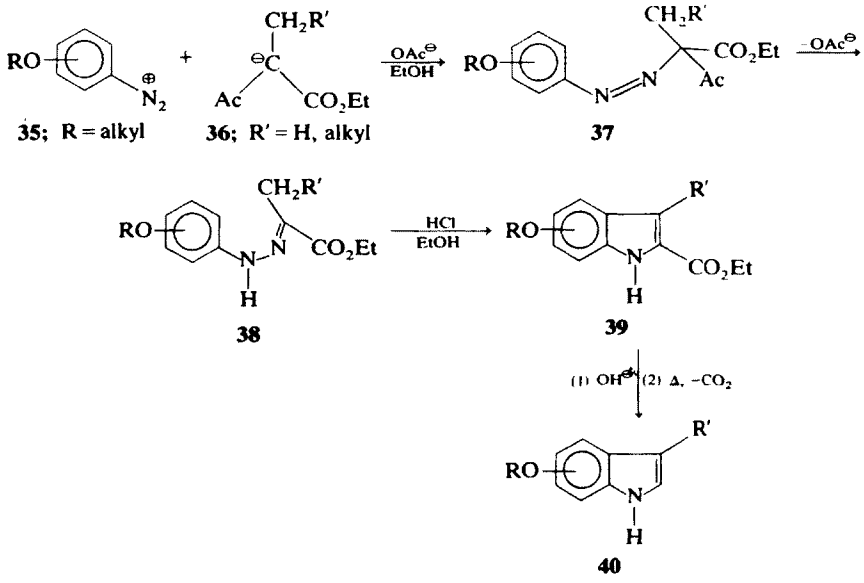
3. *The Japp–Klingemann Reaction*

The alkoxyphenylhydrazone of an α-ketoacid ester **38** can be conveniently prepared by coupling the alkoxybenzenediazonium salt **35** with ethyl acetoacetate or its α-alkyl derivatives (**36**) in alcohol containing sodium hydroxide or sodium acetate (Scheme 4). Subsequent Fischer cyclization is usually effected with HCl in ethanol without isolating the phenylhydrazone **38**. Polyphosphoric acid in toluene[56] or phosphoric acid in ethanol[57] have also been employed as catalysts. Although this synthetic procedure is limited to the preparation of *N*-unsubstituted indoles, it has supplanted the direct preparation of phenylhydrazones from α-ketoacids.

Keimatsu and Sugasawa[58] and Kobayashi[59] coupled *p*-ethoxybenzenediazonium chloride with ethyl α-ethylacetoacetate (**36**, R = CH_3) to obtain 3-methyl-5-ethoxyindole after cyclization and decarboxylation. Physostigmol ethyl ether (**28**) resulted on methylation.[58] Here, surprisingly, *N*-methylation raised the melting point.

Hughes and co-workers prepared[60] a number of 5-methoxy-, 5-ethoxy-, and 7-ethoxy-3-substituted indole-2-carboxylic acid esters from the appropriate diazonium salts and ethyl α-methyl, α-ethyl, α-butyl, and α-benzyl acetoacetates by cyclization of the resultant alkoxyphenylhydrazones **38** with HCl in ethanol.

Bell and Lindwall coupled *o*- and *p*-methoxybenzenediazonium salts with ethyl α-methylacetoacetate (**36**, R′ = H) and obtained the alkoxyindole-2-carboxylic acid esters in 30 and 52% yield. Saponification



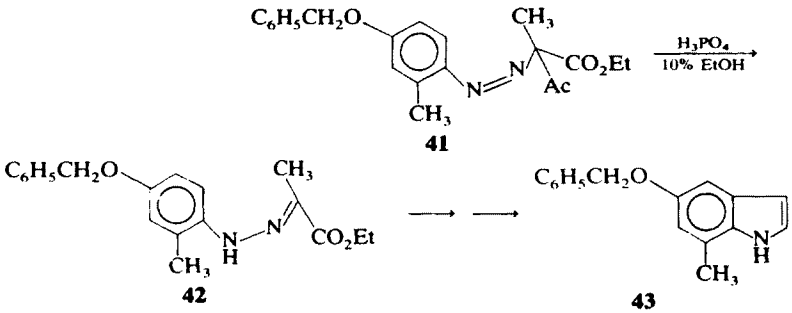
Scheme 4

and decarboxylation at 200° afforded 7- and 5-methoxyindole in 53 and 65% yield, respectively.[25]

On coupling the *p*-methoxybenzenediazonium chloride with ethyl α-methylacetoacetate, Kralt and co-workers reported the formation of ethyl 5-methoxyindole-2-carboxylate in 62% yield.[61] Saponification and copper chromite-catalyzed decarboxylation gave 5-methoxyindole in 70% yield. Julia and Manoury obtained[62] 5-methoxyindole-2-carboxylic acid in 50% yield using the same reaction. This could be decarboxylated in 73% yield by heating at 230° or in 72% yield with a mixture of cupric acetate and copper powder in refluxing quinoline.

In 1953, Boehme described[63] what was then the most practical synthesis of the versatile intermediate, 5-benzyloxyindole, using *p*-benzyloxybenzenediazonium chloride and ethyl α-methylacetoacetate. Cyclization of the intermediate with HCl in ethanol afforded ethyl 5-benzyloxyindole-2-carboxylate in 64–69% yields,[61] saponification and decarboxylation of which gave 5-benzyloxyindole in 66% yield. Ash and Wragg repeated[64] the coupling and cyclization steps and reported a 60% yield of the 5-benzyloxyindole ester. They achieved a slight improvement in the decarboxylation step (77%) using a copper chromite catalyst in quinoline at 280°.

Heath-Brown and Philpott reinvestigated this reaction[57] and were able to isolate the petroleum ether-soluble azo ester intermediates **37** formed from *p*-benzyloxy-, *p*-methoxy-, or *o*-methyl-*p*-benzyloxybenzenediazonium salts and ethyl α-methylacetoacetate. In all likelihood, the red "phenylhydrazone" mentioned by both Boehme and Ash and Wragg is the azo ester. Heath-Brown and Philpott noted that on mild acid treatment, the 2-methyl-4-benzyloxyphenyl azo intermediate **41** lost acetic acid to give the true phenylhydrazone **42**. This could be cyclized and decarboxylated to 7-methyl-5-benzyloxyindole (**43**).



Prelog and co-workers described[2] the synthesis of 3-ethyl-5-methoxyindole (**24**), a degradation product of the alkaloid aricine, using ethyl α-propylacetoacetate and diazotized *p*-anisidine. The phenylhydrazone **22** was cyclized with ethanolic sulfuric acid and the resulting indole-2-carboxylic acid ester **23** (60%) was saponified and decarboxylated at 220°.

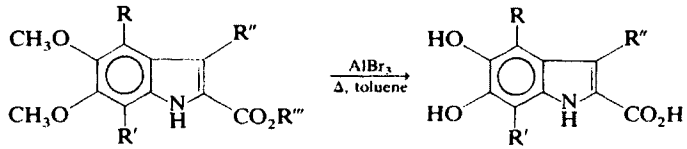
Shaw reacted the above acetoacetate derivative with *p*-benzyloxybenzenediazonium chloride and obtained ethyl 3-ethyl-5-benzyloxyindole-2-carboxylate in 50% yield. Saponification and decarboxylation (210°) afforded 3-ethyl-5-benzyloxyindole in 70% yield, which on debenzylation gave 3-ethyl-5-hydroxyindole.[65a]

Julia and Nickel synthesized 7-nitro-5-methoxyindole in approximately 30% yield by cyclizing the 2-nitro-4-methoxyphenylhydrazone of ethyl pyruvate with polyphosphoric acid in toluene; decarboxylation of the saponified indole ester was achieved with copper chromite in quinoline at 225°.[56]

Reaction of *m*-methoxy- or *m*-benzyloxybenzenediazonium chloride with ethyl α-benzylacetoacetate was reported to give fair yields (17–39%) of the ethyl 3-phenyl-6-alkoxyindole-2-carboxylates, but no structure proofs were offered.[66] The 5-methyl derivatives of these acids were prepared from the methyl or benzyl ethers of 3-amino-6-methylphenol diazonium salts. Debenzylation was effected in good yield with $AlCl_3$ in

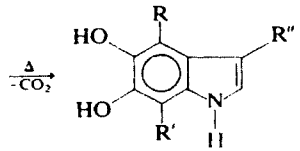
refluxing benzene.[66] Troxler and co-workers prepared 7-methyl-6-hydroxyindole from 2-methyl-*m*-anisidine and ethyl α-methyl acetoacetate. Cyclization was effected with polyphosphoric acid, the decarboxylation of the free acid with copper bronze in 2-benzylpyridine, and finally, the demethylation of the resulting 7-methyl-6-methoxyindole with aluminum chloride in benzene.[384]

Robertson and co-workers prepared model compounds for use in a study of melanogenesis by the Japp–Klingemann reaction with diazonium chlorides derived from 4- and 5-amino-3-*n*-propylveratrole and ethyl α-methyl- or α-ethylacetoacetates (Scheme 5). Compounds **44** were obtained by cyclization with HCl in ethanol. After hydrolysis to **45** and demethylation to **46**, a decarboxylative distillation yielded the 4- and 7-*n*-propyl derivatives of 5,6-dihydroxyindole (**47**, **48**) and 5,6-dihydroxyskatole (**49**, **50**). Yields in the coupling–cyclization step were 26–27% with the 4-aminoveratrole derivatives and 43–46% with the 5-aminoveratrole derivatives. Decarboxylation yields, where reported, were excellent.[67]



R, R' = H, *n*-C_3H_7; R'' = H, CH_3
44; R''' = C_2H_5
45; R''' = H

46



	R	R'	R''
47	*n*-C_3H_7	H	H
48	H	*n*-C_3H_7	H
49	*n*-C_3H_7	H	CH_3
50	H	*n*-C_3H_7	CH_3

Scheme 5

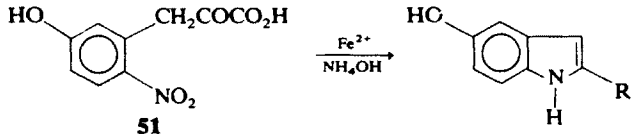
Another dihydroxyindole, 3-methyl-5,6-dihydroxyindole, was prepared[42] in 37% overall yield by successive steps of demethylation ($AlBr_3$/benzene) and decarboxylation from 3-methyl-5,6-dimethoxyindole-2-carboxylic acid, prepared following the Japp–Klingemann procedure of Lions and Spruson.[332] When the demethylation–decarboxylation order was reversed, the procedure failed.

B. Reissert Reduction

The reduction of 2-nitrophenylpyruvates is one of the earliest, yet still most widely used, methods to be applied to the synthesis of the hydroxy or alkoxyindoles.

1. *Hydroxyindoles*

Reissert reduction of 2-nitro-5-hydroxyphenylpyruvic acid (**51**) using ferrous sulfate in aqueous ammonia was employed by Robertson and co-workers, who obtained 5-hydroxyindole-2-carboxylic acid (**52**) in 77% yield.[68] On decarboxylation in glycerol at 225–230°, 5-hydroxyindole (**53**) resulted in 20% yield. The use of other decarboxylation media including diphenyl ether, aniline, or quinoline containing copper bronze failed to improve the yield, as did fusion of the acid under vacuum.



51

52; R = CO_2H
53; R = H

Cyclization of 2-nitro-4,5-diacetoxyphenylpyruvic acid with iron powder in acetic acid–alcohol gave 5,6-diacetoxyindole-2-carboxylic acid in 49% yield. Alkaline hydrolysis and sublimation of the resulting 5,6-dihydroxy acid gave 5,6-dihydroxyindole.[42]

2. *Methoxy- and Ethoxyindoles*

For their pioneering syntheses of 4-, 5-, and 7-methoxyindoles[52] as well as their synthesis of 6-methoxyindole and 6-methoxyskatole,[55] Perkin and co-workers chose the Reissert reduction. In the cyclization step, ferrous sulfate in aqueous ammonia gave yields of 63–73%. The resulting methoxyindole-2-carboxylic acids were decarboxylated in approximately 75% yield by heating above their melting points. When 2-nitro-4-methoxyphenylpyruvate was first *C*-methylated in the α-position then decarboxylated as above, 6-methoxyskatole resulted[55] (see Section III.A.2.b).

Robinson and co-workers reported[51] an improved procedure for the decarboxylation of 6-methoxyindole-2-carboxylic acid by fusion of the ammonium salt which produced 6-methoxyindole in 88% yield. Harvey and Robson prepared the same ammonium salt in 50–60% yield. On decarboxylation of the salt in hot glycerol they obtained 6-methoxyindole in 74% yield.[69] 5-Methoxyindole was synthesized in this manner by Bell and Lindwall, who reported[25] a 60% yield for the cyclization step and a 65% yield for the decarboxylation step. Marchant and Harvey applied the Reissert reduction to the preparation of 5- and 7-methoxyindole;[70] decarboxylation of the ammonium salts in glycerol proceeded in 85–90 and 60% yield, respectively.

Govindachari and co-workers obtained[71] 4-methoxyindole in 35–40% yield on decarboxylation of 4-methoxyindole-2-carboxylic acid by pyrolysis or by heating with copper sulfate in quinoline. The indolecarboxylic acid was obtained in 73% yield by Perkin's[52] procedure. Pappalardo and co-workers[43] used ferrous hydroxide in the Reissert reduction to obtain the 4-, 6-, and 7-methoxyindole-2-carboxylic acids in 65–70% yield. Decarboxylation to the methoxyindoles with copper chromite in quinoline at 200–210° gave yields of 58, 45, and 80%, respectively.

On reduction of 2-nitro-4-methoxyphenylpyruvic acid or its ethyl ester with iron powder in ethanol–acetic acid, Najer and co-workers obtained[72] 6-methoxyindole-2-carboxylic acid and its ester in 80% yields. Decarboxylation of the ammonium salt of the acid in glycerol at 210–220° gave 6-methoxyindole in 55% yield. 6-Ethoxyindole has been prepared in a similar fashion.[73a,b]

Allen and Poletto reduced 2-nitro-4-methyl-5-methoxyphenylpyruvic acid with ferrous ion in ammonia to give 5-methoxy-6-methylindole-2-carboxylic acid in 56% yield. This acid could be decarboxylated by heating to 260–270° to afford 5-methoxy-6-methylindole in 75% yield.[74]

Oxford and Raper prepared 5,6-dimethoxyindole in poor yield by reducing 2-nitro-4,5-dimethoxyphenylpyruvic acid with ferrous ion in ammonia followed by decarboxylation of the resulting 5,6-dimethoxyindole-2-carboxylic acid by fusion at 205–215°.[75] Harvey improved this synthesis by using glycerol at 200° for the decarboxylation of the ammonium salt of this acid, when the indole was obtained in 97% yield. However, yields in the cyclization step were still modest (35–41%).[76] Crohare and co-workers have successfully applied the Reissert reduction in a recent synthesis of 5,7-dimethoxyindole; 50–60% yields are reported for both the cylization and decarboxylation ($CuCrO_4$ in quinoline) steps.[378]

3. *Benzyloxyindoles*

Burton and Stoves synthesized 5- and 6-benzyloxyindole-2-carboxylic acid by reduction and cyclization of the appropriate phenylpyruvates with ferrous sulfate in dilute sodium hydroxide.[77] The acids were decarboxylated in glycerol at 210° to give 5- and 6-benzyloxyindole in 24 and 32% overall yield, respectively. Attempted debenzylation using HI or HBr was unsuccessful.

Bergel and Morrison found, however, that 5-benzyloxyindole-2-carboxylic acid, which they prepared in 70% yield by Reissert reduction, could be smoothly debenzylated by hydrogenolysis with a palladium–carbon catalyst in methanol.[78] This procedure, or slight variations, is now universally used in the preparation of hydroxyindoles from benzyloxyindoles. Decarboxylation of the resulting hydroxyacid by brief heating with copper powder under nitrogen at 250° gave 5-hydroxyindole in 15% yield. If decarboxylation was attempted before debenzylation, no 5-hydroxyindole could be obtained.

Kondo and co-workers decarboxylated 5-benzyloxyindole-2-carboxylic acid, obtained in 70% yield by Reissert reduction, with copper powder in quinoline to a 78% yield of 5-benzyloxyindole. The 6-benzyloxyindole was obtained in the same manner.[79]

The 6- and 7-benzyloxyindole-2-carboxylic acids were obtained by reductive cyclization of the appropriate benzyloxy-2-nitrophenylpyruvic acid with ferrous sulfate in aqueous ammonia.[68] Catalytic debenzylation and decarboxylation in glycerol afforded 6- and 7-hydroxyindole, respectively. Although the decarboxylation step proceeded well with the 6-hydroxy derivative (53%), the yield in the case of the 7-hydroxy isomer was poor.

Stoll and co-workers reduced 6-, 5-, and 4-benzyloxy-2-nitrophenylpyruvates with alkaline sodium dithionite and obtained 4-, 5-, and 6-benzyloxyindole-2-carboxylic acids in 64, 79, and 51% yield, respectively. Decarboxylation of the 4- and 5-benzyloxy acids with copper powder in quinaldine at 245–250° gave 4- and 5-benzyloxyindoles in 62 and 80% yield.[80] 2-Benzylpyridine was employed as the decarboxylation medium for the 6-benzyloxyacid and provided a 46% yield of product. Hydrogenolysis of these benzyloxyindoles with a palladium–asbestos catalyst in methanol afforded the hydroxyindoles. A recent application of these procedures has led to the syntheses of 4-hydroxy-5-methyl-, 5-hydroxy-4-methyl-, and 5-hydroxy-6-methylindole in good yields.[384]

Using the above dithionite procedure, Pasini and co-workers prepared 5-benzyloxy-6-methyl- and 5-benzyloxy-6-methoxyindole-2-carboxylic

acid in 40 and 50% yield, respectively. Decarboxylation of the latter to 5-benzyloxy-6-methoxyindole (38%) was achieved using copper powder in quinaldine. The methyl acid was decarboxylated in 27% yield by heating at 200° to 5-benzyloxy-6-methylindole.[81]

Schlossberger and Kuch prepared 5,6-dibenzyloxyindole in 63% yield by decarboxylation (copper powder in quinaldine) of 5,6-dibenzyloxyindole-2-carboxylic acid. The acid was obtained in a 61% yield from a reduction of the appropriate pyruvate with iron in ethanol–acetic acid.[82]

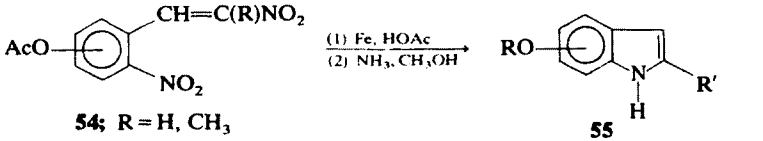
Robinson and Slaytor synthesized 4-chloro-5-benzyloxyindole by the reduction of 2-nitro-5-benzyloxy-6-chlorophenylpyruvate with ferrous sulfate in boiling aqueous ammonia followed by decarboxylation of the intermediate indole carboxylic acid with copper chromite in quinoline at 210–220°. The cyclization step was reported to proceed in at least 65% yield; the decarboxylation step in 61% yield.[83]

C. Reduction of Dinitrostyrenes

Another reductive procedure which is widely used in the preparation of *N*-unsubstituted alkoxyindoles uses the chemical or catalytic reduction of 2,β-dinitrostyrenes with alkoxy substituents in the aromatic ring. This method, which is the earlier of the two indole syntheses developed by Nenitzescu, is particularly convenient in that no decarboxylation step is required. Consequently, in modern practice this reaction has supplanted the Reissert reduction.

1. *Alkoxy- and Hydroxyindoles*

Robertson and co-workers, who were responsible for popularizing this reaction, applied it to the synthesis of 4- and 5-acetoxyindole, which were formed in 34 and 55% yield.[68] Cyclization of 2,β-dinitro-6- or -5-acetoxystyrene (**54**, R = H) was effected using iron filings in acetic acid. Deacetylation of the acetoxyindoles was accomplished with dry ammonia in methanol to afford the hydroxyindoles (**56**, R = H). A similar reduction



54; R = H, CH_3

55

55; R = CH_3CO, R′ = H, CH_3

56; R = H; R′ = H, CH_3

of 2,β-dinitro-5-acetoxy-β-methylstyrene (**54**, $R = CH_3$) gave 2-methyl-5-acetoxyindole (**55**, $R = CH_3$) (28%), convertible into 2-methyl-5-hydroxyindole (**56**, $R = CH_3$) in 80% yield.

Burton and Leong reported the synthesis of 5-benzyloxyindole using an iron–acetic acid reduction of the appropriate dinitrostyrene.[84] An Upjohn patent describes[105] the synthesis of this indole and of its 2-alkyl derivatives using iron in ethanol–acetic acid for the reduction.

Ek and Witkop synthesized 5- and 7-benzyloxyindole in 61 and 75% yield, respectively, using iron powder in ethanolic acetic acid.[85a,b] Hydrogenolysis (Pd/C) gave 5- and 7-hydroxyindoles in 98% yield. An analogous synthesis of 6-benzyloxyindole was reported by Suvorov and co-workers.[86] Ek and Witkop observed that reduction of 3-acetoxy-2, β-dinitrostyrene proceeded abnormally and gave, in 87% yield, a product of unkown structure.[85b]

Woodward and co-workers prepared 6-methoxyindole, a starting material in their reserpine synthesis, in 67% yield using a palladium–carbon-catalyzed hydrogenation of 2,β-dinitro-4-methoxystyrene in ethyl acetate–ethanol–acetic acid.[87] This modification of the Nenitzescu reduction had been introduced earlier by Heubner and co-workers[88] and is now more popular than the chemical reductions. Kralt and co-workers adopted this procedure for their synthesis of 6-ethoxyindole, which was obtained in 50% yield.[61] Kalir and co-workers obtained 7-methoxyindole (68%) when the appropriate dinitrostyrene was reduced with Pd/C in ethyl acetate containing some acetic acid.[91]

6-Methoxyindole has also been synthesized using the iron–alcoholic acetic acid procedure, with 43[89] and 63%[90a,b] yields.

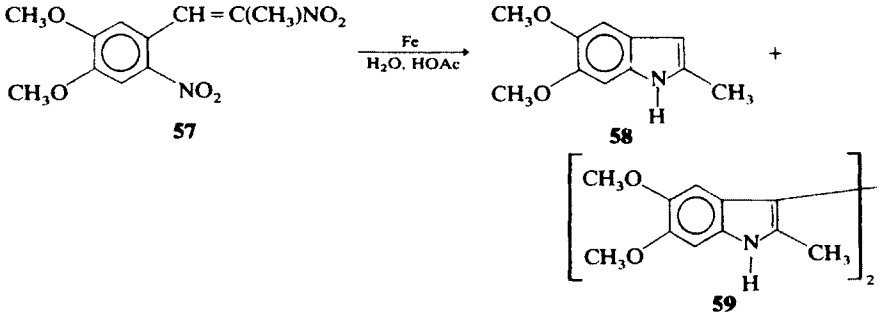
2. *Dialkoxy- and Dihydroxyindoles*

Robertson and co-workers in the first of their important papers on melanin[92a,b] described the preparation of 5,6-dihydroxyindole and its 2-methyl derivative in 60 and 39% yield respectively, by the reduction of the corresponding 5,6-diacetoxydinitrostyrenes with iron in alcoholic acetic acid followed by alkaline hydrolysis of the resulting 5,6-diacetoxyindoles. Likewise, 6-acetoxy-5-methoxyindole,[92a,b] 6-acetoxy-7-methoxyindole,[93] and 5-acetoxy-6-methoxyindole[92a,b] were produced in 53, 55, and 63% yield, respectively. Deacetylation was accomplished with dry ammonia in methanol or with aqueous alkali in the presence of dithionite to give the hydroxymethoxyindoles. Mason and Peterson report[333] improved yields of 5,6-dihydroxyindole (22%) using the former procedure under a hydrogen atmosphere. Burton and co-workers reported[334a,b] achieving the

partial deacetylation of 5,6-diacetoxyindole with dilute phosphoric acid in ethanol to the 5- or 6-acetyl derivative of 5,6-dihydroxyindole in 27% yield.

Using the same conditions 2-methyl-5-hydroxy-6-methoxyindole (57%), 2-methyl-5-methoxy-6-hydroxyindole (57%), 6-methoxy-7-hydroxyindole (41%), and 2-methyl-6-methoxy-7-hydroxyindole (29%) were synthesized.[93] Burton and Duffield obtained[336] 5,6-methylenedioxyindole (82%) and its 2-methyl derivative (100%) on reduction of the appropriate dinitrostyrenes with iron in aqueous acetic acid. Removal of the methylene group with pyridine hydrochloride gave the dihydroxyindoles in poor yield.

Harley-Mason, in the course of his studies of the melanization process, reported[94] that iron in aqueous acetic acid reduction of the dinitrostyrene **57** gave 2-methyl-5,6-dimethoxyindole (**58**) in 63% yield and 14% of the dimer **59**.



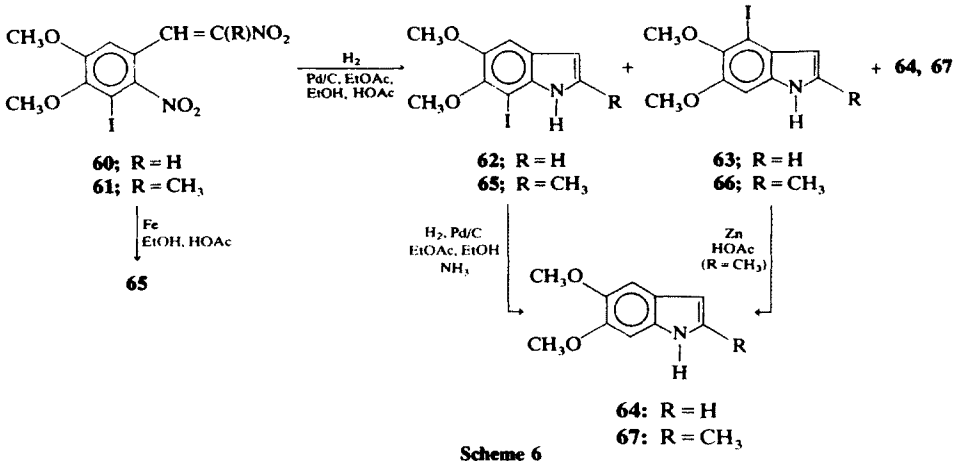
57 **58** **59**

Using a Nenitzescu reduction with iron in acetic acid, Salgar and Merchant obtained 4,5-dimethoxyindole and 5-methoxy-6-ethoxyindole[95] and Mulligan and La Berge, 5,7-dimethoxyindole (57%).[335] Rodighiero and co-workers prepared 4,7-dimethoxyindole in 58% yield with iron in ethanolic acetic acid.[96] Using these conditions, Mishra and Swan obtained 5-ethoxy-6-methoxyindole and 5-methoxy-6-ethoxyindole in yields of 35 and 40%, respectively.[97] Schlossberger and Kuch obtained the useful intermediate 5,6-dibenzyloxyindole (58%) in the same manner.[82]

Reducing the appropriate dinitrostyrene with iron in aqueous acetic acid, Julia and co-workers synthesized the following methoxybenzyloxyindoles: 4-benzyloxy-5-methoxy- (64%), 5-methoxy-6-benzyloxy- (45%), and 6-benzyloxy-7-methoxy- (76%).[98] Using similar conditions, Benigni and Minnis obtained[337] 5,6-dibenzyloxyindole, 5-benzyloxy-6-methoxyindole, and 5-methoxy-6-benzyloxyindole in yields of 52, 50, and 55%, respectively. Catalytic debenzylation gave 5,6-dihydroxyindole, 5-hydroxy-6-methoxyindole, and 5-methoxy-6-hydroxyindole in yields of 89, 72, and 94%, respectively.

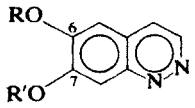
Heubner and co-workers introduced in 1958 a useful large-scale modification of the dinitrostyrene reduction.[88] By means of hydrogenation with a palladium–carbon catalyst in a mixture of ethanol and ethyl acetate containing four equivalents of acetic acid, they obtained 5,6-dimethoxyindole in 60% yield from 4,5-dimethoxy-2, β-dinitrostyrene. Benington and co-workers used it in their preparation of 6,7-dimethoxyindole (23%),[113] although in this instance, it seems less satisfactory than the older procedure, which in the hands of DeAntoni and co-workers afforded[338] a 55% yield.

Witkop, Heacock, and co-workers used the catalytic hydrogenation of 3-iodo-4,5-dimethoxy-2,β-dinitrostyrene (**60**) and its β-methyl derivative (**61**) for the preparation of 7-iodo-5,6-dimethoxyindoles (Scheme 6).[99] When **60** was reduced with a palladium–carbon catalyst, a 23% yield of the 7-iodoindole **62** was obtained, along with a lesser yield of the isomeric 4-iodoindole **63** and an 18% yield of the iodine-free 5,6-dimethoxyindole (**64**.) The 4-iodoindole may arise from a catalyst-induced migration of iodine. The indole **64** was shown to arise by loss of iodine from either iodoindole. When **61** was reduced under similar conditions, the corresponding 7-iodo (**65**) and 4-iodo (**66**) 2-methylindoles resulted in 10 and 15% yield, together with some 2-methyl-5,6-dimethoxyindole (**67**). Deiodination of **65** and **66** to **67** in 47 and 39% yield occurred on reduction with a palladium–carbon catalyst or with iron–acetic acid, respectively. When **61** was reduced with iron in alcoholic acetic acid, no rearrangement took place and the 7-iodoindole (**65**) resulted in 47% yield. This reduction, however, failed with **60**.



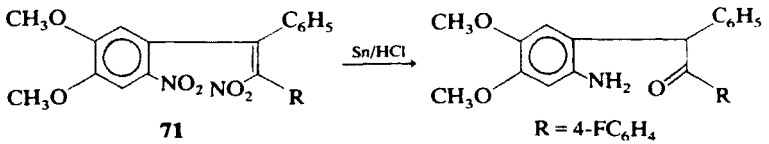
Scheme 6

Baxter and Swan have reported[100] that hydrogenation of 4-benzyloxy-5-methoxy-2,β-dinitrostyrene with a palladium catalyst in ethyl acetate–ethanol–acetic acid gives a mixture of 5-methoxy-6-hydroxyindole (6%) and 5-methoxy-6-benzyloxyindole (13%). Reduction of 4,5-dimethoxy-2,β-dinitrostyrene with lithium aluminum hydride in THF afforded 5,6-dimethoxyindole in 20% yield along with the major product, 6,7-dimethoxycinnoline (**68**). Likewise, 4-benzyloxy-5-methoxy- and 4,5-dibenzyloxy-2,β-dinitrostyrene gave the corresponding cinnolines **69** and **70** as the major products in this reduction along with minor amounts of the expected 5-methoxy-6-benzyloxy- and 5,6-dibenzyloxyindole.[100]

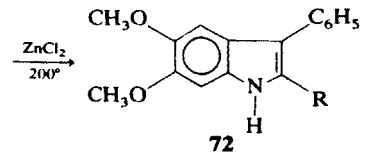


68; R = R′ = CH_3
69; R = CH_3, R′ = $C_6H_5CH_2$
70; R = R′ = $C_6H_5CH_2$

A two-step conversion of the dinitrostyrene derivative **71** to the 5,6-dihydroxyindole **72** has been reported.[376]



71 R = 4-FC_6H_4



72

3. *Tri- and Polyalkoxyindoles*

The Nenitzescu reduction has been used to make 5,6-methylenedioxyindole and 4-methoxy-5,6-methylenedioxyindole in 33 and 35% yields using iron powder in acetic acid. In the case of a series of tri- and tetrahydroxyindole ethers, the yields ranged from 80 to 90%.[101]

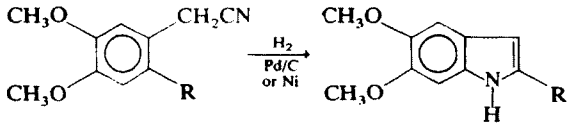
Merchant and Salgar report[102] the synthesis of 4,5,7-trimethoxyindole using iron powder in 80% aqueous acetic acid. Benington and co-workers

achieved[103] the first synthesis of 5,6,7-trimethoxyindole, a possible intermediate in the metabolism of mescaline using iron and ethanolic acetic acid. Hardegger and Corrodi showed that the use of HCl-activated iron in this reduction led to improved yields.[104]

D. Other Reduction Procedures

1. *Reduction of Alkoxybenzylnitriles*

Plieninger and Nógrádi have described[106a,b] the high-pressure hydrogenation of 2-nitro-4,5-dimethoxyphenylacetonitrile (**73**) in ethyl acetate with Raney nickel to give a 50% yield of 5,6-dimethoxyindole (**76**) (Scheme 7). When the hydrogenation was interrupted at the uptake of three moles of hydrogen, the intermediate aminonitrile **74** could be isolated. Further reduction, either catalytically or with sodium in amyl alcohol, gave the indole.



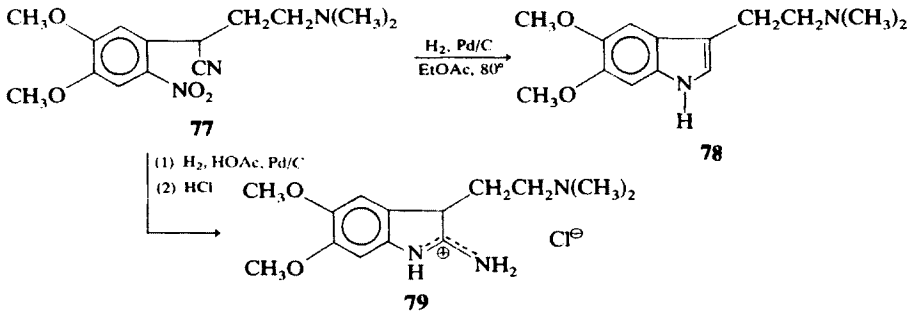
73; R = NO_2
74; R = NH_2

75; R = NH_2
76; R = H

Scheme 7

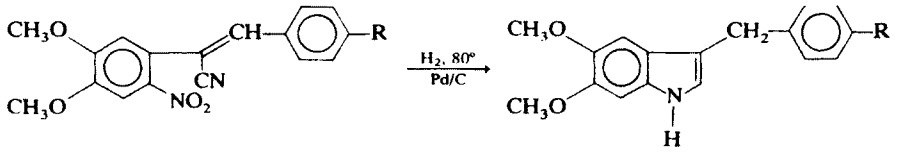
Walker discovered independently that **73** could be reduced to **74** using a palladium–carbon catalyst in ethyl acetate at room temperature.[107] However, when the hydrogenation was conducted at 80°, four moles of hydrogen were consumed—three rapidly, the fourth slowly—and 5,6-dimethoxyindole (**76**) was isolated in 60% yield. Ring closure to the 2-aminoindole **75** was proposed,[107] and support for this intermediate was obtained in the course of the reduction of the nitrile **77** (Scheme 8). In ethyl acetate at 80°, **77** yielded the expected tryptamine derivative **78**. When the hydrogenation was carried out in acetic acid, an aminoindole, presumably **79**, could be isolated and characterized as the hydrochloride. The 2-aminoindole is apparently stabilized by salt formation in acid.

Upon exhaustive hydrogenation at 80° the benzylidene derivative **80** absorbed 5 moles of hydrogen and afforded 3-benzyl-5,6-dimethoxyindole (**81**) in 49% yield.[107] Likewise the *p*-*N*,*N*-dimethylaminobenzylidene derivative **82** was converted into 3-(*p*-*N*,*N*-dimethylaminobenzyl)-5,6-dimethoxyindole (**83**) in 74% yield.[108] The formation



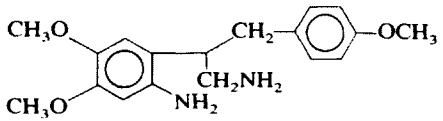
Scheme 8

of the closely related *p*-methoxy analogue **85** has been reported by Govindachari and co-workers as a by-product in the reduction of **84** to the amine derivative **86**.[109]



80; R = H
82; R = $N(CH_3)_2$
84; R = OCH_3

81; R = H
83; R = $N(CH_3)_2$
85; R = OCH_3

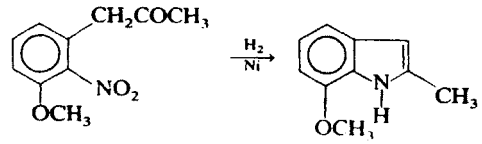


86

Snyder and co-workers applied Walker's procedure to the synthesis of 5-hydroxyindole via 2-nitro-5-benzyloxyphenylacetonitrile in an overall yield of 75%.[110] Ek and Witkop failed to prepare 5-benzyloxyindole by cyclization of this nitrile using Stephen's reduction.[85b]

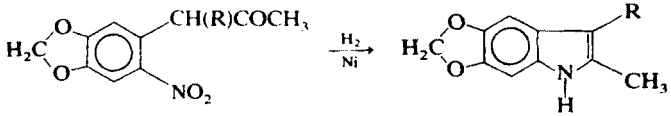
2. *Reduction of 2-Nitrophenylacetone Derivatives*

Blair and Newbold described[111] the synthesis of 2-methyl-7-methoxyindole (**88**) in 98% yield by hydrogenation of the nitro ketone **87** in ethyl acetate in the presence of Raney nickel.



87 **88**

Fujisawa and Okada obtained very good yields of 2-methyl-5,6-methylenedioxyindole (**90**) by reduction of the 2-nitrophenylacetone derivative **89** with either Raney nickel in ethanol (83% yield) or iron powder in acetic acid (93% yield).[112] They report that quantitative yields of 2,3-dimethyl-5,6-methylenedioxyindole (**92**) result when the methylated 2-nitrophenylacetone derivative **91** is reduced with Raney nickel in ethanol.

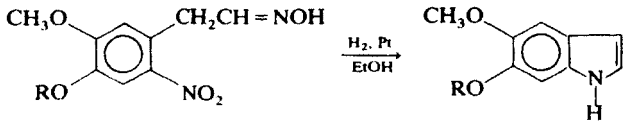


89; R = H
91; R = CH_3

90; R = H
92; R = CH_3

3. *Reduction of Oximes*

The *o*-nitrophenylacetaldehyde oximes **93** and **94**, conveniently prepared by hydrogenation of the appropriate 2,β-dinitrostyrenes in the presence of 5% rhodium on alumina, can be completely reduced using a platinum catalyst to give **95** and **96** in 50 and 21% yield, respectively.[114]



93; R = CH_3
94; R = $C_6H_5CH_2$

95; R = CH_3
96; R = $C_6H_5CH_2$

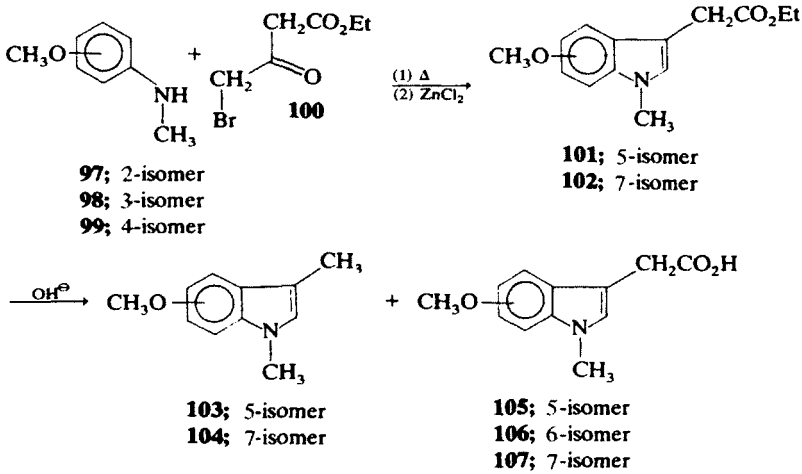
E. Methoxyindoles from the Bischler Reaction

The reaction of anisidines with α-haloketones, in the presence of the anisidine hydrohalide, has provided indole chemists with a remarkably convenient route to 5-, 6-, and 7-methoxyindoles. The generally modest

yields of the reaction are usually more than offset by the ready availability of the starting materials and the ease of carrying out the reaction. In a few instances, zinc chloride has been employed as an auxiliary catalyst, though there seems no clear-cut justification for this practice. For example, Julia and Lenzi obtained[115] equivalent yields with and without zinc chloride.

1. *Nonaromatic α-Haloketones*

Janetzky and co-workers prepared[116] 1,3-dimethyl-5-methoxyindole (**103**) using *N*-methyl-*p*-anisidine (**99**), bromoacetone, and the anisidine hydrochloride (Scheme 9). Mann and Tetlow described the same reaction, but no yield was given.[39] Julia and Lenzi isolated **103** and 1,3-dimethyl-7-methoxyindole (**104**) in 20 and 47% yield, respectively, in the course of the preparation of 1-methyl-5-methoxy- (**105**) and 1-methyl-7-methoxyindole-3-acetic acid (**107**). Compounds **103** and **104** resulted from a spontaneous decarboxylation during the hydrolysis of the methoxyindole-3-acetic acid esters, **101** and **102**, prepared from *N*-methyl-*p*-anisidine (**99**) or *N*-methyl-*o*-anisidine (**97**) and the β-keto-γ-bromoester **100**. The indole-3-acetic acid **106** formed from *N*-methyl-*m*-anisidine (**98**) was apparently stable.[115]

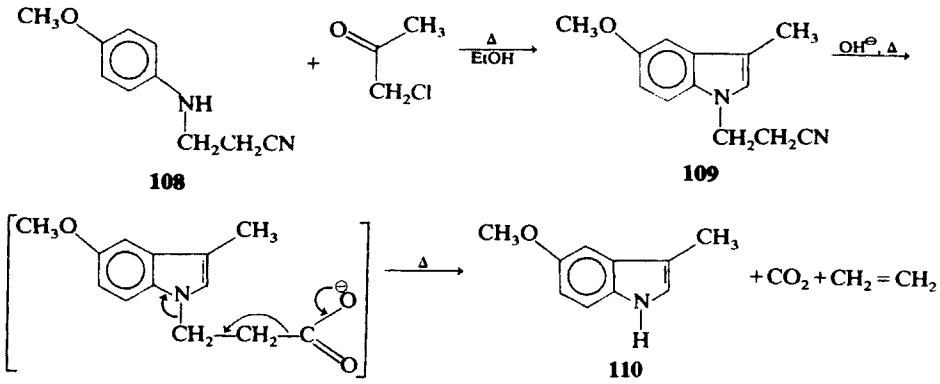


Scheme 9

Janetzky and Verkade prepared 2,3-dimethyl-5-methoxyindole (84%) using *p*-anisidine, 3-bromo-2-butanone, and zinc chloride.[117] This bromoketone and 2,5-dimethoxyaniline afforded Blackhall and Thomson 2,3-dimethyl-4,7-dimethoxyindole in 61% yield. Demethylation with

$AlCl_3$ in boiling benzene was reported to give the 4,7-dihydroxyindole (54%).[339] Berger has recently shown,[753] however, that this compound is really the 4,7-dioxo tautomer rather than the hydroquinone. It isomerizes in alkali to the hydroquinone and gives with acetic anhydride, a 4,7-diacetoxy derivative, as originally reported.[339] Earlier Rodighiero and co-workers had attempted[96] the demethylation of 4,7-dimethoxyindole itself with HI, HBr, or HCl without success. They were successful, however, with the aluminum chloride procedure.[323a] They showed that the reaction product in this case as well as the 2-methyl derivative[323b] is the 4,7-dioxo compound. Interestingly, 2-phenyl-4,7-dimethoxyindole, on demethylation, does afford a dihydroxy product.[323b]

Julia and Lenzi have described[118] the synthesis of 3-methyl-5-methoxyindole (**110**) in low overall yield via the *p*-anisidine–acrylonitrile adduct **108** in order to protect the nitrogen by a removable blocking group (Scheme 10). This improved the yield of the Bischler reaction with chloroacetone to 38%. The β-cyanoethyl group on the indole **109** could be removed by alkaline hydrolysis and heating in 34% yield.



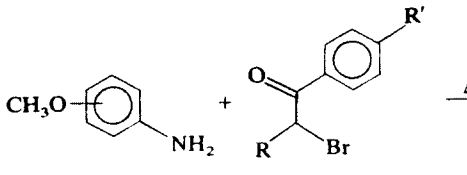
Scheme 10

Although α-haloaldehydes are rarely used, Troxler and co-workers did achieve[384] a 6% yield of 4-benzyloxy-7-methylindole from 4-benzyloxy-2-aminotoluene and chloroacetaldehyde diethyl acetal.

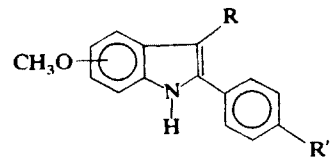
2. *Aromatic α-Bromoketones or Benzoin*

Mentzer and co-workers reported that bromoacetophenone (**111**) and *o*- or *p*-anisidine on heating to 180° for 5 minutes afforded 2-phenyl-7-methoxyindole (**116**)[119a,b] (27–45%) and 2-phenyl-5-methoxyindole

(**115**),[120a] respectively. With the α-bromopropiophenone **114** and *p*- or *m*-anisidine, Mentzer obtained the 5- and 6-methoxy-2-*p*-anisyl-3-methylindoles, **121** and **122** (85%), respectively,[120a,b] and the acetophenone analogue **112** with *p*-anisidine gave 2-aryl-5-methoxyindole **117** in 14% yield.[120a] Clerc–Bory using a ratio of 1 : 5 of either *p*- or *m*-anisidine and α-bromopropiophenone (**113**) obtained 5- and 6-methoxy-2-phenyl-3-methylindole (**119** and **120**) in 68 and 50% yield, respectively.[121] Under the same conditions, *o*-anisidine and **112** afforded 37% of 2-*p*-anisyl-7-methoxyindole (**118**).[122]



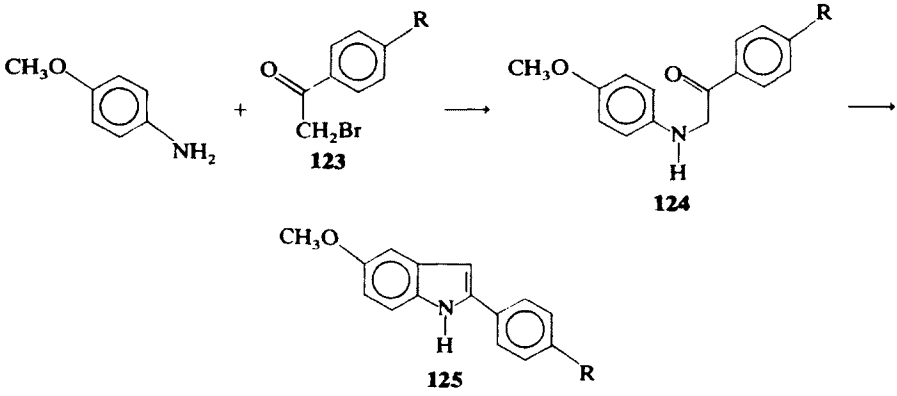
	R	R′
111	H	H
112	H	OCH_3
113	CH_3	H
114	CH_3	OCH_3



	R	R′	isomer
115	H	H	5
116	H	H	7
117	H	OCH_3	5
118	H	OCH_3	7
119	CH_3	H	5
120	CH_3	H	6
121	CH_3	OCH_3	5
122	CH_3	OCH_3	6

Terentev and Preobrazhenskaya have used the Bischler reaction and Clerc–Bory's ratio of reactants to prepare a series of 2-aryl-substituted 5-methoxyindoles (**125**) from *p*-anisidine and various *p*-substituted bromoacetophenones (**123**).[123] Similar syntheses have been reported by Buchmann and Lindow.[124] The intermediate α-anilinoacetophenones **124**, in this case, were cyclized with catalytic amounts of HBr in refluxing aniline. Some typical yields reported by these two groups are below.

The structure of the major reaction product (85%) from benzoin and *m*-aminophenol (**126**) has occasioned some controversy. Orr and Tomlinson showed that this product **131** could be methylated to the 6-methoxyindole derivative **132**, clearly different from its 4-methoxy isomer **136** unambiguously synthesized from 2-chloro-5-methoxyaniline (**129**) and benzoin via **135**[125] (Scheme 11). Teuber and Schnee argued that since the latter product in their hands was identical with that formed in a Bischler reaction of *m*-anisidine (**127**) and benzoin, ring closure must have been *ortho* to the methoxyl group in *both* **127** and **129**.[126] Tomlinson and co-workers suggested[33] that Teuber and Schnee's results stemmed from

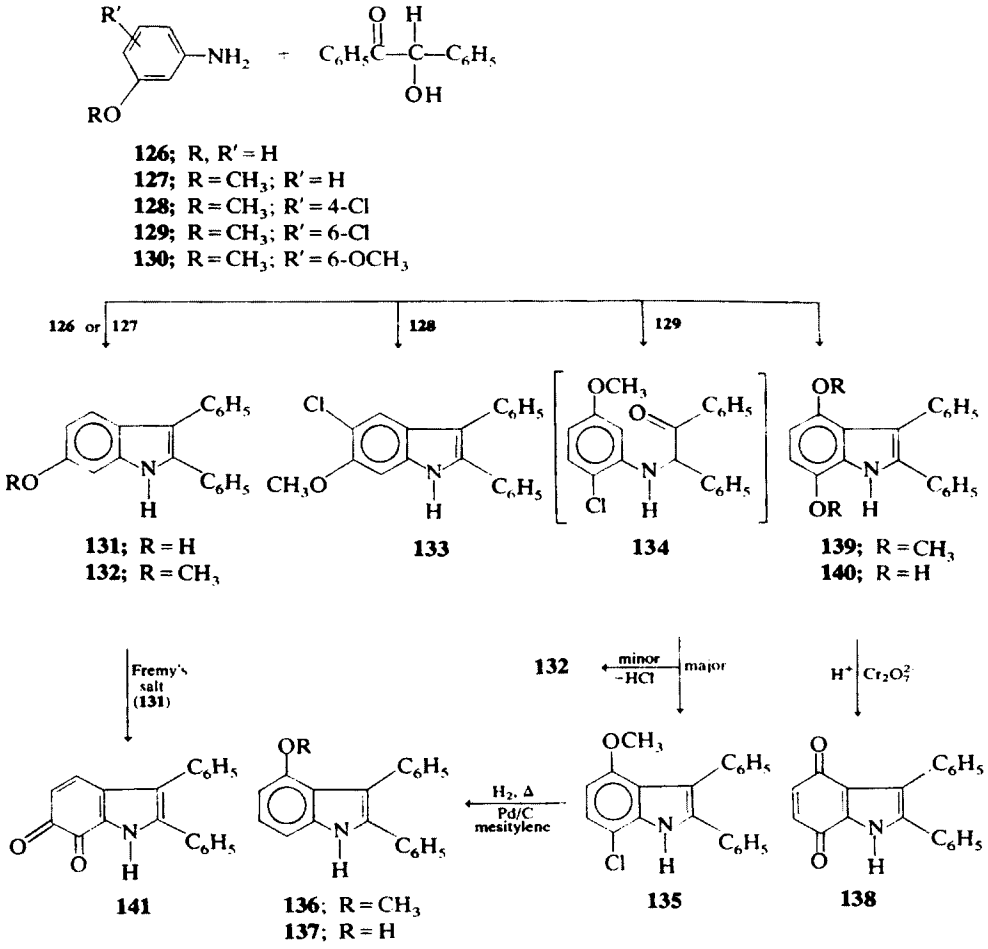


R	%(Ref. 123)	%(Ref. 124)
H	59	28
OCH_3	28	49
OCH_2CH_3	—	71
O-*n*-C_3H_7	—	58
CH_3	59	—

the isolation, in low yield, of the sparingly soluble by-product **132**, produced in a side reaction by the extrusion of chlorine during the cyclization of **134**.

The assignments of Orr and Tomlinson, that is, cyclization *para* to the hydroxyl or methoxyl group in *m*-aminophenol or *m*-anisidine, were corroborated by oxidation of the *m*-aminophenol product **131** and 2,3-diphenyl-4-hydroxyindole (**137**) with potassium nitrosodisulfonate (Fremy's salt).[33] Oxidation of **137** afforded a quinone identical with that obtained on dichromate oxidation of 2,3-diphenyl-4,7-dihydroxyindole (**140**) which must therefore be the 4,7-quinone **138**. The dihydroxy compound **140** was synthesized via **139** by the route shown. Quinone **138**, which does not form a phenazine derivative with *o*-phenylenediamine, is clearly different from the quinone obtained on oxidation of **131**, which does form such a derivative. The latter quinone must therefore be an orthoquinone, most probably the 6,7-quinone **141**. The results again support a 6-hydroxyindole structure for the *m*-aminophenol–benzoin product.

Tomlinson and co-workers also synthesized 2,3-diphenyl-5-chloro-6-methoxyindole (**133**) from **128** by the route shown as an independent check to show that no chlorine migration occurred during the Bischler reaction of benzoin with **129**. The expected 6-methoxyindole **132** resulted after catalytic hydrogenation[33] (see also Ref. 366).

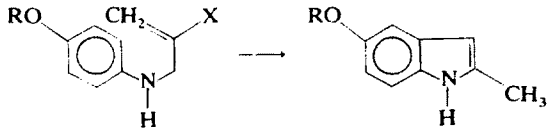


Scheme 11

Teuber and Staiger proposed[127] that the structure of the reaction product (68%) from 3-methoxy-4-methylaniline and benzoin was 2,3-diphenyl-4-methoxy-5-methylindole. It would seem that this assignment is also questionable.

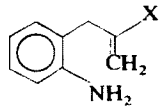
3. *Related Syntheses*

A patent by Towne and Hill[128] describes the synthesis of 2-methyl-5-hydroxyindole (**143**, R = H) from *p*-aminophenol and α-chloroallyl chloride by cyclizing the intermediate *N*-(2-chloroallyl)arylamine (**142**,

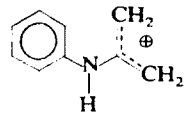


142; R = H, CH_3
X = Cl, Br

143; R = H, CH_3



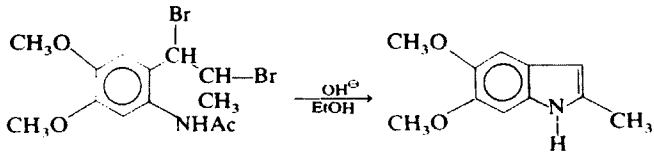
142a; X = Cl, Br



142b

R = H, X = Cl) with anhydrous HF at 200° in an autoclave. 2-Methyl-5-methoxyindole (**143**, R = CH_3) has recently been synthesized from *p*-anisidine and α-bromoallyl bromide using boron trifluoride as a catalyst.[370] Extensive demethylation of the product by the catalyst limited the yield to 30%, though the yields of other indoles made by this method generally exceeded 90%. Hudson and co-workers, using ^{14}C-labeled intermediates, carried out a mechanistic study of this rearrangement and suggested that the reaction proceeded by two concurrent mechanisms, a Claisen rearrangement (via **142a**) and a pathway involving an allylic carbonium ion (**142b**), produced in a 1 → 2 nitrogen shift.[370]

Lions has reported[129] the synthesis of 2-methyl-5,6-dimethoxyindole (**145**) when 5-acetylamino-4-allylveratrole dibromide (**144**) is treated with ethanolic hydroxide.



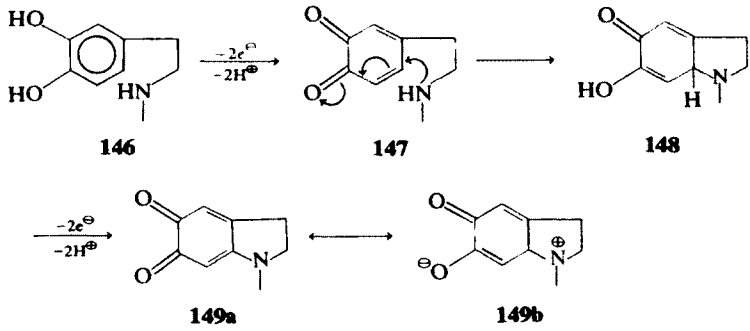
144 **145**

F. 5,6-Dihydroxyindoles from Aminochromes

1. *Introduction*

This section and the following deal with the direct synthesis of hydroxyindoles via quinone intermediates. Several recent reviews on the chemistry of aminochromes briefly treat their conversion into 5,6-dihydroxyindoles.[130-132]

Aminochromes (**149a** ↔ **149b**), the deeply colored, unstable, crystalline substances obtained on oxidation of 3,4-dihydroxyphenylethylamines **146**—most typically with alkaline ferricyanide or silver oxide—are considered to arise from an intramolecular Michael addition (**147** → **148**) of the ethylamino side chain to an initially formed orthoquinone **147** (Scheme 12). A second oxidation step produces the aminochromes. On

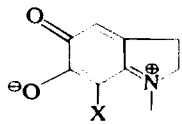


146 **147** **148**

149a **149b**

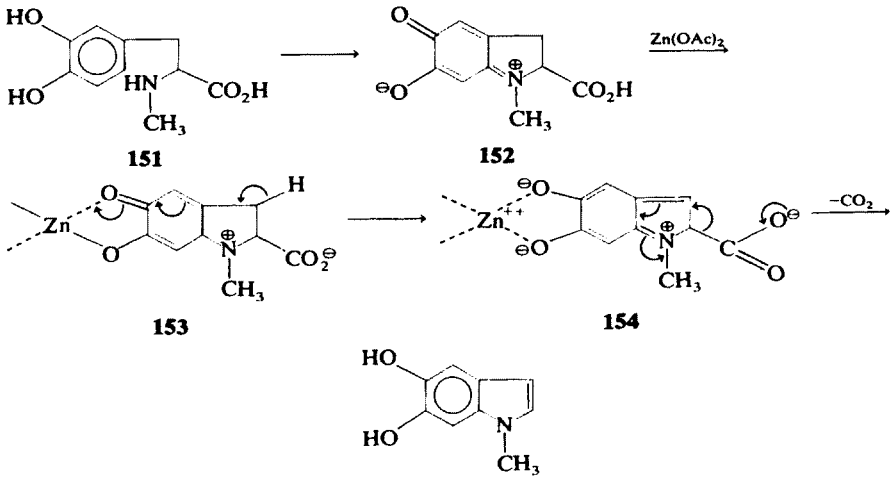
Scheme 12

the basis of their solubilities, their monoderivatives with carbonyl-group reagents and their spectroscopic properties, they are most correctly represented by the zwitterionic structure **149b**.[133a,b] The aminochromes are of three principal types (excluding the halogenated derivatives **150**, which will be discussed separately): (1) aminochromes derived from 3,4-dihydroxyphenylalanine ("dopa") derivatives, (2) those derived from simple 3,4-dihydroxyphenylethylamines ("dopamines"), and (3) the *adrenochromes*. The last group, by far the largest and most thoroughly investigated, results on oxidation of adrenaline (epinephrine) (**159**), noradrenaline, or their derivatives. Chapter 9 treats the preparation and reactions of aminochromes in greater detail.



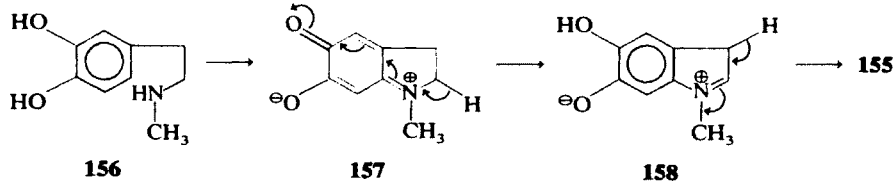
150; X = Br, I

If the aminochrome is of either type 1 or 2, a simple rearrangement with concomitant decarboxylation (Scheme 13) or prototropic shift (eq. 5) affords the dihydroxyindole, generally in good yield. These rearrangements, which are usually quite facile, are spontaneous in some cases,[134a,b] or can be catalyzed with zinc salts,[135a,b] alkali,[140] pyridine–acetic anhydride,[134b] or palladium on carbon.[134a,b] Bu'Lock and Harley-Mason have



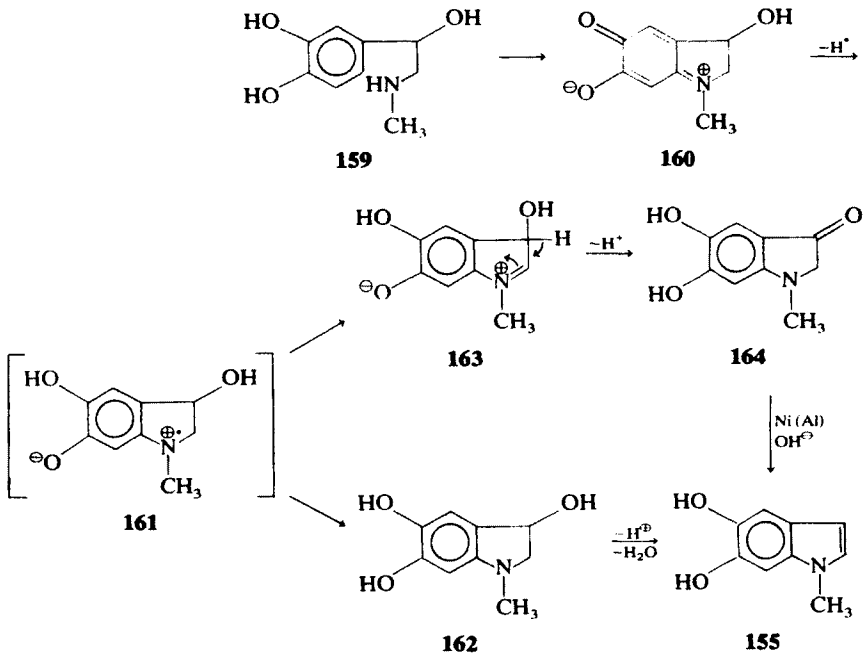
Scheme 13

proposed[135b] structure **153** for the zinc–aminochrome complex from *N*-methyl dopa (**151**). Similar structures were also proposed for the complexes with dopachrome and epinochrome (**157**). Coordination with the zinc ion was envisioned as providing the driving force for the loss of the proton from the 3-position. Isomerization with concerted loss of CO_2 produces 1-methyl-5,6-dihydroxyindole (**155**). Other variants of this mechanism are possible.



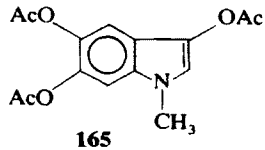
(5)

The adrenochromes, on the other hand, require both a reduction and a dehydration step in order to form 5,6-dihydroxyindoles. The most widely accepted mechanism for the formation of 5,6-dihydroxyindoles by catalytic or dithionite reduction of adrenochromes is that proposed by Harley-Mason,[133a,b] who observed that hydrogenation of adrenochrome (**160**) was complete after the uptake of *one-half* mole of hydrogen per mole and that 1-methyl-5,6-dihydroxyindole (**155**) and 1-methyl-3,5,6-trihydroxyindole (**164**) were produced in equimolar quantities (Scheme 14). He proposed the initial formation of an unstable zwitterionic semiquinone **161** which disproportionates to 1-methyl-3,5,6-trihydroxyindole



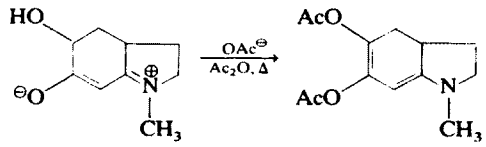
Scheme 14

(**162**) and the indoxyl precursor **163**. Dehydration of the former and rearrangement of the latter (catalyzed by dilute alkali) afford the indole **155** and the indoxyl **164**, respectively. It would seem that this mechanism may require some modification when other reducing agents are employed since reductions of adrenochrome with ascorbic acid[138] or sodium borohydride[137] have been reported as producing **155** in yields substantially greater than 50%. In these cases, some reduction, either of the indoxyl precursor **163** or of the indoxyl itself, may be occurring. Harley-Mason did observe[133b] that **164** could be reduced to **155** in 44% yield using alkali and Raney nickel alloy, presumably via the unstable hydroxyindoline **162**.



165

When adrenochromes are treated with pyridine and acetic anhydride, acetylated indoxyl derivatives analogous to **165** result.[132] Epinochrome (**157**) likewise gives 1-methyl-5,6-diacetoxyindole.[134b]



166 **167**

When either epinochrome (**157**) or **155** is hydrogenated for extended periods, a slow uptake of two moles of hydrogen is observed. The reduction product (80%) is thought to have the zwitterionic structure **166**. On acetylation, the interesting tetrahydro-5,6-diacetoxyindole derivative **167** is formed.[134b]

2. *Preparation of* 1-*Methyl*-5,6-*dihydroxyindole* (**155**)

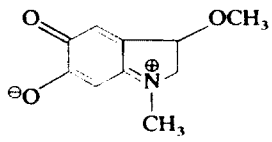
All three aminochrome pathways were utilized to prepare **155** by Harley-Mason and Bu'Lock in a pioneering study on the chemistry of the aminochromes. Adrenochrome (**160**), prepared using Burton's procedure [354] with silver oxide in methanol, was reduced with hydrogen and a palladium–carbon catalyst or with aqueous dithionite to give **155** in 33% yield.[133a,b] Compound **155** could also be prepared in overall yields of 40 and 71%, respectively, from the *N*-methyl "dopachrome" (**152**) and epinochrome (**157**) by rearrangement in the presence of zinc acetate. The aminochromes were prepared by oxidation of *N*-methyl dopa (**151**) and epinine (**156**) with ferricyanide in aqueous bicarbonate.[135a,b]

Austin and co-workers synthesized **155** in 80% yield by oxidizing epinine (**156**); the intermediate epinochrome (**157**) could be rearranged to **155** either spontaneously or by using a palladium–carbon catalyst.[134a,b]

Heacock and Laidlaw have described the use of a number of reducing agents including zinc in aqueous acetic acid, sodium borohydride, thiols, bisulfite, and ascorbic acid which can be used to convert adrenochrome to **155**.[136a,b]

Heacock and co-workers obtained **155** in 74% yield from adrenochrome by borohydride reduction or in 48% overall yield from adrenaline using a silver oxide oxidation followed by the same reduction. Reduction of **160** with zinc in 2% acetic acid gave **155** in 38% yield. Oxidation of adrenaline (**159**) with silver oxide followed by reduction with either borohydride or zinc in acetic acid and acetylation gave the diacetate of **155** in 32 and 19% yield, respectively.[137]

Mattok and Heacock have reported improved yields of **155** (57%) using a two-phase ether–water system for the oxidation of adrenaline with



168

alkaline ferricyanide and the subsequent adrenochrome reduction with ascorbic acid. The indole concentrates in the ether layer preventing its further oxidation by dihydroascorbic acid.[138]

The zinc–acetic acid reduction of adrenochrome methyl ether (**168**), arising by oxidation of adrenaline methyl ether, gave **155** in low yield.[139]

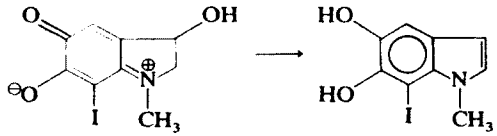
3. *Preparation of Other 1-Alkyl-5,6-dihydroxyindoles*

1-Ethyl- and 1-isopropyl-5,6-diacetoxyindole were prepared in 23 and 11% yield, respectively, from the corresponding *N*-alkylnoradrenalines by silver oxide oxidation, followed by borohydride reduction and acetylation. When the reduction was effected with zinc in aqueous acetic acid, 1-isopropyl-5,6-diacetoxyindole resulted in 42% yield after acetylation.[137]

4. *Preparation of 7-Halo-5,6-dihydroxyindoles*

The structures of the halogenated aminochromes have recently been reinvestigated by Witkop, Heacock, and co-workers, and the early assignments of the 2- or 3-position for the halogen atom have been revised. The halogen atom has now been shown to occupy the 7-position.[99]

When adrenaline is oxidized with potassium iodate[141,142] or iodic acid,[142] 7-iodoadrenochrome (**169**) results. Mattok and Wilson have recently shown[143] that iodination of adrenochrome with iodine affords the same product, suggesting that iodination occurs as the last step in the formation of this compound. On dithionite reduction, **169** yields 1-methyl-5,6-dihydroxy-7-iodoindole (**170**) in 25% overall yield from adrenaline.[142]



169 **170**

In view of the fact that dopa, on ferricyanide oxidation and dithionite reduction, gives low and irreproducible yields of 5,6-dihydroxyindole, the alternative synthesis devised by Heacock and co-workers is of interest. Deiodination of 5,6-diacetoxy-7-iodoindole with zinc–acetic acid—a reaction first reported by Bergel and Morrison[141]—yielded 5,6-diacetoxyindole.[137] The iodoindole could be obtained in 41% yield using an iodate oxidation of noradrenaline followed by reduction with ascorbic acid and acetylation with acetic anhydride in pyridine.[137]

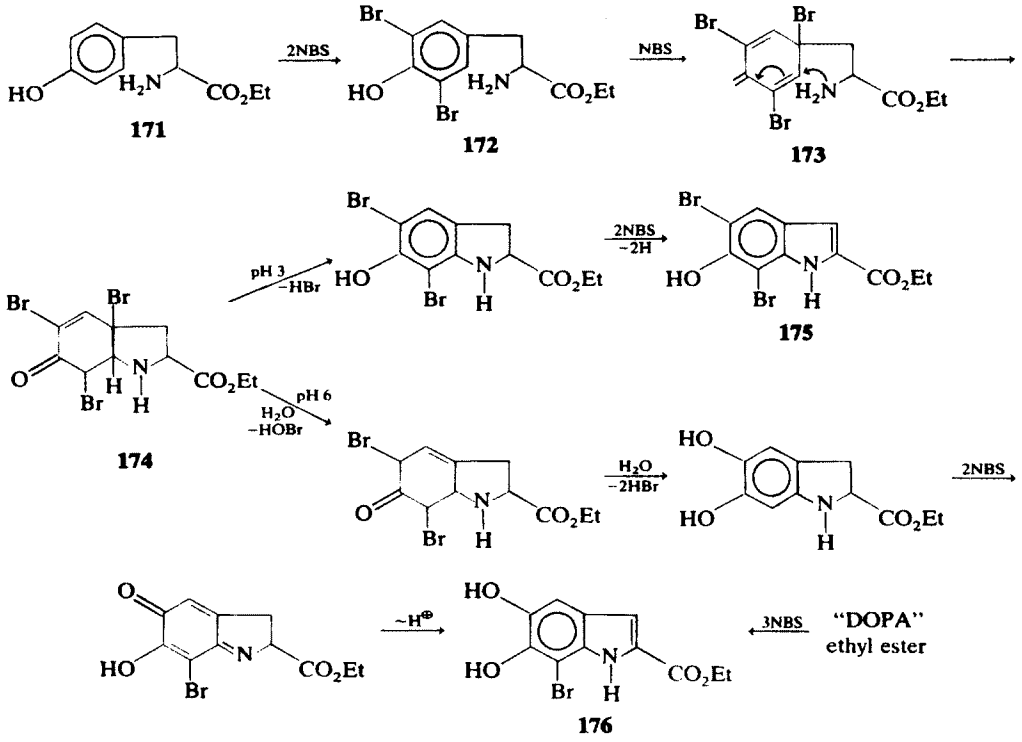
1-Ethyl-5,6-diacetoxy-7-iodoindole was obtained in 41% yield by dithionite reduction of 1-ethyl-7-iodonoradrenochrome followed by acetylation. Reduction of 1-isopropyl-7-iodonoradrenochrome with aqueous dithionite or borohydride and subsequent acetylation furnished 1-isopropyl-5,6-diacetoxy-7-iodoindole in 32 and 56% yield, respectively.[144]

Harley-Mason obtained 1-methyl-5,6-dihydroxy-7-bromoindole (42%) using a bromine oxidation of adrenaline in acetate buffer, followed by dithionite reduction.[133b]

5. *Other 7-Halo-5,6-dihydroxyindoles*

Wilchek and co-workers have described the synthesis of ethyl 5,6-dihydroxy-7-bromoindole-2-carboxylate (**176**) in 25% yield by oxidation of dopa ethyl ester with three equivalents of *N*-bromosuccinimide (NBS) (Scheme 15). When the intermediate "dopachrome" was reduced with dithionite, a low yield of the 2,3-dihydro derivative of **176** could also be isolated.[145b] An analogous iodo derivative has also been reported by Bu'Lock and Harley-Mason.[135b]

It is interesting to note that under certain conditions **176** is also formed by cyclization of tyrosine ethyl ester (**171**) with NBS. Wilchek and co-workers had discovered that tyrosine amides and esters could be cyclized to derivatives of 6-hydroxyindole with four equivalents of this oxidant in aqueous acetic acid. Tyrosine ethyl ester gave 21% of 5,7-dibromo-6-hydroxyindole-2-carboxylate (**175**) as well as **176** (5%). When the pH of the reaction mixture was adjusted to 6 after the NBS addition, the dihydroxyindole **176** was the major (28%) product and the monohydroxyindole (**175**) now the minor (5%) product. Both products can be considered to arise via an intermediate tetrahydroindole **174**, formed by an intramolecular Michael addition of the α-amino group to the initially formed tribromodienone **173**. Supporting this mechanism are the observations that dibromotyrosine ethyl ester **172** affords the same products and that in certain cases tribromodienone intermediates can be isolated



Scheme 15

and characterized.[145a,b] Probable pathways (**174** → **175** + **176**) are shown below, although the proposed intermediates are purely speculative.

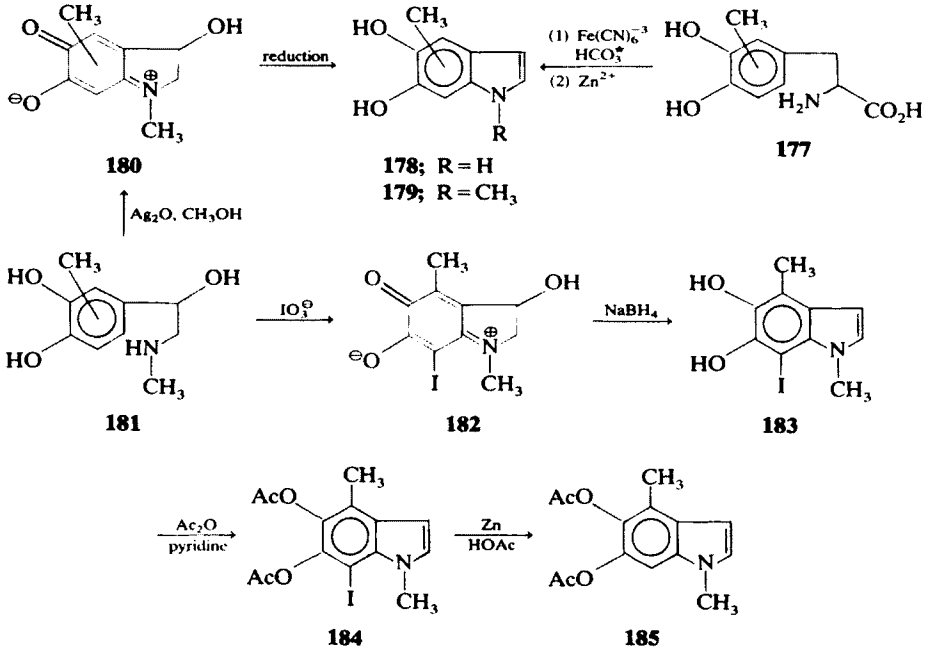
Dukler and co-workers have recently shown[340] that aqueous solutions of Fremy's salt (potassium nitrosodisulfonate) at pH 8 also convert tyrosine derivatives to 5,6-dihydroxyindole-2-carboxylic acid derivatives, in yields of roughly 40%. In this case, no halogen is incorporated into the product.

6. *C-Methyl-5,6-dihydroxyindoles*

The 4- and 7-methyl-5,6-dihydroxyindoles **178** were prepared in 40 and 12% yields, respectively, by Cromartie and Harley-Mason by oxidation of 2- and 5-methyl dopa (**177**) with alkaline ferricyanide, followed by isomerization with zinc sulfate[146] (Scheme 16).

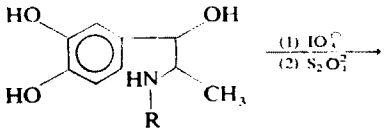
Likewise, 1,4-dimethyl- and 1,7-dimethyl-5,6-dihydroxyindoles (**179**)

were obtained in 41 and 22% yields, respectively, on oxidation of the appropriate adrenalines **181** with silver oxide in methanol followed by reduction of the intermediate 4- and 7-methyladrenochromes (**180**) with ascorbic acid.[147] 7-Iodo-4-methyladrenochrome (**182**) was formed when the adrenaline **181** was oxidized with iodate. Borohydride reduction gave 1,4-dimethyl-5,6-dihydroxy-7-iodoindole (**183**) in 40% overall yield. 5-Methyladrenaline, on the other hand, failed to yield an iodoaminochrome on oxidation with iodate, and instead gave 7-methyladrenochrome. 1,4-Dimethyl-5,6-diacetoxy-7-iodoindole (**184**), prepared from **183** with acetic anhydride and pyridine, was deiodinated with zinc in boiling acetic acid to afford 1,4-dimethyl-5,6-diacetoxyindole (**185**).[147]

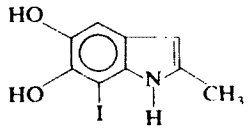


Scheme 16

Witkop, Heacock, and co-workers have reported[99] that 2-methyl-5,6-dihydroxy-7-iodoindole (**189**) could be obtained in 34% yield by iodate oxidation of α-methylnoradrenaline (**186**) followed by dithionite reduction. Deiodination with zinc in boiling acetic acid afforded 2-methyl-5,6-dihydroxyindole. When **189** was acetylated first, deiodination afforded 2-methyl-5,6-diacetoxyindole (**190**) in 46% yield.



186; R = H
187; R = CH_3
188; R = C_2H_5



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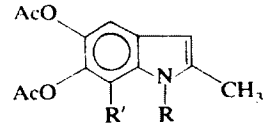


190; R = R′ = H
191; R′ = H; R = CH_3 or C_2H_5
192; R′ = I, R = CH_3 or C_2H_5

Hutzinger and Heacock have described[148] the synthesis, in very low yield, of 1-methyl- and 1-ethyl-2-methyl-5,6-diacetoxyindoles (**191**) by ferricyanide oxidation of α-methyladrenaline (**187**) and α-methyl-*N*-ethylnoradrenaline (**188**), respectively, followed by a borohydride reduction and acetylation. On iodate oxidation, **187** and **188** were converted into the 7-iodoindole derivatives **192** in 12 and 30% yield, respectively.

The preparation of acetylated 1-methyl-2-(3,4-dihydroxybenzyl)-[377] and 1-(3-hydroxybenzyl)-5,6-dihydroxyindole[368b] by alkaline ferricyanide oxidation of the appropriate *N*-alkyl dopamines followed by acetylation has been reported.

G. The Nenitzescu Synthesis of 5-Hydroxyindoles

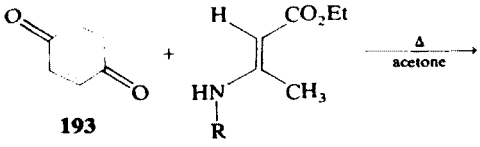
1. *Introduction*

This reaction has recently been reviewed by Domschke.[149] This section is concerned mainly with the application of this reaction to the preparation of 3-unsubstituted 5-hydroxyindoles. The route involves condensations of *p*-benzoquinones with β-aminocrotonate esters; the resultant indole esters are readily saponified and decarboxylated. The synthesis of other 5-hydroxyindole derivatives is discussed where important deductions have been drawn concerning the mechanism of the reaction.

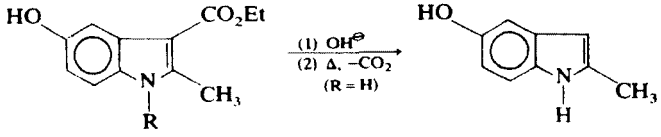
There has recently been a resurgence of interest in the Nenitzescu synthesis as a convenient route to intermediates for the preparation of

mitomycin and its analogues[150,151c] and the antiserotonin drug, 1-benzyl-2-methyl-5-methoxytryptamine.[152,153] A brief survey of its early development follows.

In 1929, Nenitzescu reported[154] that *p*-benzoquinone (**193**) and ethyl β-aminocrotonate (**194**: EAC) in boiling acetone afforded ethyl 2-methyl-5-hydroxyindole-3-carboxylate (**197**) in 30% yield. This was converted to 2-methyl-5-hydroxyindole (**200**) in poor overall yield by separate steps of saponification and decarboxylation. Similarly, *N*-phenyl (**195**) or *N*-carboethoxymethylene (**196**) crotonates afforded the *N*-substituted indoles **198** and **199**.



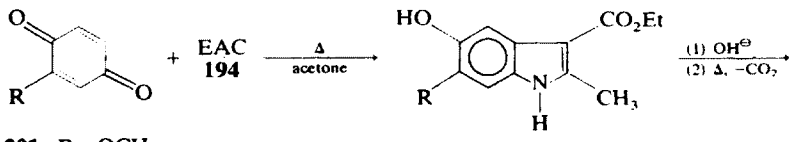
194; R = H (EAC)
195; R = C_6H_5
196; R = CH_2CO_2Et



197; R = H
198; R = C_6H_5
199; R = CH_2CO_2Et

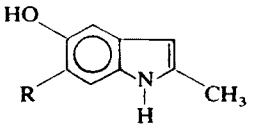
200

This synthesis lay dormant in the literature until revived and extended by Robertson and co-workers,[93] who confirmed the identity of Nenitzescu's 2-methyl-5-hydroxyindole by comparison with material prepared by an unambiguous synthesis. In addition they discovered that the 5-hydroxyindole-3-carboxylic acid esters prepared by Nenitzescu underwent appreciable decarboxylation during alkaline hydrolysis, which accounts for Nenitzescu's low yield of the 3-carboxylic acids. In an extension of the reaction, they achieved satisfactory syntheses using substituted *p*-benzoquinones. With EAC and methoxy- (**201**) or methyl-substituted (**202**) *p*-benzoquinone, the 6-substituted 5-hydroxyindoles, **204** and **205**, were obtained in 24 and 45% yield. Hydroxy-*p*-benzoquinone (**203**) was reported to give the 5,6-dihydroxyindole derivative **206**, although the yield was not stated. When 2-hydroxy-5,6-dimethyl-*p*-benzoquinone (**210**) was employed, ethyl 2,4,7-trimethyl-5,6-dihydroxyindole-3-carboxylate was formed in 48% yield. A one-step saponification and decarboxylation of these materials was developed using boiling dilute alkali under nitrogen and gave the 6-methoxy (**207**), 6-methyl (**208**),



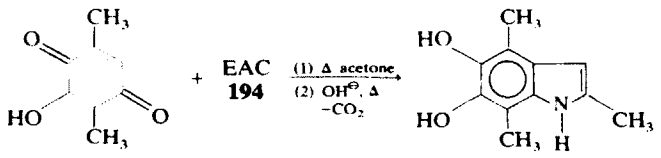
201; R = OCH_3
202; R = CH_3
203; R = OH

204; R = OCH_3
205; R = CH_3
206; R = OH



207; R = OCH_3
208; R = CH_3
209 R = OH

6-hydroxy (**209**), and 6-hydroxy-4,7-dimethyl (**211**) derivatives of 2-methyl-5-hydroxyindole in 72, 87, 46, and 91% yield, respectively. Although the structure of 2-methyl-5-hydroxy-6-methoxyindole (**207**) was confirmed by an independent synthesis from the appropriate dinitrostyrene the structures of the reaction products from the methyl and hydroxy *p*-benzoquinones were assigned by analogy.

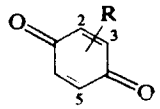


210 **211**

Since this work was published, many other substituted *p*-benzoquinones have been employed in the Nenitzescu reaction. The effect of substituents in the quinone ring on the structure of the resulting 5-hydroxyindoles is discussed in Section III.G.4.

2. *Scope of the Reaction*

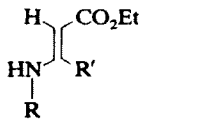
a. QUINONE COMPONENT. The following monosubstituted *p*-benzoquinones (**212**) have been employed in the Nenitzescu reaction: fluoro,[155] chloro,[155,156] bromo,[155] iodo,[155] methyl,[93,151a–d,157–159] ethyl,[151a–c] trifluoromethyl,[155] methoxy,[93,151a–c,160] carbomethoxy,[161] and benzylthio.[162]



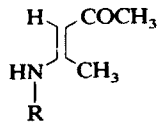
212; R = monosubstituent
213; R = 2, 3-Cl_2
214; R = 2, 5-Cl_2
215; R = 2, 3-$(CH_3)_2$
216; R = 2-Cl, 3-CF_3
217; R = 2-Cl, 5-CF_3
218; R = 2-OCH_3, 5-CF_3

Disubstituted *p*-benzoquinones that have been used are the 2,3-dichloro (**213**),[163–166] 2,5-dichloro (**214**),[166] 2,3-dimethyl (**215**),[157] 2-chloro-3-trifluoromethyl (**216**),[155] 2-chloro-5-trifluoromethyl (**217**),[155] 2-chloro-5-methyl, and 2-methyl-5-trifluoromethyl (**218**)[155] *p*-benzoquinones.

b. Enamine Component. In addition to EAC and its *N*-alkyl or *N*-aryl derivatives **219**, the following enamines have been employed in the Nenitzescu reaction: ethyl β-aminocinnamate (**220**)[167] and its *N*-*n*-butyl and *N*-benzyl derivatives,[159] β-aminocinnamonitrile,[167] ethyl β-ethylaminopentenoate (**221**),[151c,d] β-aminocrotonanilide and β-methylaminocrotonanilide,[168] the acetylacetonimines **223**[163,165,166,169] and imine derivatives of acetone dicarboxylic acid ethyl ester **222**.[171] Table I in the Appendix of Tables summarizes the enamines **219–223** which have been employed in the Nenitzescu reaction.

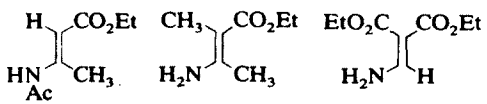


219; R′ = CH_3
220; R′ = C_6H_5
221; R′ = Et
222; R′ = CH_2CO_2Et

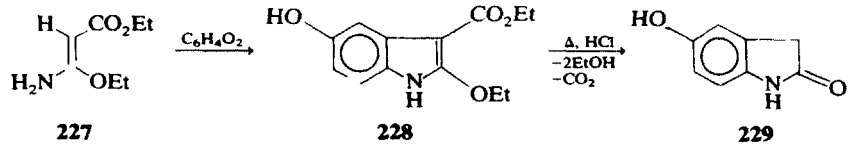


223

Robertson and co-workers have shown[160] that ethyl *N*-acetyl-β-aminocrotonate (**224**), ethyl β-amino-α-methylcrotonate (**225**), and ethyl aminomethylenemalonate (**226**) fail to react with *p*-benzoquinone in a Nenitzescu reaction.



224 **225** **226**



227 228 229

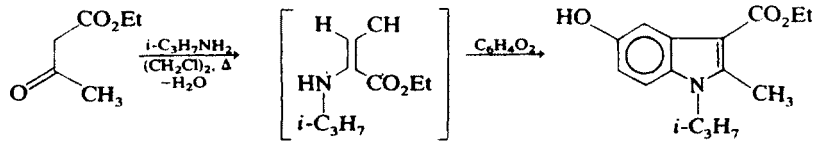
In a novel oxindole synthesis, Robertson and co-workers employed ethyl β-amino-β-ethoxyacrylate (**227**) and *p*-benzoquinone and obtained the 2-ethoxyindole derivative **228**, which could be converted into 5-hydroxyoxindole (**229**) with dilute HCl in good yield.[160]

3. *Synthetic Procedures*

Although Nenitzescu and a number of subsequent investigators employed refluxing acetone for this condensation,[151a–d,156,162–164,166] the use of solvents capable of forming an azeotrope with water seems now to be preferred. Among the solvents employed for this purpose are chloroform,[172] benzene,[172] and dichloroethane.[158,164,171,175] In addition, methanol,[155] ethanol,[159,161] and acetic acid[159,167] are reported to work well.

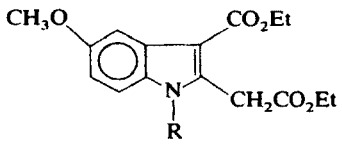
Although Domschke and Fürst have advocated[172] a 100% excess of crotonate over quinone, current practice favors equimolar proportions of the two reactants, although excesses of quinone are apparently not deleterious.[159]

Grinev and co-workers have described the generation *in situ* of *p*-benzoquinone using *p*-hydroquinone and potassium bromate.[165] In another variation of the Nenitzescu reaction, these workers also generated the crotonate component *in situ*; a number of *N*-substituted 3-aminocrotonates were prepared using aromatic amines and ethyl acetoacetate in refluxing dichloroethane containing HCl.[170,174] On addition of *p*-benzoquinone, *N*-substituted 2-methyl-5-hydroxyindoles resulted in 27–32% yield. Wrotek and co-workers employed a mixture of ethyl acetoacetate, isopropylamine, and *p*-benzoquinone in refluxing dichloroethane and obtained ethyl 1-isopropyl-2-methyl-5-hydroxyindole-3-carboxylate (eq. 6).[177]

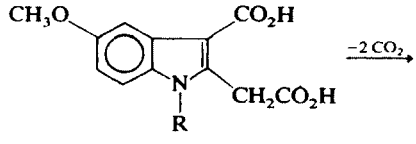


(6)

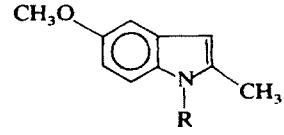
The conversion of 5-hydroxy- or 5-methoxyindole-3-carboxylic acid esters into the 3-unsubstituted 5-hydroxyindole can be accomplished with either acid or base hydrolysis. Grinev and co-workers have employed acetic acid containing either sulfuric[152,174] or phosphoric acid,[178] which gives the hydroxyindoles directly. Alternatively, a two-step procedure with a pyrolytic decarboxylation step could be used.[179a,b] Allen and co-workers have obtained 60–80% yields of hydroxyindoles using 20% HCl.[151c,d] Raileanu and Nenitzescu employed refluxing 2*N* NaOH to convert ethyl 2-phenyl-5-hydroxyindole-3-carboxylate to 2-phenyl-5-hydroxyindole in 67% yield.[167] The *N*-*n*-butyl and *N*-benzyl derivatives of the same indole were prepared in 65 and 67% yield, respectively, using a two-step saponification–decarboxylation.[159] Trofimov and co-workers have described[171] the decarboxylation of the 5-methoxyindole dicarboxylic acid **231** to *N*-methyl- or *N*-ethyl-2-methyl-5-methoxyindole (**232**) in hot ethylene glycol containing urea. The acid **231** was prepared by saponification of the methylated Nenitzescu product **230** which arises from *p*-benzoquinone and $EtO_2CCH_2C(NHR)=CHCO_2Et$ (R = Me or Et).



230; R = CH_3 or C_2H_5



231; R = CH_3 or C_2H_5

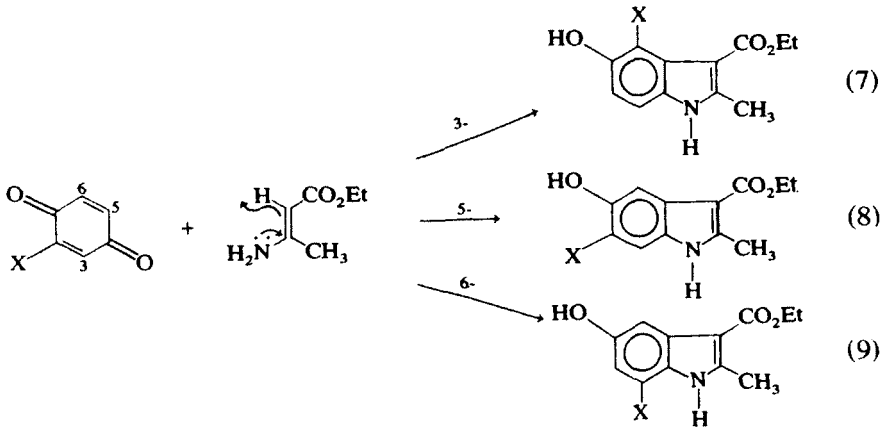


232; R = CH_3 or C_2H_5

4. *Orientation Effects*

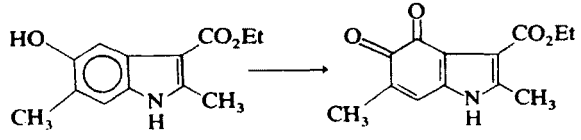
Disubstituted *p*-benzoquinones having identical substituents, for example, 2,3- and 2,5-dichloro-*p*-benzoquinones, afford indoles with only one possible structure. A monosubstituted *p*-benzoquinone could, however, conceivably yield 4-, 6-, or 7-substituted 5-hydroxyindoles (or a mixture of the three) as seen in equations 7–9.[151c,162]

Robertson and co-workers assumed that 6-substituted 5-hydroxyindoles were formed from methyl-, methoxy-, and hydroxy-*p*-benzoquinones and EAC, although the structure was established only in the



case of the methoxy derivative.[93] Grinev and co-workers isolated a chloro-5-hydroxyindole (17%) using chloro-*p*-benzoquinone and EAC, but did not propose a structure for it.[156] It now appears that they had isolated ethyl 2-methyl-6-chloro-5-hydroxyindole-3-carboxylate.[155]

On the basis of presumed intermediates in a rather unlikely mechanism for the Nenitzescu reaction, Steck and co-workers first suggested that if the quinone substituent were *ortho–para* directing, a 6-substituted 5-hydroxyindole should predominate in the reaction product.[162] Consequently they formulated the product, formed in 46% yield, from the reaction of benzylthio-*p*-benzoquinone and EAC as a 6-benzylthio derivative.[162] Teuber and Thaler assigned a 6-methyl structure to the product **233** from toluquinone and EAC since a 4,5-quinone **234** resulted on oxidation with potassium nitrosodisulfonate.[157]

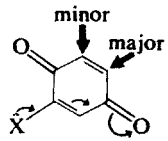


233 **234**

Allen and co-workers undertook a careful study of the reaction products of methyl- and ethyl-*p*-benzoquinone with EAC and various *N*-substituted aminocrotonates using a 1:1 ratio of reactants in acetone.[151a–c] They reported that, in most cases, minor amounts of 7-alkyl-5-hydroxyindoles accompanied the major product, the 6-alkyl derivative. In the case of toluquinone and EAC, approximately equal amounts of the two isomers resulted, although the overall conversion to

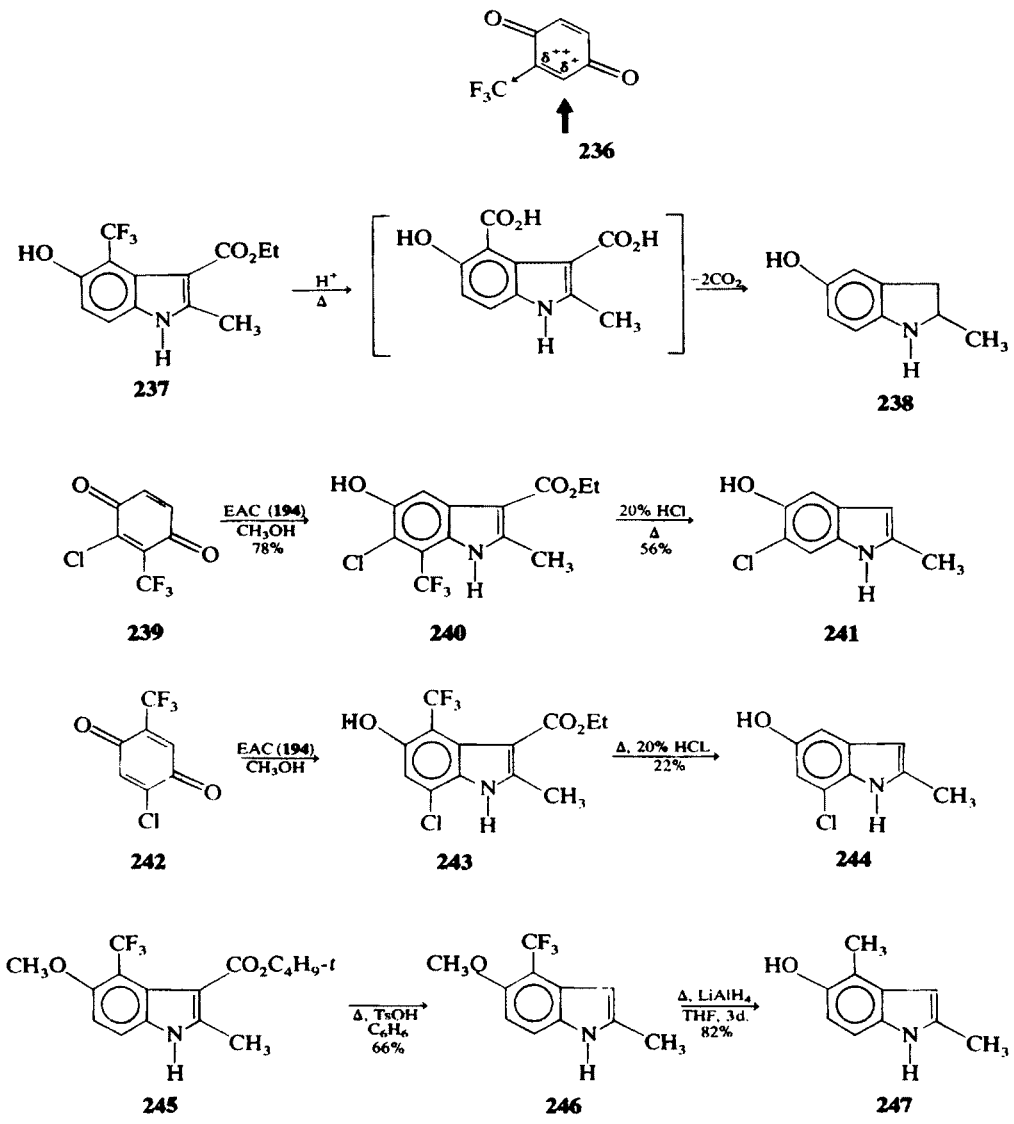
indoles was low. With *N*-methyl-3-aminocrotonate and toluquinone, the ratio of the 6-methyl to the 7-methyl isomer was 2:1. For the first time, the structures of the various 6- and 7-alkyl-5-hydroxyindoles were rigorously established by means of nmr spectroscopy, conversion to known indoles, and oxidation to quinones. Extrapolating from a somewhat limited number of examples, they generalized that the ratio of 6-alkyl- to 7-alkyl-5-hydroxyindoles increased with the increasing size of the quinone substituent and/or the nitrogen substituent of the aminocrotonate. The ratio, however, appeared to be independent of the size of the β-alkyl substituent on the aminocrotonate. Furthermore, Allen and co-workers noted[151c] that failure to detect any 4-alkyl-substituted indoles could be taken as additional evidence for the sensitivity of the initial Michael addition (see eq. 7) to steric effects.

Similarly, mixtures of 6- and 7-halo-5-hydroxyindoles were obtained with chloro-, bromo-, or iodo-*p*-benzoquinone and EAC in methanol.[155] With either methoxy-*p*-benzoquinone or fluoro-*p*-benzoquinone, however, only the 6-methoxy-5-hydroxyindole (63%)[151c] or 6-fluoro-5-hydroxyindole[155] derivatives could be detected, which was interpreted as indicating the overriding importance of resonance interaction of these quinone substituents in determining the position of the initial Michael addition (see structure **235**).



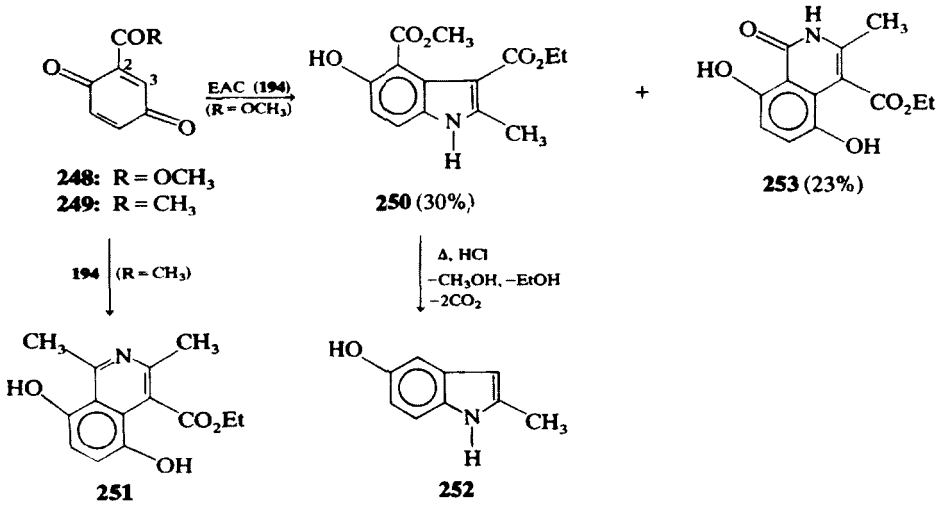
235

A trifluoromethyl substituent on the quinone ring exhibits only a feeble resonance interaction with the ring, but activates, through its inductive effect, the adjacent position toward enamine addition (see structure **236**). The result is the exclusive formation of the 4-trifluoromethyl-5-hydroxyindole (**237**).[155] In the case of the two disubstituted quinones **239** and **242**, the sole product in either case, **240** and **243**, could be predicted on the assumption that the inductive effect of the CF_3 group would outweigh the combined inductive and resonance effects of the chlorine substituent. The removal of the CF_3 group (by hydrolysis to a carboxyl group) was used in the conversion of the trifluoromethylindoles to previously characterized indoles, for example, **237** → **238**, **240** → **241**, and **243** → **244**. The directive effect of the CF_3 group and its hydrogenolysis with lithium



aluminum hydride (**246** → **247**) provided Littel and Allen with an ingenious synthesis of 2,4-dimethyl-5-methoxyindole (**247**), an indole which could not be prepared using toluquinone in the Nenitzescu synthesis.[155]

Carbomethoxy and acetyl substituents on *p*-benzoquinone resemble the trifluoromethyl group in directing addition of the enamine. Thus **248** and **249** afforded products **250** and **253** and **251** derived by addition of the



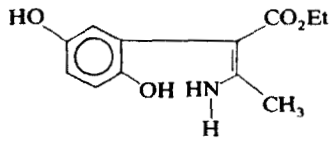
Scheme 17

enamine to the terminus of the cross-conjugated double bond. The indole ester **250** could be decarboxylated to 2-methyl-5-hydroxyindole (**252**) by acid hydrolysis[161] (Scheme 17).

Although, as mentioned above, chloro- or methyl-*p*-benzoquinone and aminocrotonates give mixtures of 6- and 7-substituted 5-hydroxyindoles, only one product, a 4-chloro-7-methyl derivative, was obtained by Poletto and Weiss when 2-chloro-5-methyl-*p*-benzoquinone was reacted with *t*-butyl 3-aminocrotonate in acetic acid.[341] In this case, the inductive effect of the chloro substituent must outweigh its steric effect. Hydrolysis and decarboxylation with *p*-toluenesulfonic acid in toluene, followed by hydrogenolysis of the chloro substituent, gave 2,7-dimethyl-5-hydroxyindole.

5. *Mechanism*

It has been principally the isolation and study of acyclic precursors that has led to the presently accepted reaction pathway for the Nenitzescu reaction. Robertson and co-workers first suggested in 1953[160] that hydroquinone adducts (e.g., **254**) might be intermediates and that these cyclize to the 5-hydroxyindoles with loss of water in some unspecified fashion. No such intermediates were actually detected until 1961, when Grinev and co-workers isolated and characterized the crotonanilide adducts (**255**, R = H, Et, $CH_2C_5H_5$) of *p*-benzoquinone in 41, 62, and 35% yield,



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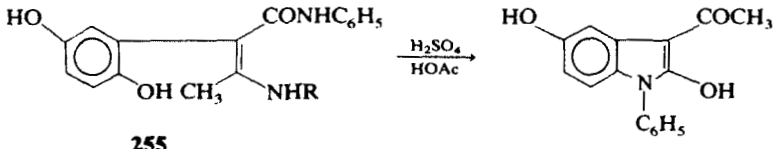
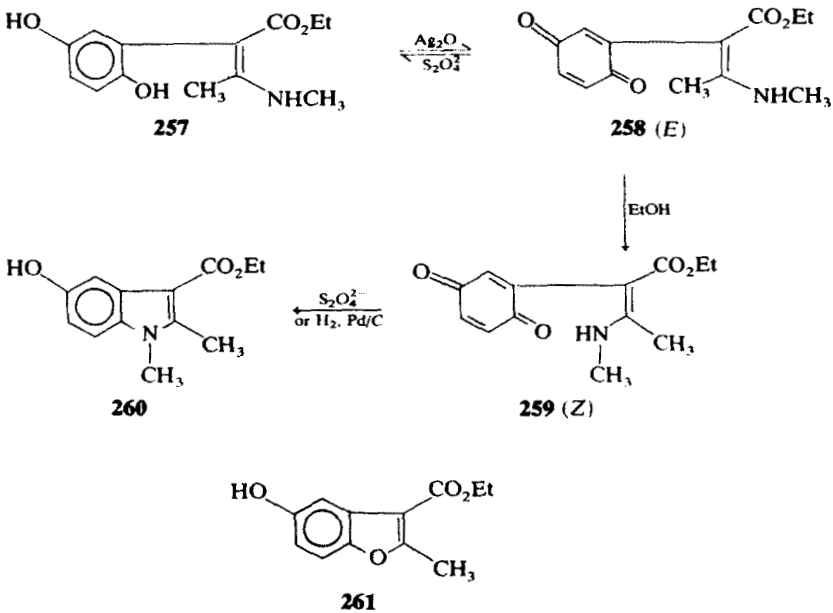


255 **256**

respectively.[168] Unexpectedly, these cyclized to 1-phenyl-3-acetyl-5-hydroxyoxindole (**256**) rather than to the 5-hydroxyindoles, on acid treatment.

In 1962, Grinev and co-workers, using a substantial excess of enamine component as first suggested by Domschke and Fürst,[172] were able to isolate 6.4% of the hydroquinone adduct **257** in addition to 47% of ethyl 1,2-dimethyl-5-hydroxyindole-3-carboxylate (**260**) (Scheme 18). A



257 **258** (*E*) **260** **259** (*Z*) **261**

Scheme 18

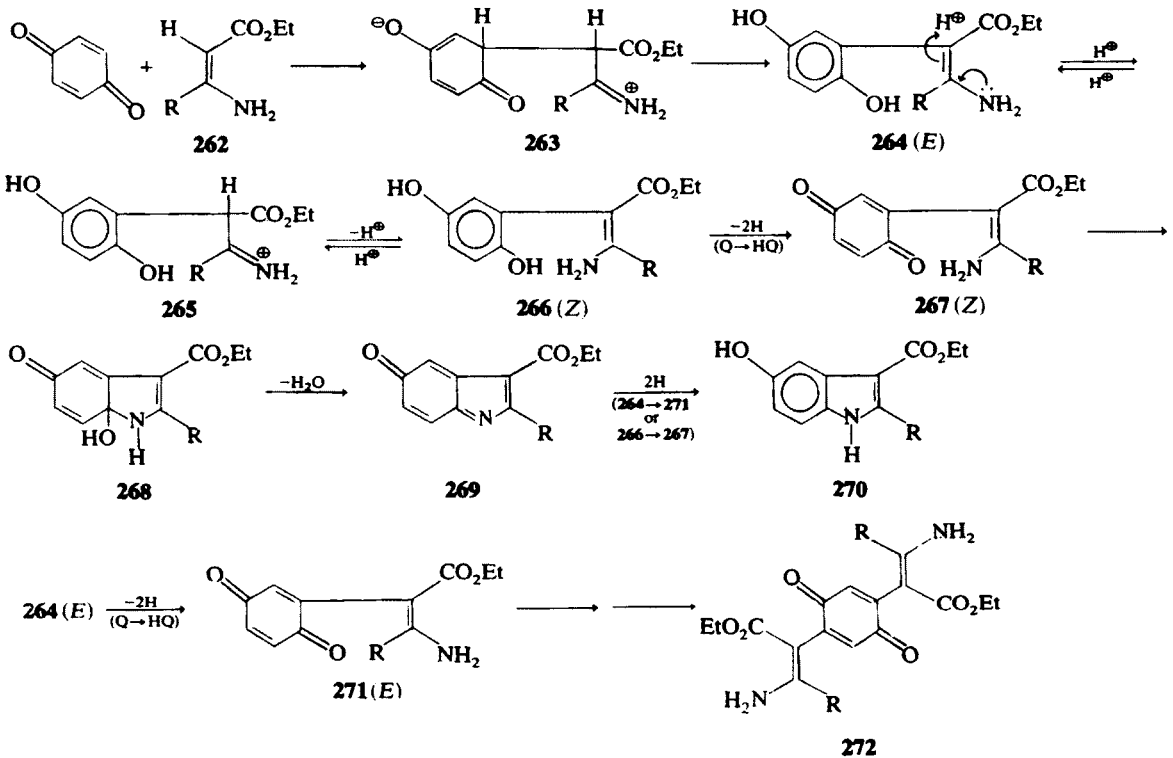
"*trans*" or *E*-configuration was assigned to the adduct on the basis of the following evidence: (1) It could be cyclized to the benzofuran derivative **261** in good yield. (2) Oxidation with silver oxide gave a quinone, presumably **258**, which on reduction with dithionite regenerated the starting hydroquinone adduct. (3) Exposure of the quinone to ethanol afforded an isomeric quinone (presumably the *Z*-isomer **259**), which on reduction with either dithionite or hydrogen and a palladium catalyst produced the indole.[180]

In 1965, Raileanu and Nenitzescu isolated an analogous hydroquinone adduct (**264**, $R = C_6H_5$) as the main product (25%) in the reaction of *p*-benzoquinone with ethyl β-aminocinnamate (**262**) in either chloroform or benzene[167] (Scheme 19). A disubstituted quinone **272**, probably the same one reported by Nenitzescu in 1929, was also isolated in 3.5% yield, but none of the expected hydroxyindole **270** could be detected. However, when the reaction was conducted in refluxing acetic acid, 2-phenyl-5-hydroxyindole (**270**) could be obtained in 46% yield. Furthermore, the significant observation was made that on refluxing in acetic acid with a *catalytic* amount of *p*-benzoquinone, the hydroquinone adduct **264** could be converted into the indole in comparable yield. On the basis of these observations, the complex "redox" mechanism given in Scheme 19 was proposed.

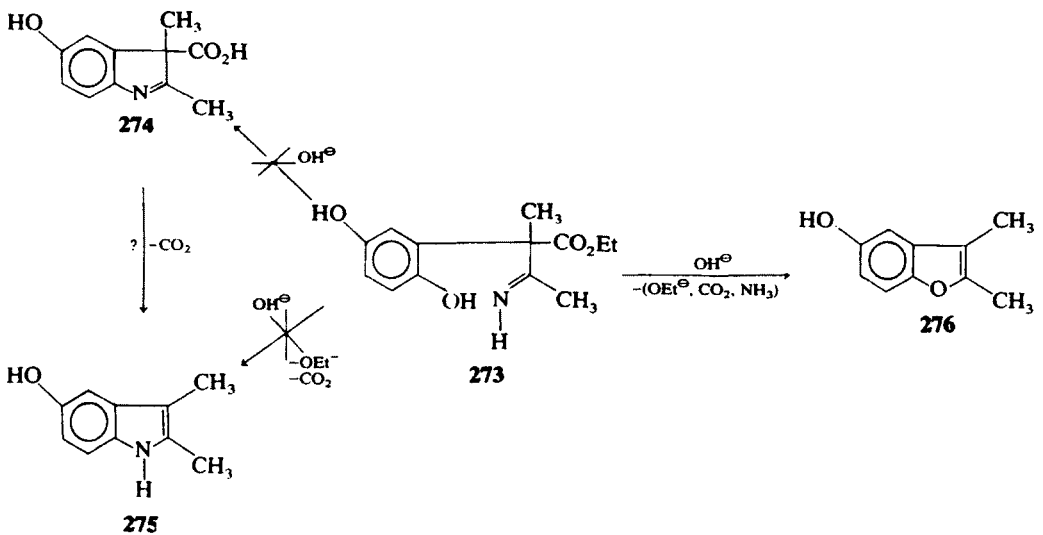
The authors postulated, as have others,[160,172] an initial Michael addition of the crotonate to the quinone to form **263**. Robertson and co-workers noted[160] that 5-hydroxyindoles resulted in the Nenitzescu synthesis, in accordance with the formation of such an intermediate, rather than 6-hydroxyindoles, which would result if the amino group added initially to the quinone double bond. From the reaction of *p*-benzoquinone and ethyl α-methyl-β-aminocrotonate, they isolated an unstable hydroquinone, for which they assumed structure **273**, by analogy with the primary alkylation product **263** postulated as an intermediate in the cinnamate reaction by Raileanu and Nenitzescu (Scheme 20). Although **273** might be expected to cyclize to either an indole **275** or conceivably even an indolenine **274**, only the hydroxybenzofuran **276** was formed with alkali.

Raileanu and Nenitzescu invoked the principle of overlap control to explain why the *E*-isomer of the hydroquinone adduct **264** is formed under the conditions of *kinetic* control pertaining in nonequilibrating solvents, for example, chloroform or benzene. In acetic acid, on the other hand, isomerization to the *Z*-isomer **266** occurs via the immonium ion **265**. Oxidation to the *Z*-quinone **267** by *p*-benzoquinone* followed by

* Apparently Domschke and Fürst were the first to suggest that hydroquinone adducts could be oxidized to quinones by excess *p*-benzoquinone.[172] Quinone adducts earlier had been proposed[160] by Harley-Mason as intermediates in the Nenitzescu reaction.


262
263
264 (E)
265
266 (Z)
267 (Z)
268
269
270
271 (E)
272
-H⊕
H⊕
-2H
(Q→HQ)
-H2O
2H
(264→271
or
266→267)
264 (E)

Scheme 19


HO
CH3
CO2H
N
CH3
274
OH⊖
? -CO2
HO
CH3
CO2Et
OH
N
H
CH3
273
OH⊖
-(OEt⊖, CO2, NH3)
HO
CH3
O
CH3
276
OH⊖
-OEt⁻
-CO2
HO
CH3
N
H
CH3
275

Scheme 20

ring closure and loss of water (**267** → **268** → **269**) affords the quinone imine **269**. Reduction of this intermediate with either the *Z*- or the *E*-hydroquinone adduct produces the 5-hydroxyindole together with more quinone adduct. The *E*-adduct **271** may react with a second mole of the cinnamate to afford the disubstituted quinone **272** in a secondary reaction.

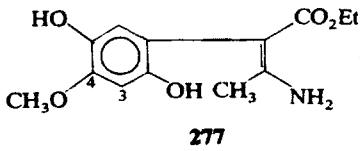
Domschke and Fürst had considered the likelihood of quinone intermediates such as **267** in the Nenitzescu reaction.[172] These were erroneously regarded as undesirable by-products formed by the action of excess quinone on the hydroquinone adducts. To minimize their formation, they suggested the use of large excesses of enamine component and were actually able to obtain improved yields (50–60%) in Nenitzescu's original procedure. They also introduced the use of solvents such as chloroform and benzene which are capable of removing the water produced in the reaction by azeotrope formation. The later practice has been followed by most investigators, though the former has been discontinued in favor of only slight, if any, excesses of enamine.

It now appears, from the work of Raileanu and Nenitzescu and Allen and co-workers, that quinone adducts such as **271** *are* intermediates in the Nenitzescu reaction, and although they are formed by the mechanism first suggested by Domschke and Fürst, only a small amount of "primer" quinone is necessary to sustain the reaction.

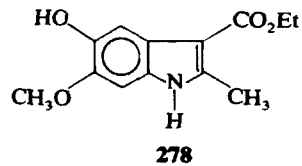
Allen and co-workers independently confirmed the essentials of the Raileanu–Nenitzescu mechanism and made a number of important additional contributions toward understanding the final reduction step.[151a–c] Using methyl- and ethyl-*p*-benzoquinone and either ethyl β-aminocrotonate or ethyl β-*N*-alkylaminocrotonates, they isolated, in addition to the 6- and 7-alkyl-5-hydroxyindoles (see Section III.G.4), the hydroquinones **279** and **280**.[151c]

In an important experiment they showed that the hydroquinone adduct **277** with only 0.1 equivalent of toluquinone under equilibrating conditions afforded the indole **278** in 55% yield, whereas *one* equivalent of toluquinone afforded an intermediate (probably the quinone imine or immonium salt **281**) which gave the indole in 51% yield only after dithionite reduction. This result indicates that it is the hydroquinone adduct **277** rather than toluhydroquinone which reduces **281** in the final step. The authors suggest that a different situation may occur with quinone immonium intermediates **282** from *N*-substituted crotonates. Here the simple hydroquinones may be able to effect the final reduction step, although this remains to be tested.

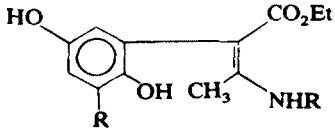
In another experiment,[151c] the quinone adduct **285**, isolated in 10% yield from methoxy-*p*-benzoquinone and EAC, cyclized to the indole **278** (22%) in refluxing acetone only when dithionite was present.



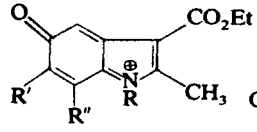
277



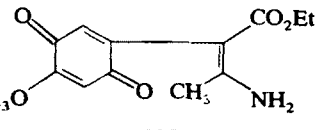
278



279; R = R′ = C_2H_5 (0.3%)
280; R = CH_3, R′ = *i*-C_3H_7 (18%)



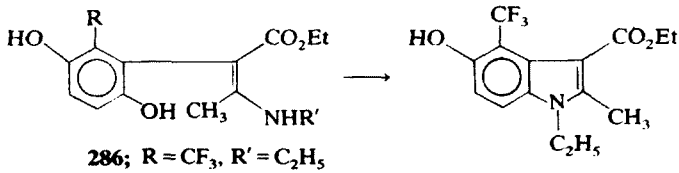
281; R = R″ = H, R′ = CH_3
282; R = R′ = alkyl, R″ = H
283; R = C_2H_5, R′ = CH_3, R″ = H
284; R = C_2H_5, R′ = H, R″ = CH_3



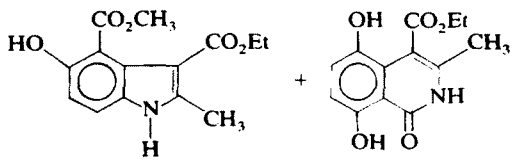
285

In related experiments, it was also shown that the hydroquinone adduct **279** with a catalytic amount of acid, excess toluquinone and *N*-ethyl EAC, gave, in addition to the expected 6- and 7-methyl-5-hydroxyindoles, the 7-ethyl-5-hydroxyindole derived from **279**. In this case, either toluquinone or the quinone immonium salt mixture (**283** and **284**) could function as oxidants for the hydroquinone adduct. The adduct **280** could not, however, be cyclized to the indole under similar conditions. This failure may be related to steric factors.

Allen and co-workers have reported[155,161] the isolation in good yields of the 6-substituted hydroquinone adducts **286** and **287** in reactions employing equimolar quantities of quinone and crotonate (Scheme 21).



286; R = CF_3, R′ = C_2H_5
287; R = CO_2CH_3, R′ = H

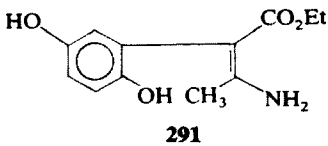


289 **290**

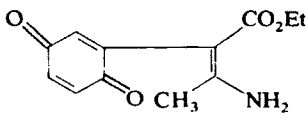
Scheme 21

On addition of "some" trifluoromethyl-*p*-benzoquinone, the former cyclized to the indole **288** in 86% yield. Adduct **287**, isolated from a reaction carried out in ethanol, gave the indole **289** (30%) on treatment with additional quinone as well as the carbostyril derivative **290** (23%). It is not clear why the normal Nenitzescu cyclization is interrupted in these cases.

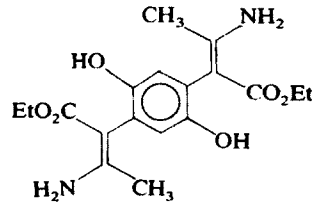
Monti has also described[158] the isolation of hydroquinone adducts from EAC and *p*-benzoquinone or toluquinone. With equivalent amounts of *p*-benzoquinone and EAC in dichloroethane, the expected indole (30%) was accompanied by the hydroquinone adduct **291** (15%), the corresponding quinone **292**, and the disubstituted hydroquinone **293**, the last two products in a combined yield of 10%. Monti was able to demonstrate the presence of two toluhydroquinone adducts in the reaction mixture from toluquinone and EAC. One, isolated in 5% yield, proved to be identical with that isolated earlier by Allen and co-workers, that is, **277**; the other (1%) was the previously unreported 3-methyl isomer.



291



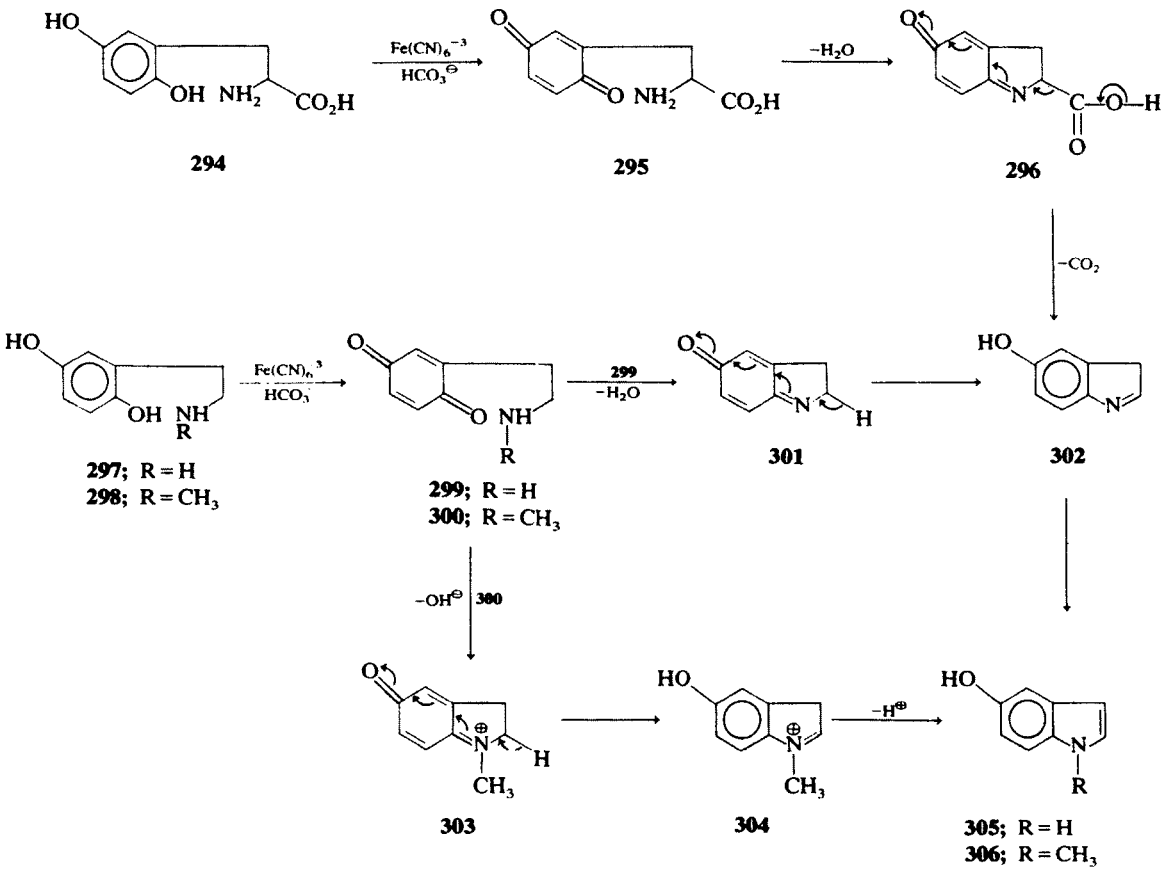
292



293

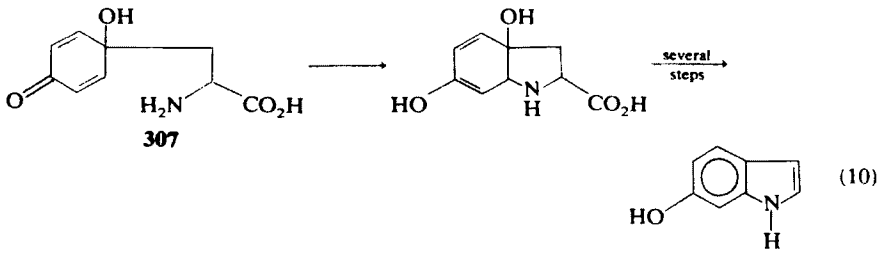
6. *Analogous Indole Syntheses*

Harley-Mason and co-workers have described syntheses of 5-hydroxyindole[181] and of its 1-methyl derivative[182] which proceed via *p*-benzoquinone intermediates. These were generated *in situ* using alkaline ferricyanide oxidation of 2,5-dihydroxyphenylethylamine derivatives (**297** and **298**) (Scheme 22). The reaction differs from the Nenitzescu synthesis in that a saturated side chain undergoes cyclization. 5-Hydroxyindole (**305**) was obtained in 85% yield from 2,5-dihydroxyphenylalanine (**294**)[181] and in 70% yield from **297**.[181] Compound **298** afforded 1-methyl-5-hydroxyindole (**306**) in unspecified yield.[182] As in the cyclization of 3,4-dihydroxyphenylethylamine derivatives to 5,6-dihydroxyindoles (see Section III.F.1), different mechanisms must be involved in the case of the phenylalanine derivatives and the amines, **297** and **298**. In


HO
OH NH2
CO2H
294
Fe(CN)6 -3
HCO3 Θ
O
O NH2
CO2H
295
-H2O
O
N
C
O
H
O
296
-CO2
HO
OH NH
R
297; R = H
298; R = CH3
Fe(CN)6 -3
HCO3
O
O NH
R
299; R = H
300; R = CH3
299
-H2O
O
N
H
301
HO
N
302
-OH Θ
300
O
N
H
CH3
303
HO
N
CH3
304
-H Θ
HO
N
R
305; R = H
306; R = CH3

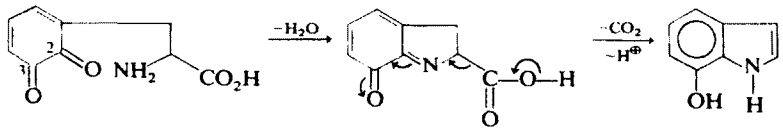
Scheme 22

the former, indolization is accompanied by decarboxylation (**295** → **296** → **302** → **305**), whereas in the latter two cases, only the loss of the elements of water from the quinone intermediate is required (**299** → **301** → **302** → **305**; **300** → **303** → **304** → **306**). These transformations using possible tyrosine metabolites suggested to Harley-Mason the intriguing possibility that certain naturally occurring 5-hydroxyindoles might have their origin in tyrosine or phenylalanine rather than tryptophan.[181] Earlier, Robinson had proposed[343] that another possible tyrosine metabolite, the quinol **307**, might be the precursor of the 6-hydroxyindole system (see Section III.F.5 for the first chemical realization of this reaction).



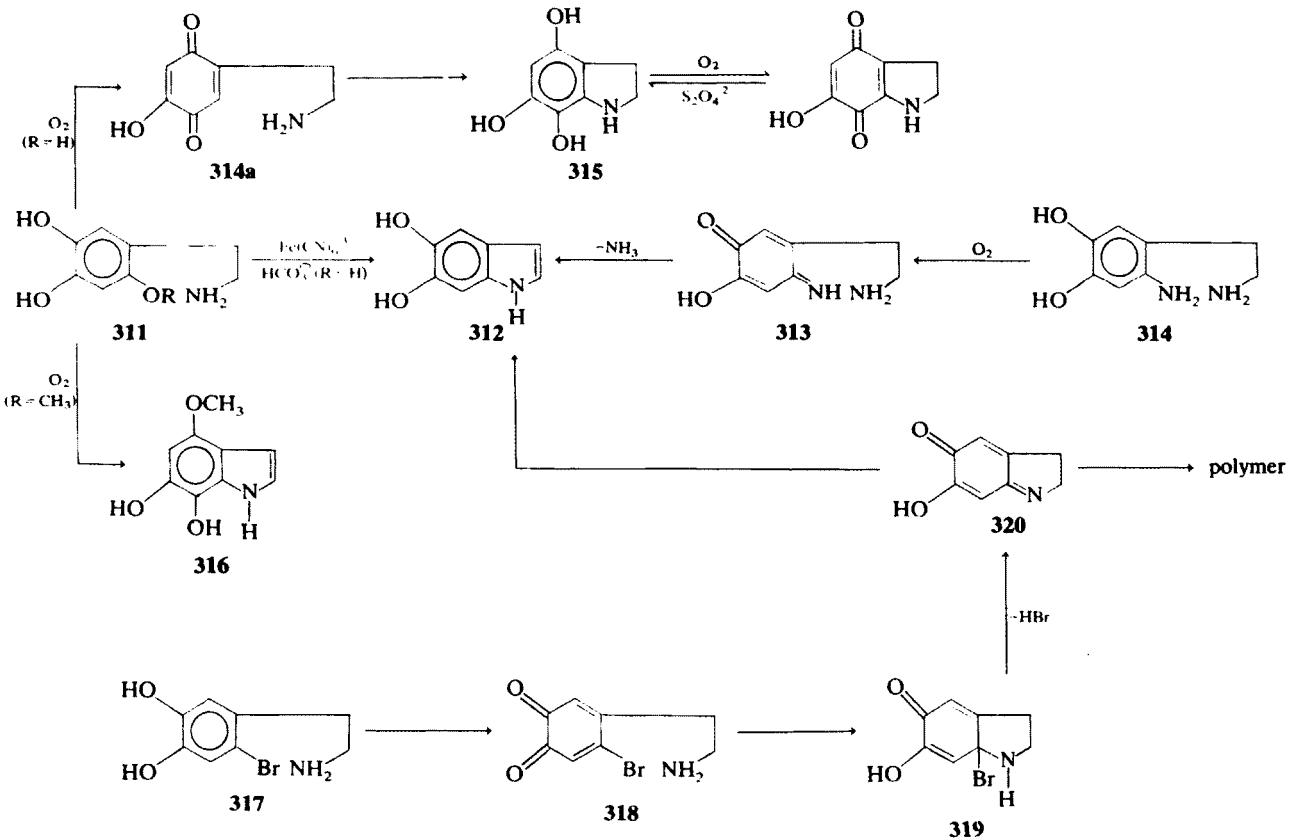
307 (10)

7-Hydroxyindole (**310**) could be obtained in 20% yield from alkaline ferricyanide oxidation of 2,3-dihydroxyphenylalanine.[181] In this transformation, the orthoquinone **308** is a likely intermediate. Cyclization to the orthoquinone imine **309** with decarboxylation and isomerization to **310** may again be the operative mechanism.



308 **309** **310**

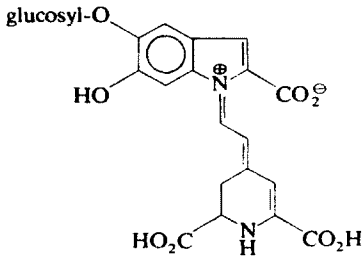
In a closely related cyclization, Harley-Mason has successfully converted the trihydroxyphenylethylamine **311** (R = H) to 5,6-dihydroxyindole (**312**) in 50% yield[94] (Scheme 23). The amino analogue **314** on air oxidation afforded **312** in 30–50% yield, perhaps via the quinone imine **313**. Senoh and Witkop have observed[367] that **311** (R = H), a dopamine metabolite, undergoes an easy autoxidation via a *p*-benzoquinone intermediate **314a** to a 2,3-dihydro-4,7-indoloquinone which can be reduced with dithionite to 4,6,7-trihydroxyindoline (**315**), whereas the 2-methyl ether derivative of **311** affords a trihydroxyindole derivative, **316**, *directly*


O2
(R = H)
314a
315
O2
S2O4 2
311
312
-NH3
313
O2
314
O2
(R = CH3)
316
320
polymer
-HBr
317
318
319

Scheme 23

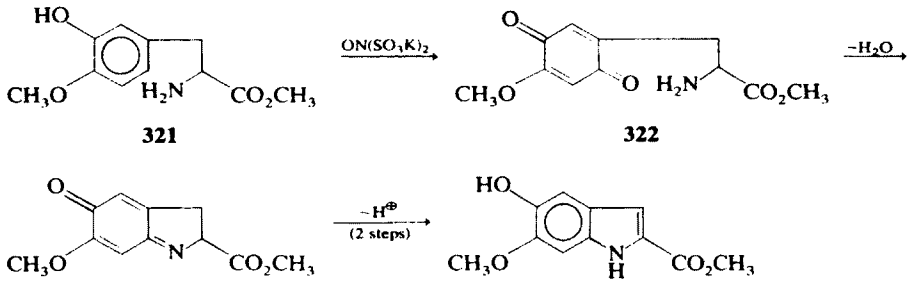
via an orthoquinone. The action of ferricyanide on the bromodihydroxyphenylethylamine **317** gave **312** in only 8% yield together with melanin-like material. In this instance, intramolecular Michael addition in an intermediate orthoquinone (**318** → **319**), followed by elimination of HBr could generate the aminochrome **320**. This could isomerize to the indole or polymerize to the melanin (Scheme 23).

Dreiding and co-workers have utilized[184] a similar reaction in their synthesis of methyl 5-hydroxy-6-methoxyindole-2-carboxylate (**324**), a compound essential for the structure proof of betanin, the red pigment of the beet. A two-phase oxidation system consisting of ethyl acetate and an



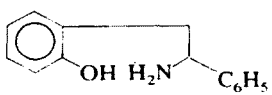
betanin

alkaline aqueous solution of Fremy's salt was used to produce **324** in 68% yield from 3-hydroxy-4-methoxyphenylalanine methyl ester (**321**). in this case, the presumed *p*-benzoquinone intermediate **322** is formed by oxidation after an initial hydroxylation step (Scheme 24).

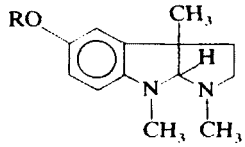


Scheme 24

Also using a Fremy's salt oxidation and a two-phase system (chloroform–aqueous acetic acid), Teuber and Glosauer converted the aminophenol **325** to 2-phenyl-5-hydroxyindole (20–30%). Four moles of the reagent in aqueous media at pH 7, produced instead, the 4,5-indolequinone related to the above indole.[346]



325



325a

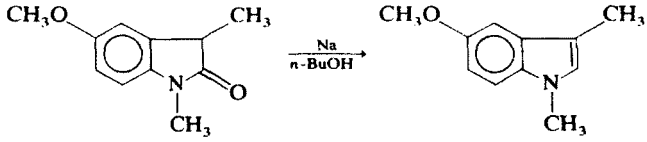
R = H (eseroline)
R = CH_3NHCO (physostigmine)

Harley-Mason and Jackson have been successful in applying cyclizations involving quinone intermediates to practical syntheses of bufotenine, 6-hydroxybufotenine, serotonin, and eseroline (**325a**) (see Section V.C.4).[185]

H. Alkoxy- and Hydroxyindoles Using Miscellaneous Procedures

1. *Reductions of Oxindoles and Isatins with Metals or Metal Hydrides*

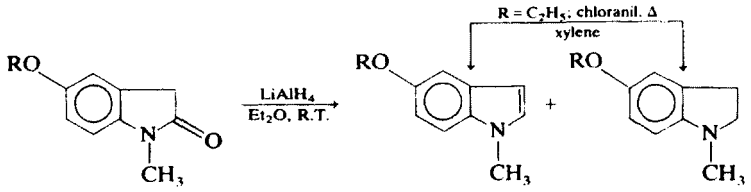
In 1953 Kolosov and co-workers showed[50] that reduction with sodium–butanol of the *N*-methyloxindole **326** gave physostigmol methyl ether (**326a**). However, when 1-methyl-5-methoxyoxindole was similarly reduced, dimerization (24%) took place.



326 **326a**

On lithium aluminium hydride reduction of the oxindole **328**, Julian and Printy obtained[186] 1-methyl-5-ethoxyindole (**330**) in 60% yield and the derived indoline **332** (6%), along with recovered starting material (27%) (Scheme 25). The indoline could be dehydrogenated to the indole in approximately 50% yield with chloranil. The reduction was reported to fail with oxindoles lacking the *N*-methyl group. Ek and Witkop have reported[85b] however, that 7-benzyloxyindoline could be obtained in low yield on hydride reduction of 7-benzyloxyoxindole.

1-Methyl-5-methoxyindole (**329**) has been synthesized using lithium



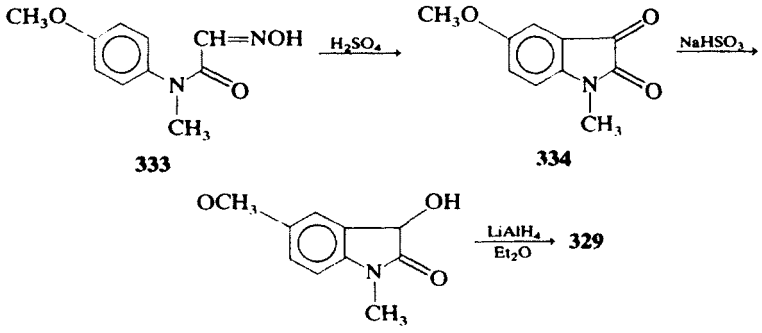
327; R = CH_3
328; R = C_2H_5

329; R = CH_3
330; R = C_2H_5

331: R = CH_3
332: R = C_2H_5

Scheme 25

aluminum hydride reduction by two different groups. Cook and co-workers obtained[49] this material in a 40% yield along with a small quantity of the indoline **331** from the reduction of **327**. Benington and co-workers[187] employed a hydride reduction of the dioxindole **335** for the preparation of **329** in 86% yield. The dioxindole was obtained in approximately 80% overall yield from **333** using the two steps shown.

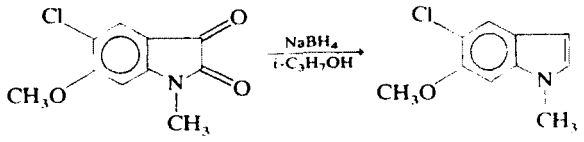


333

334

335

In an interesting analogous reaction, Reimann and Jaret reported[188] the direct reduction of 5-chloro-6-methoxy-1-methylisatin (**336**), a metabolite of *Micromonospora carbonacea*, to the indole **337** with excess sodium borohydride in isopropanol.



336 **337**

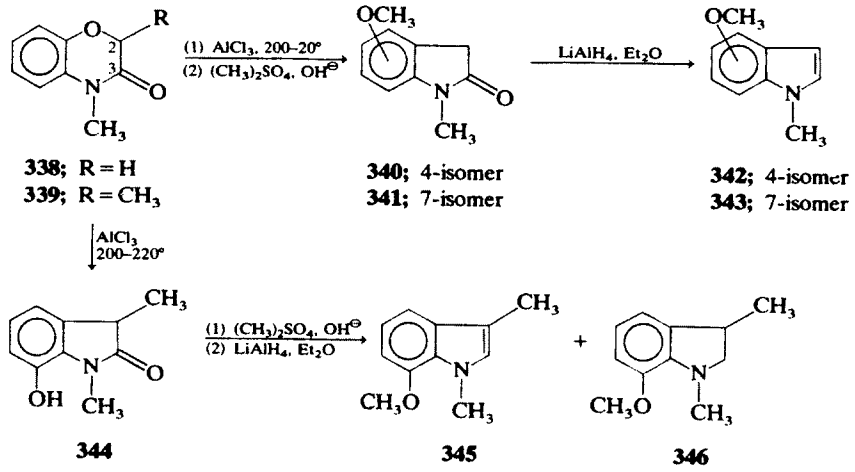
Kishi and co-workers prepared[60b] 1-methyl-5-chloro-6,7-dimethoxyindole, an intermediate in their synthesis of sporidesmin A, by chlorination, then *N*-methylation of 6,7-dimethoxyoxindole, and a final reduction

with diisobutylaluminum hydride in ether at −78°. The overall yield was 71%. Lithium aluminum hydride reduction of the chlorodimethoxyoxindole at 0° produced a small amount of indoline in addition to the indole.

Two groups have reported the one-step reduction of methoxyisatins to indoles with lithium aluminum hydride. Using this reagent in pyridine at room temperature, Carlsson and co-workers reduced 4,5,6-trimethoxyisatin to the indole in 47% yield.[189] Brown and co-workers employed the reagent in refluxing dioxane to reduce 4,6-dimethoxyisatin to 4,6-dimethoxyindole in 43% yield. A sodium–butanol reduction was less successful and gave the indole (16%) together with some oxindole.[349]

Using lithium aluminum hydride in ether, Cook and co-workers synthesized both 1-methyl-4-methoxy- (**342**) and 1-methyl-7-methoxyindole (**343**) from the corresponding oxindoles[26] (Scheme 26). Both oxindoles afforded small amounts of the indolines in addition to the indoles. With the 4-methoxy isomer, indole (67%) and indoline (16%) were obtained, together with 10% recovered starting material. A mixture of the two oxindoles **340** and **341** results in 78% yield (after a methylation step) when 2,3-dihydro-3-keto-4-methylbenz(1,4)oxazine (**338**) is rearranged with aluminum chloride.[26,191] Neither 2,3-dihydro-3-ketobenz(1,4)-oxazine nor its 2-methyl derivative yields appreciable amounts of oxindoles under these conditions.[26,191]

Loudon and Ogg similarly effected the rearrangement of the 2-methylbenzoxazine **339** and obtained 99% of 1,3-dimethyl-7-hydroxyoxindole (**344**). After methylation and hydride reduction, a mixture of 1,3-dimethyl-7-methoxyindole (**345**) and the indoline **346** was obtained.[191]



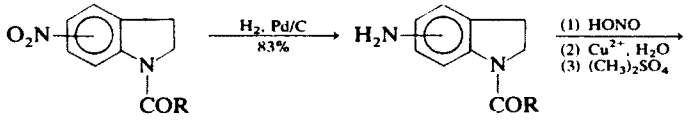
Scheme 26

2. *Miscellaneous Dehydrogenations*

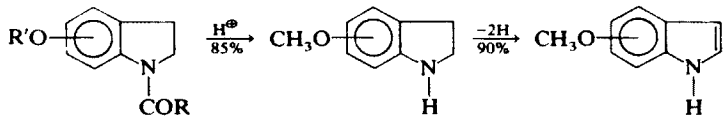
a. FROM INDOLINES. Hunt and Rickard employed the five-step synthesis shown in Scheme 27, starting with 5-, 6-, or 7-nitro-*N*-acetylindoline (**347**, R = CH_3), to produce 5-, 6-, or 7-methoxyindole (**350**) in overall yields of 15–25% (yields in Scheme 27 are for the 5-methoxy isomer).[193]

Reduction of the nitro group, diazotization of the resulting amine, and decomposition of the diazonium salt in boiling copper sulfate solution afforded the hydroxyindolines (**348a**, R = CH_3). Methylation of the 5- and 6-hydroxy-*N*-acetylindolines proceeded well (70%); however, the 7-hydroxy isomer required more vigorous conditions and proceeded in only 30% yield. The ir spectrum of 1-acetyl-7-hydroxyindoline indicated an intramolecular hydrogen bond between the amide carbonyl group and the hydroxyl group. This effect, as well as a steric factor, may account for the difficulty in methylating the 7-hydroxyl group. In this context it is interesting that Morimoto and Oshio report failure to methylate 7-hydroxytryptamine with either dimethyl sulfate or diazomethane[194] and Cook and co-workers record that 1-methyl-7-methoxyindole as well as the corresponding oxindole and indoline derivatives do not behave normally in *N*-methyl determinations.[26]

Hydrolysis with 6 *N* HCl removed the acetyl group from the 1-acetyl methoxyindolines (**348b**, R = CH_3) to give **349** and a final dehydrogenation step using palladium–carbon in refluxing xylene afforded the methoxyindoles **350**.



347; R = CH_3, $C_6H_5CH_2$



348a; R′ = H (77%)
348b; R′ = CH_3 (70%)

349

350

Scheme 27

A similar sequence of steps has been employed by Gerecs and co-workers for the preparation of 6-hydroxy-, 6-methoxy-, and 6-benzyloxyindoline from 1-benzoyl-6-nitroindoline (**347**, R = C_6H_5).[195a–c] Deacylation in this case was accomplished with dilute alkali and the

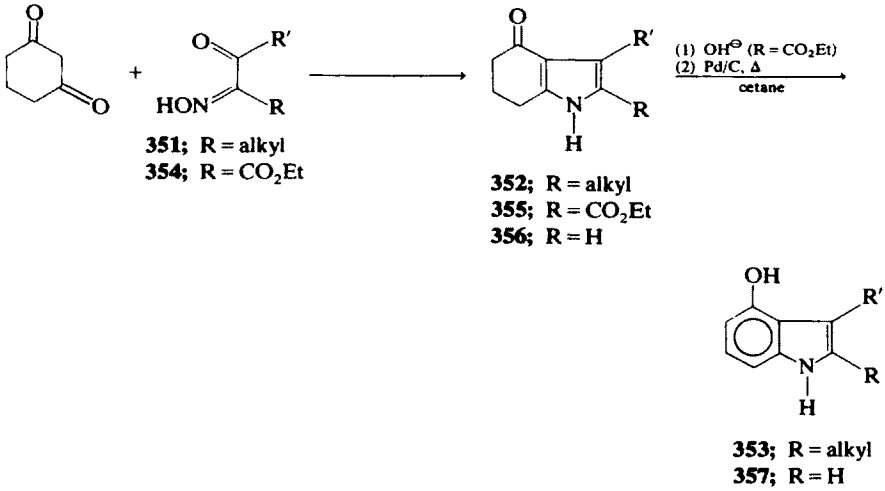
dehydrogenation of the 6-hydroxy- and 6-benzyloxyindolines was achieved with wet Raney nickel in butyl acetate and toluene, respectively.

1-Acetyl 5- and 6-methoxyindolines (**349**, $R = CH_3$) have been employed in turn by Pinder and Rickard[196] for the synthesis of 5,6-dialkoxyindoles using as the first step nitration to 1-acetyl-5-methoxy-6-nitroindoline (50% yield) and 1-acetyl-5-nitro-6-methoxyindoline(62%), respectively, with subsequent steps as outlined above. 5,6-Dimethoxyindole, 5-ethoxy-6-methoxyindole, and 5-methoxy-6-ethoxyindole were prepared in this manner in overall yields of 8–12%.

Yakhontov and co-workers report that 6-methoxyindoline can be dehydrogenated in 78% yield using sodium in liquid ammonia.[364]

b. 4-Hydroxyindoles by Dehydrogenation of 4-Oxotetrahydroindoles. Hauptmann and co-workers prepared[197] a series of 3-alkyl- and 2,3-dialkyl-4-hydroxyindoles using palladium–carbon in refluxing cetane for the dehydrogenation of 4-oxo-4,5,6,7-tetrahydroindoles. The ketones could be prepared in yields of 50–70% from cyclohexane-1,3-dione (**350**) and the isonitrosoketones **351** or isonitroso-β-oxo acid esters **354** (the Knorr synthesis).[198] In the latter case, hydrolysis of the ester **355** and decarboxylation of the resulting acid by pyrolysis afforded 2-unsubstituted 4-oxotetrahydroindoles **356** in yields of 56–77%. On aromatization of **352** or **356**, the 4-hydroxyindoles **353** and **357** were obtained in 40–60% yield.

A number of other procedures exist for preparing the 4-oxotetrahydroindole intermediates. Stetter and Lauterbach devised[199] a procedure using



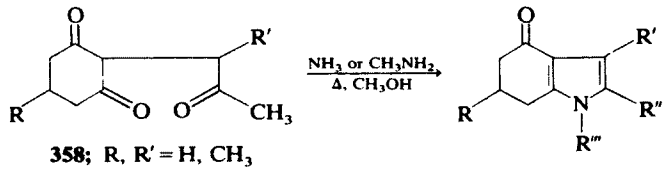
351; R = alkyl
354; R = CO_2Et

352; R = alkyl
355; R = CO_2Et
356; R = H

353; R = alkyl
357; R = H

Scheme 28

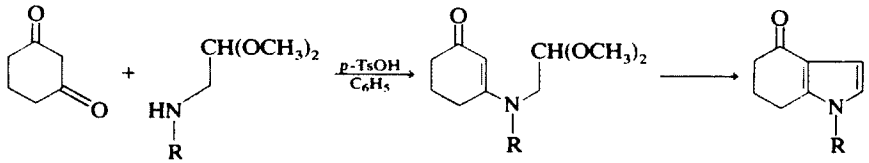
2-acetonyl-1,3-cyclohexanedione (**358**) or its 5-methyl derivative and ammonia, methylamine, or aniline. When they were heated together in an autoclave at 150° in methanol, excellent yields (73–96%) of 4-oxotetrahydroindole or the 1-, 2-, 3-, or 6-methyl derivatives **359** resulted. Allen and Poletto[200] and Remers and Weiss[201a,b] describe the convenient preparation of *N*-substituted 4-oxotetrahydroindoles using this reaction. Dehydrogenation with palladium–carbon in refluxing cumene was used to prepare 1-ethyl-2-methyl-4-hydroxyindole.



358; R, R′ = H, CH_3

359; R, R′, R″ = H, CH_3
R‴ = H, CH_3, C_6H_5

Bobbitt and Dutta have developed[202] a synthesis of 4-oxotetrahydroindoles using an acid-catalyzed condensation (**361** → **362**) between aminoacetaldehyde dimethyl acetal (**360**) or its *N*-alkyl derivatives and 1,3-cyclohexanediones. Yields were typically 50–70%. Aromatizations were described in the case of 4-hydroxyindole and its *N*-benzyl derivative.

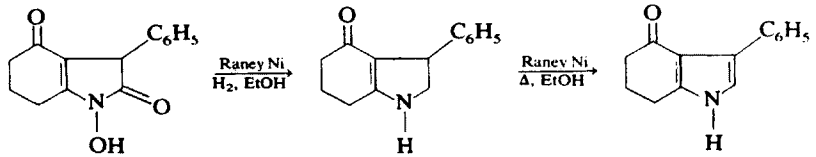


360; R = H, CH_3, $C_6H_5CH_2$ **361** **362**

Roth and Hagen have recently reported two new routes to 2,3-disubstituted 4-oxotetrahydroindoles using a formic acid-catalyzed reaction between **350** and $C_6H_5NHC(C_6H_5)=C(C_6H_5)OH$[347] or enamine derivatives of **350** and acetoin or benzoin.[348]

Troxler and co-workers have observed the formation of 2-methyl-4-oxotetrahydroindole in variable yields as a by-product when 4-benzyloxyisogramine is hydrogenolyzed in methanol.[750]

An interesting synthesis of 3-phenyl-4-oxotetrahydroindole (**365**) was achieved when **363**, obtained unexpectedly from cyclohexane-1,3-dione

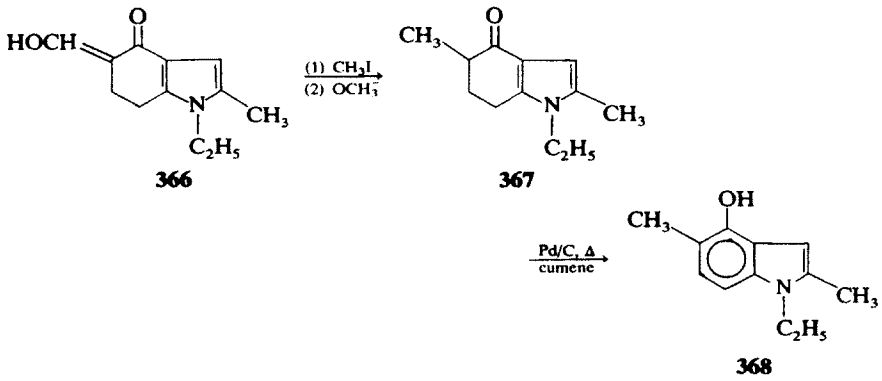


363 364 365

and β-nitrostyrene, was reduced to **364** with hydrogen and Raney nickel in ethanol followed by dehydrogenation.[350]

Plieninger and Klinga have reported[203] that 4-hydroxyindole (57%) is formed by palladium–carbon dehydrogenation of 4-oxotetrahydroindole in refluxing mesitylene. A Russian patent records[204] the use of the same catalyst in diethylene glycol for similar dehydrogenations.

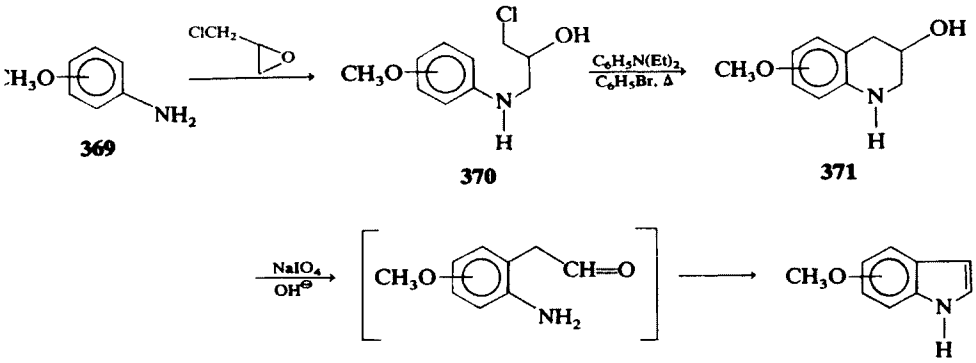
The 5-methyl-4-hydroxyindole **368** was obtained by Remers and Weiss[205] by methylation of the 5-hydroxymethylene derivative **366** and subsequent aromatization of the intermediate **367**. Dehydrogenation in this case was adversely affected by the 5-methyl group, for **368** could be obtained in only 13% yield.



366 367 368

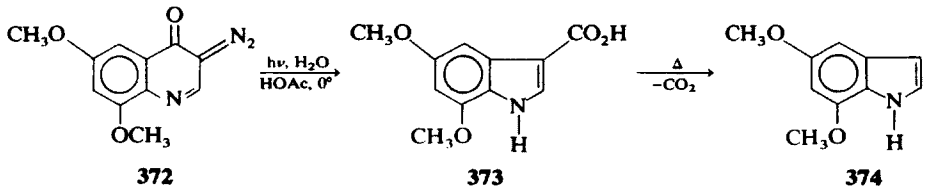
3. *Methoxyindoles by Ring Contraction of Quinoline Derivatives*

Oxidation of 6-, 7-, and 8-methoxytetrahydroquinolin-3-ols (**371**) with alkaline sodium iodate produces 5-, 6-, and 7-methoxyindoles in yields of 35–43%[206,207] (Scheme 29). The intermediate **371** may be synthesized conveniently and in good yield from *o*-, *m*-, or *p*-anisidine (**369**) and epichlorohydrin. Cyclization of the intermediate anilino-3-chloro-2-propanols **370** was accomplished with an excess of diethylaniline in refluxing bromo- or dichlorobenzene in 50% yield.



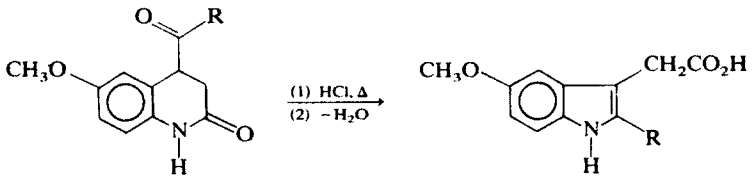
Scheme 29

Süs and co-workers showed [208a,b] that photolytic ring contraction of the α-diazoketone **372** with sunlight leads to 5,7-dimethoxyindole-3-carboxylic acid (**373**) in 37% yield, which decarboxylates at 230–270° to give 5,7-dimethoxyindole (**374**). This work has recently been challenged.[378] 5-Phenoxyindole-3-carboxylic acid was prepared (87%) in a similar fashion and decarboxylated to 5-phenoxyindole.[209]



372 **373** **374**

Ochiai and Takahashi have reported[210a,b] the synthesis of 2-methyl- and 2-phenyl-5-methoxyindole-3-acetic acid (**376**) in 85 and 53% yield, respectively, by ring contraction of 4-acetyl- or 4-benzoyl-6-methoxy-3,4-dihydrocarbostyril (**375**).



375; R = CH_3, C_6H_5 **376**; R = CH_3, C_6H_5

4. *Other Syntheses*

a. ALKOXYINDOLINES. Julia and Gaston–Breton have prepared 4- and 6-methoxyindoline and some of their *N*-alkyl derivatives in good yields by means of the "aryne" cyclization of the appropriate chloromethoxyphenylethylamines (**377** and **383**)[211] (Scheme 30). The "aryne" intermediates were produced in the presence of excess diethylamine with either a slight excess of phyenyllithium in refluxing ether or sodium naphthalide in refluxing tetrahydrofuran. Yields ranged from 26–81% for the 4-methoxyindolines and 22 to 66% for the 6-methoxyindolines. In the former case, it would seem that two possible "arynes" could be intermediates (**378a,b**); in the latter case, only one would be possible (**384**).

The indolines **379** and **385** could be dehydrogenated in good yield to the corresponding indoles **381** and **387** with cupric chloride in refluxing pyridine or with palladium–carbon and cinnamic acid in refluxing mesitylene. Demethylation of the methoxyindolines to **380** and **386** was effected with HBr in approximately 70% yield. 1-Methyl-4-hydroxyindoline was dehydrogenated to **382** in 30% yield using Raney nickel and maleic anhydride in aqueous alkali.[211]

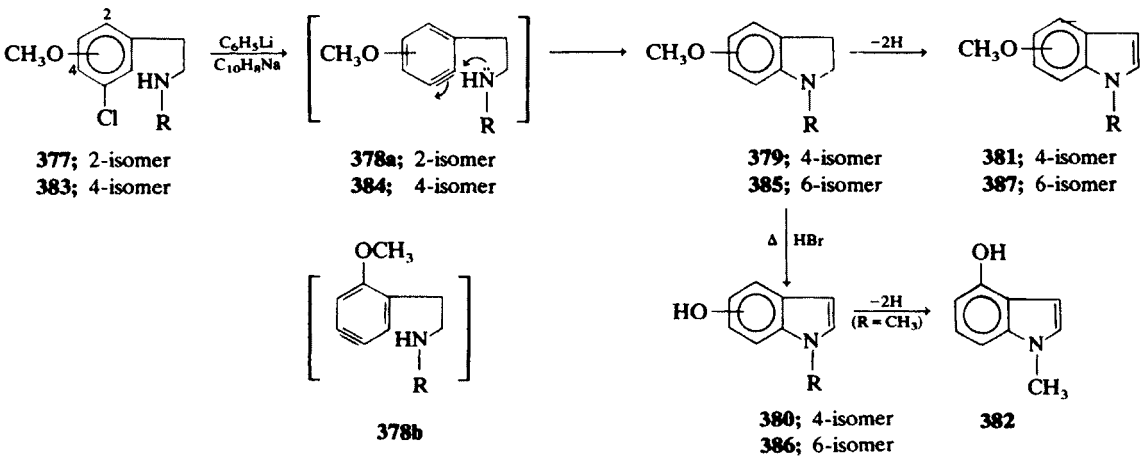
The synthesis of 4- and 6-methoxyindoline (**390**) in approximately 50% yield was reported by Wieland and Unger,[215] who reduced the thiooxindoles **389** at a lead cathode according to the procedure of Sugasawa and co-workers[351] (Scheme 31). The thiooxindoles are prepared from the oxindoles **388** and phosphorus pentasulfide in xylene.

Cromartie and co-workers have observed[216] an interesting intramolecular displacement of an aromatic halogen atom which resulted in an indoline. When **392** was prepared by the action of iodine monochloride on the dialkylamine **391** in benzene, it cyclized spontaneously to the indoline hydroiodide **393**.

Mishra and Swan have described[217] the synthesis of 1-tosyl-5,6-dimethoxyindoline (**395**) in 60% yield on cyclization of the ditosyl derivative **394** with pyridine. Tosyl chloride served as a catalyst in a reaction mechanism which has not been elucidated so far.

b. HYDROXYINDOLES. The structure of adrenochrome monosemicarbazone (**396**) was established by Iwao[212] by catalytic reduction to the 6-hydroxyindole derivative **397** in 60% yield. On methylation and pyrolysis in glycerol, 1-methyl-6-methoxyindole (**398**) was produced in 22% yield. This product establishes the fact that reaction of adrenochrome with semicarbazide occurs at the 5-position.

Heacock and Hutzinger[213] have devised a more convenient and practical procedure for this conversion by subjecting the semicarbazones **399** to



377; 2-isomer
383; 4-isomer

378a; 2-isomer
384; 4-isomer

379; 4-isomer
385; 6-isomer

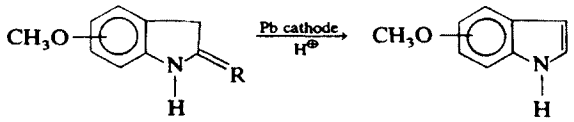
381; 4-isomer
387; 6-isomer

378b

380; 4-isomer
386; 6-isomer

382

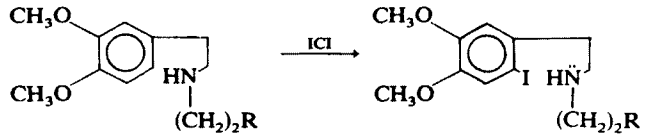
Scheme 30



388; R = O
389; R = S

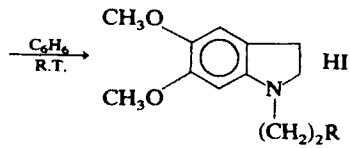
390

Scheme 31



391; R = 3, 4-$(OCH_3)_2C_6H_3$

392



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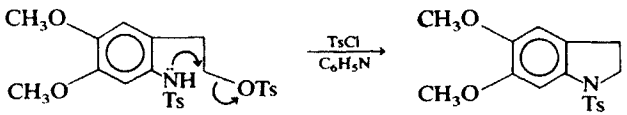
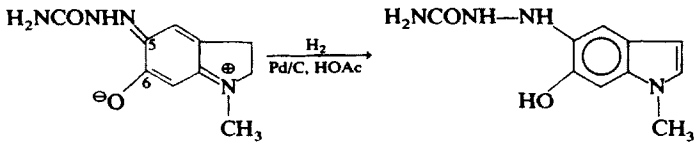
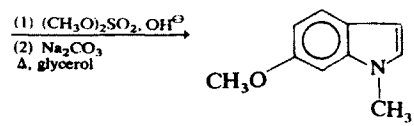


394 **395**



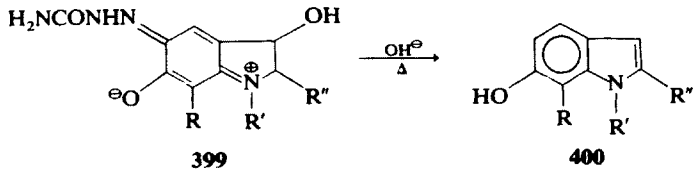
396 **397**



398

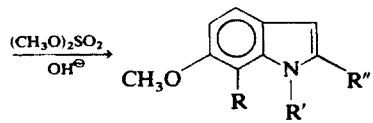
degradation in strong alkali. The resulting 6-hydroxyindoles **400** were isolated as their methyl ethers **401** after treatment with dimethyl sulfate in yields from 38–46%.

2-Phenyl-5-hydroxyindole (**403**) was synthesized in 57% yield from 4-hydroxy-2-iodoaniline (**402**) and cuprous phenylacetylide in dimethylformamide.[214]

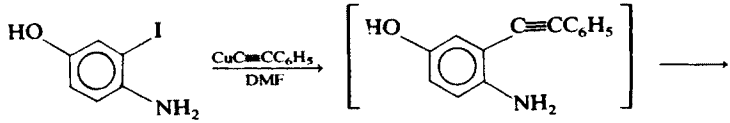


399

R, R′ R″ = H or CH_3



401



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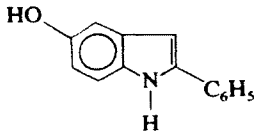
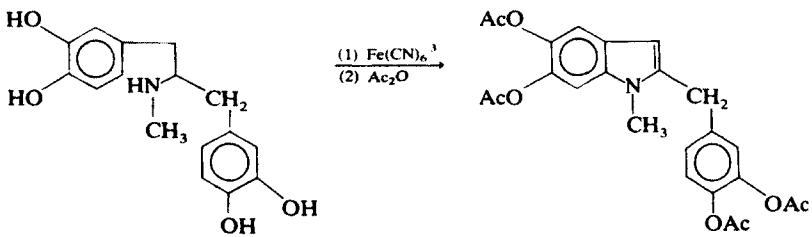


403

Kanaoka has described[377] the ferricyanide cyclization of the *N*-methyl dopamine derivative **404** to the indole **405**. A similar, presumably radical, pathway to hydroxyindoles has recently been described by Kametani and co-workers.[368a,b] 5-Hydroxy-6-methoxyindole (11%) and its *N*-ethyl derivative result when the catecholamine derivatives, **406** (R = H or C_2H_5) are oxidized with ferric chloride. This indolization is thought to proceed via a diradical **407**; a coupling step and tautomerization afford the indolines **408** (R = H or C_2H_5), which are subsequently oxidized to the indoles



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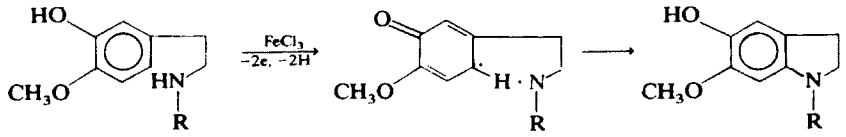
405



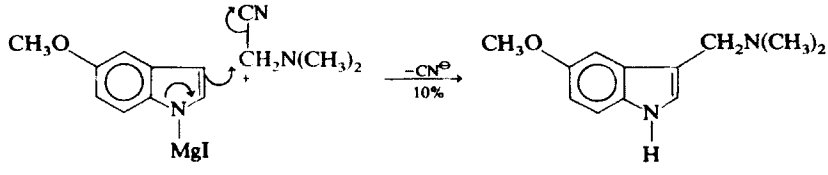
406; R = H, C_2H_5 **407** **408**; R = H, C_2H_5

1,3-Dimethyl-5-hydroxyindole (physostigmol) has been sythesized in low yield by the oxygenation of the Grignard derivative from 1,3-dimethyl-5-bromoindole.[643]

IV. The Alkoxygramines

A. Synthesis

5-Methoxygramine (**411**) was first made by Wieland and Hsing,[218] who displaced cyanide ion from dimethylaminoacetonitrile (**410**) with the Grignard derivative of 5-methoxyindole (**409**).



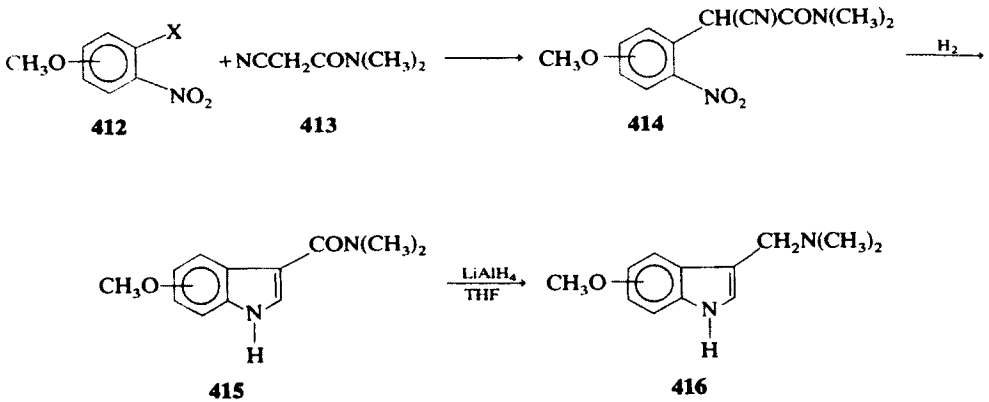
409 **410** **411**

With few exceptions however, the alkoxygramines have been prepared using the Mannich reaction. Typically, two equivalents of aqueous dimethylamine (33%) in acetic acid are cooled to 0–5°, then slightly more than two equivalents of aqueous formaldehyde (37–40%) are added and, finally, one equivalent of the alkoxyindole. When this procedure was applied to 5-methoxyindole, 5-methoxygramine resulted in yields of 72[25] or 86%.[49] Other alkoxygramines synthesized in this manner are 1-methyl-4-[26] and 5-methoxygramine,[49] 5-ethoxygramine (59%),[46] 5-benzyloxygramine,[219a,b] and 7-methoxygramine (53%).[25] When applied to 2-methyl-5-methoxyindole, the gramine resulted in only 8% yield.[25] Variations in the above procedure include the use of equimolar or only slightly excessive amounts of reagents, for example, in the successful preparations of 5-benzyloxy-7-methylgramine (82%)[57] and 4,6-[349] and 5,7-dimethoxygramine,[378] and the use of other concentrations of dimethylamine. Twenty-five percent aqueous solutions of dimethylamine

were employed successfully in the synthesis of 4-methoxygramine,[220] 6-methoxygramine (85%),[90a,b] 7-methoxygramine,[220] 5,6-dimethoxygramine (50%),[88] and 4,6-dimethoxygramine (23%).[349] A 12% solution was used in the preparation of 5,7-dimethoxygramine (36%)[378] and a 55% solution in obtaining 6-methoxygramine (59%).[221]

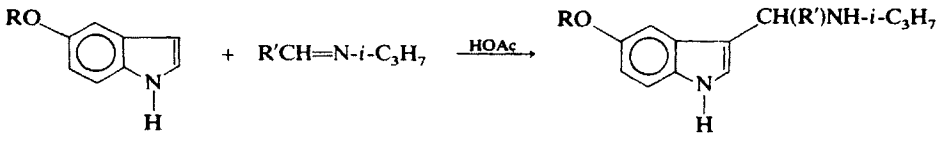
A widely used Mannich reaction modification, used in some of the above syntheses, was introduced by Ek and Witkop,[85b] who employed a 1:1 mixture of dioxane and acetic acid as the solvent for the Mannich reaction in their preparation of 5- and 7-benzyloxygramine, which resulted in 95 and 93% yields, respectively. This variation has been employed by Heinzelman and co-workers[222a,b] for their syntheses of 1- and 2-methyl-5-benzyloxygramine (80 and 73% yield), by Wintersteiner and co-workers[223] for 6-methoxygramine (74%), by Schlossberger and Kuch[224a,b] for 5,6-dibenzyloxygramine (80%), and by Kalir and co-workers[91] for 7-methoxygramine (75%). Stoll and co-workers used a 1:1 mixture of ethanol and acetic acid as a solvent in the Mannich reaction and obtained 4-, 5-, and 6-benzyloxygramine in 89, 84, and 80% yield, respectively.[80]

Recently, Bourdais and Germain, employing a variation of Plieninger's and Walker's procedures (see Section III.D.1), have reported the synthesis of gramine derivatives by way of the hydrogenation of *o*-nitrophenylacetonitriles **414** (Scheme 32). These were prepared in high yield by the reaction of *N,N*-dimethyl-α-cyanoacetamide (**413**) with various 2-halonitrobenzene derivatives **412**. Indole-3-carboxamides, **415**, result (40–80% yield), which can be reduced to the gramines with lithium aluminum hydride. 4- and 6-methoxygramine (**416**) have been prepared in this manner.[379]



412 413 414 415 416

Scheme 32



417; $R' = CH_3$, $i\text{-}C_3H_7$

418; $R = CH_3$, $R' = i\text{-}C_3H_7$
419; $R = C_6H_5CH_2$, $R' = CH_3$

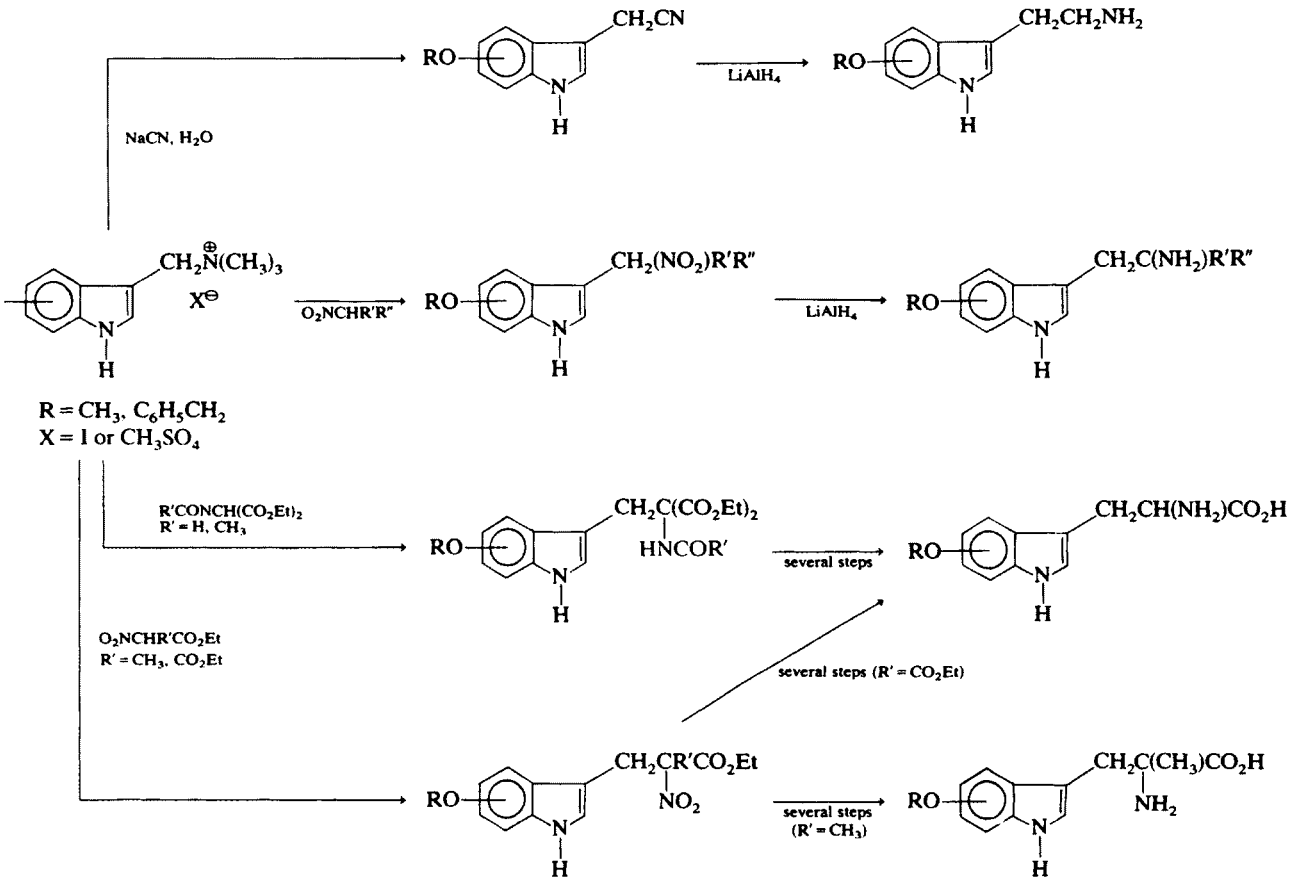
An acid-catalyzed alkylation of 5-methoxy- and 5-benzyloxyindole with the aldamines **417** has been used to prepare the gramine **418**[381] and **419**.[380] Other 5- and 6-alkoxy- and 5,6-dialkoxy-substituted gramines have been prepared in this way.[381]

When 5-hydroxyindole,[225] 2-methyl-5-hydroxyindole,[385] 5-hydroxyindole-2-carboxylic acid,[225] or ethyl 2-methyl-5-hydroxyindole-3-carboxylate[385,386] were reacted with dimethylamine or piperidine under Mannich conditions, substitution occurred in the 4-position only (see Section VII.F). An earlier report[226] of reaction at the 6-position in 5-hydroxyindole-3-carboxylic acid esters was shown[386] to be in error. All four hydroxygramines have, however, been synthesized by reduction of the benzyloxygramine hydrochlorides with a palladium catalyst in methanol.[227a,b]

B. Reactions

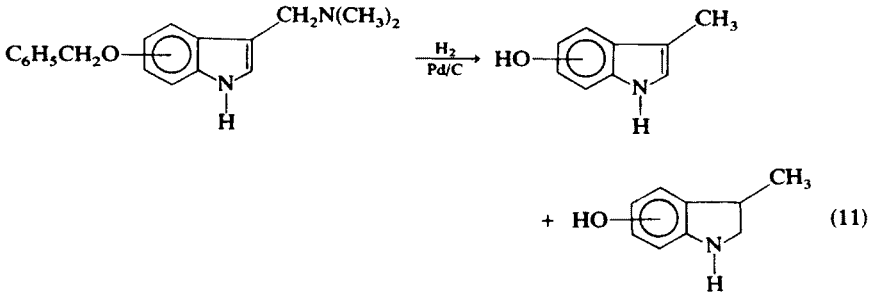
The alkoxygramines are important intermediates in the synthesis of alkoxytryptamines and alkoxytryptophans (Scheme 33). The principal route to the former has been the action of cyanide ion on the methosulfate or methiodide salts of the gramine followed by lithium aluminum hydride reduction of the resulting alkoxyindole-3-acetonitrile (see Section V.C.1). The sodium salts of nitroalkanes have also been employed to displace trimethylamine from the gramine salts, in which case α-alkylated alkoxytryptamines result.[222,235a,b,q2,28,229] When diethyl *N*-formyl aminomalonate,[85a,b,224a,b,380] diethyl *N*-acetylaminomalonate,[88,190,220,221,230,231,380] nitromalonate,[222] or ethyl 2-nitropropionate[235a–c] sodium salts are employed as nucleophiles, intermediates convertible to alkoxytryptophans result.

Hydroxyskatoles are obtained when benzyloxygramines are catalytically reduced. Acheson and Hands obtained[232a,b] 5-hydroxyskatole in 72% yield when a methanol solution of 5-benzyloxygramine was hydrogenated in the presence of a platinum catalyst. Reduction to 5-benzyloxyskatole occurred when zinc dust in methanolic sodium hydroxide was used.[232a,b] Marchand has reported obtaining 5-hydroxyskatole by


NaCN, H2O
CH2CN
RO
N
H
LiAlH4
CH2CH2NH2
CH2(CH3)3
X⊖
O2NCHR'R"
CH2(NO2)R'R"
CH2C(NH2)R'R"
R = CH3, C6H5CH2
X = I or CH3SO4
R'CONCH(CO2Et)2
R' = H, CH3
CH2C(CO2Et)2
HNCOR'
several steps
CH2CH(NH2)CO2H
O2NCHR'CO2Et
R' = CH3, CO2Et
several steps (R' = CO2Et)
CH2CR'CO2Et
NO2
several steps
(R' = CH3)
CH2C(CH3)CO2H
NH2

Scheme 33

reduction (30 hours) of 5-benzyloxygramine hydrochloride with a palladium–carbon catalyst in ethanol, and reduction for 16 minutes gave 5-hydroxygramine hydrochloride.[233] All four hydroxyskatoles have been prepared (12–62%) by hydrogenolysis (Pd/C) of benzyloxygramines in ethyl acetate[234a,b] accompanied, in the case of the 4- and 6-benzyloxygramines, by 21 and 11% yields, respectively, of indolines (eq. 11). Similarly, 5,6-dibenzyloxygramine could be reduced to 5,6-dihydroxyskatole in 38% yield.[234a]



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Reductive deamination (Pd/Al_2O_3) of a series of hydroxygramines and hydroxyisogramines was used by Troxler and co-workers to prove the structures of various Mannich reaction products from hydroxyindoles. The methylated hydroxyindoles prepared in this way were 4-hydroxy-5-methyl-, 4-methyl-5-hydroxy-, 6-hydroxy-7-methyl-, 6-methyl-7-hydroxy-, 3,4-dimethyl-5-hydroxy-, and 3,7-dimethyl-6-hydroxyindole.[384]

5-Benzyloxygramine on nitration yields the 4-nitro derivative (70%), a key intermediate in the synthesis of dehydrobufotenine (**554**).[396]

V. Hydroxytryptamines

A. Introduction

The discovery in nature of the physiologically active 5-hydroxytryptamines, bufotenine, serotonin, and melatonin and the hallucinogenic 4-hydroxytryptamines, psilocin and psilocybin, has stimulated an avalanche of syntheses of these relatively simple structures and a practically endless number of their analogues. In the case of serotonin, many closely related structures were synthesized as potential serotonin antagonists, whereby,

in blocking the normal pressor action of serotonin, therapeutic antipressor activity was anticipated. This hope was realized in the potent antiserotonin drugs 1-benzyl-2,5-dimethylserotonin (BAS) and 2-methyl-3-ethyl-5-dimethylaminoindole.[403]

A brief account of the isolation, original synthesis, and occurrence of the four most important naturally occurring hydroxytryptamines follows in the order of their discovery. Naturally occurring 5-hydroxytryptamines and their sources are listed in Table XI in the Appendix of Tables. Surprisingly no simple 6-hydroxytryptamines appear to have been found yet in nature, although mammalian liver microsomes are known to hydroxylate skatole,[13] tryptamine,[330a–c] α-methyltryptamine,[404] α-ethyltryptamine,[405] and *N,N*-dimethyl-[14] and *N,N*-diethyltryptamine[406a,b] specifically in that position. The 5-hydroxytryptamines in plants probably arise by the pathway demonstrated in animals, namely, the decarboxylation of 5-hydroxytryptophan, produced by the hydroxylation of tryptophan.[407] Psilocin and psilocybin, however, arise in at least the mushroom *Psilocybe cubensis* by hydroxylation of *N,N*-dimethyltryptamine, produced by stepwise methylation of tryptamine.[408a,b]

1. *Bufotenine*

The first hydroxytryptamine discovered in nature was isolated from the parotid glands of the toad *Bufo vulgaris* by Wieland and co-workers in 1931. Although an N,N^{α},N^{α}-trimethyltryptophan structure was originally proposed,[409] this was challenged[424a] and soon revised[279] to N^{ω},N^{ω}-dimethyl-5-hydroxytryptamine when it was observed that the natural material possessed a phenolic group which on methylation led to a compound identical with synthetic N^{ω},N^{ω}-dimethyl-5-methoxytryptamine. This compound[244b] and its ethyl ether homologue[244a] were successfully dealkylated by Hoshino and Shimodaira for the first syntheses of bufotenine.

In the toad, bufotenine is accompanied by the *N*-methylbetaine congener, bufotenidine[279] and the *O*-sulfate (bufothionine) of dehydrobufotenine,[410] whose structure has recently been shown to be **554**.[411,412] All three products have been found in the skins of a number of South American toads (see Table XI).

Bufotenine occurs widely in the plant world, being found in a number of mushrooms of the *Amanita* genus. the Australian grasses *Phalaris tuberosa* and *P. arundinacea*, where it may be the cause in grazing sheep of the serious "staggers" disorder, two Indian plants of the genus *Desmodium*, reputed to have medicinal value, and lastly in the seeds and

seed pods of a number of shrubs of the *Piptadenia* genus, which have been implicated as the chief ingredient of the hallucinatory *cohoba* or *epená* snuffs used by Caribbean or South American Indians, respectively. Bufotenine appears to have little hallucinogenic activity, however; the activity of the epená snuff seems to be due to the accompanying methyl ether[413a,b] (see Table XI).

An enzyme capable of methylating bufotenine has been found in the skin of the toad, *Bufo alvarius*, a good source of bufotenine and also of its *O*-sulfate (bufoveridine) and methyl ether.[414] Bufotenine N^{ω}-oxide, another naturally occurring bufotenine derivative, results in the laboratory on oxidation of bufotenine with hydrogen peroxide.[415]

2. *Serotonin*

The vasoconstricting principle of bovine serum was first purified by Rapport and co-workers[444a,b] and characterized as an indole derivative on the basis of simple color tests and its uv spectrum. Rapport subsequently demonstrated[445] that this crystalline material was a hydrated creatinine sulfate complex whose uv spectrum more closely agreed with that of a 5-hydroxyindole (see Section VIII.A). He correctly proposed 5-hydroxytryptamine as a tentative structure for serotonin, even though zinc dust distillation failed to produce indole. This identification was confirmed three years later by the nearly simultaneous syntheses of Hamlin and Fischer[219a] and the Speeter group.[236] The synthetic material was shown to have identical uv[219a,236] and ir[236] spectra, identical melting points of the creatinine sulfate complex[219a,236] and picrate,[219a,236] and identical behavior in stimulating the contraction of smooth muscle[236] or increasing blood pressure.[219a,236] A wealth of excellent reviews on serotonin, particularly dealing with its pharmacology and clinical applications, is available.[440,446–456]

Serotonin (**446**) has since been found to be widely distributed in the animal world, occurring in mammals chiefly in the gastrointestinal tract, spleen, and in the blood stream where it is bound to platelets. Lower levels are found in the kidney, liver, and brain.

Serotonin occurs fairly commonly in the plant world as well, having been found, for example, in a number of edible fruits including bananas, papaws, plantain, mushrooms, eggplant, passion fruit, pineapple, red plums, walnuts, tomatoes, and avocados (see Appendix 1 in Ref. 440 for a comprehensive tabulation of animal and plant sources) and in the stinging plants, cohosh and nettles, where, as in the Portuguese man-of-war, it is responsible for the inflammation reaction. Its occurrence in

mammalian brain tissue has stimulated a number of hypotheses on its role there. Although its function as a neurotransmitter appears likely, its implication in certain abnormal mental states has yet to be proved. LSD and reserpine, interestingly, apparently elicit their responses in the brain by displacing bound stores of serotonin.[453] The close relationship between serotonin and potent hallucinogens such as 5-methoxy-N^{ω},N^{ω}-dimethyltryptamine[457] has generated speculation that certain mental disturbances such as schizophrenia might arise from the abnormal metabolism, for example, *N*,*N*-dimethylation, of serotonin or its immediate precursor, 5-hydroxytryptophan, to generate an endogenous hallucinogen.[457–460]

Szara has speculated[406b] that schizophrenics might abnormally hydroxylate tryptamine or some derivative to 6-hydroxytryptamines—which by analogy to harmaline would be expected to manifest psychomimetic activity. However, the few 6-hydroxytryptamines that have been tested for hallucinogenic activity, 6-hydroxy-α-methyl-[461] or -α-ethyltryptamine,[405] appear to be only weakly active. 6-Hydroxy-*N*,*N*-diethyltryptamine does, however, have appreciable activity.[406b]

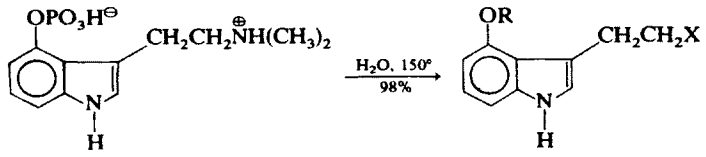
5-Methoxytryptamine has been detected in the urine of rheumatic fever patients.[462] Another serotonin metabolite, 5-hydroxyindole-3-acetic acid, is detected at elevated levels in the urine of patients afflicted with carcinoid tumors and is used to diagnose this condition.[463]

Many reports have appeared[464–479] on the efficacy of serotonin,[464,467–469] bufotenine,[470,473,474] and particularly 5-methoxytryptamine[470,475–479] in offering protection against the whole-body irradiation of rats and mice. A review on this application is available.[480]

Doepfner and Cerletti have reported[481] that the ultraviolet irradiation of aqueous solutions of 5-hydroxytryptophan produces serotonin in several percent yield.

3. *Psilocybin and Psilocin*

To date the only examples of simple 4-hydroxytryptamines in nature are the hallucinogenic principles, psilocin (**421**) and its *O*-phosphate, psilocybin (**420**), first isolated by Hofmann and co-workers from the Mexican mushroom *Psilocybe mexicana*.[482] The major component, psilocybin, which, interestingly, is the only representative now known of a natural product containing both indole and phosphorus, was shown[483] to yield the minor component, psilocin, and one mole of phosphoric acid on sealed tube hydrolysis. Psilocybin and/or psilocin have been found in a number of other Mexican mushrooms of the *Psilocybe* or *Stropheria*



420

421; R = H, X = $N(CH_3)_2$
422; R = $PO_3H^{\ominus}$, X = $NH_2CH_3^{\oplus}$

genera[259b] (see also Refs. 484 and 485) where psilocybin usually predominates. The structures of both were proved by the syntheses[259a,b] outlined in Section V.C.2. A host of psilocin and psilocybin analogues have been synthesized by Troxler and co-workers[227] including OH-positional isomers, alkylated side-chain derivatives, various *N*-alkyl analogues, and other 4-hydroxytryptamine esters.

Psilocybin has since been found in varying proportions in the following North American mushrooms: *Psilocybe baeocystis*,[484,486] *P. caerulipes*,[486] *P. cyanescens*,[484] *P. strictipes*,[486] and *Conocybe cyanopus*,[484] as well as the European species *P. semilanceata*[485] and *P. cubensis*.[408a,b] Psilocin occurs in *P. caerulipes*,[486] *P. cyanescens*,[484] and in *P. baeocystis*,[484,487] where it dominates psilocybin.[484]

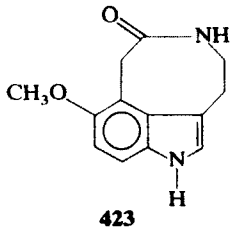
Brack and co-workers demonstrated that tryptophan served as a precursor of psilocybin in the mushroom *P. semperviva*, though they left open the stage at which hydroxylation occurred.[488] Agurell and Nilsson, conducting more thorough biosynthetic studies with *P. cubensis*, proposed the following pathway for psilocin and psilocybin synthesis which places the hydroxylation step at the dimethyltryptamine stage: tryptophan → Δ tryptamine → *N*-methyltryptamine → *N,N*-dimethyltryptamine → psilocin → psilocybin.[408a,b] The isolation of baeocystin (**422**) from *P. baeocystis* by Leung and Paul[489] suggests that, at least in that genus, hydroxylation can occur at or before the monomethylated tryptamine stage. 4-Hydroxytryptamine can also be converted to psilocin in *P. cubensis*, although this is apparently a minor route.[408a,b]

Kalberer and co-workers, studying the metabolism of psilocin in the rat, found that a small amount (ca. 4%) is metabolized to 4-hydroxyindole-3-acetic acid, 25% is excreted unchanged, and the rest appears in the urine as conjugates.[490]

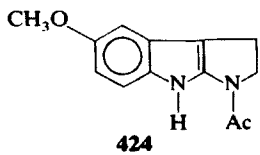
The hallucinatory effects of psilocin and psilocybin are reported[482,491,492] to resemble LSD or mescaline but to be of shorter duration. They are reported[492] to be equipotent on a molar basis, which suggests that psilocin is the form in which psilocybin manifests its activity. A review on psilocybin is available.[493]

4. *Melatonin*

In 1959, Lerner and co-workers reported the isolation of a hormone from bovine pineal glands which bleached frog skin previously darkened by exposure to the melanocyte-stimulating hormone (α-MSH).[436] This substance, named melatonin, was also found in the peripheral nerves of man, monkey, and cow.[436] It was identified as N^{ω}-acetyl-5-methoxytryptamine[436,494] by comparison with authentic material prepared by Szmuszkovicz and co-workers.[494,275] The activity of a number of melatonin analogues including 5-ethoxy analogues, α-methylmelatonin, and *N*-formyl- or *N*-propionyl-5-methoxytryptamines have been studied by Lerner and the Upjohn group (see Ref. 286, p. 105), although none surpass the activity of melatonin, the most potent lightening agent yet discovered. At the incredibly low concentration of 10^{-7} ng/ml, it reverses or prevents the darkening action of α-MSH on frog skin. The two "dehydro" melatonins **423** and **424** are essentially devoid of activity[495]; the "anhydro" melatonin **425**—a harmaline isomer—has, however, appreciable activity.[496]



423



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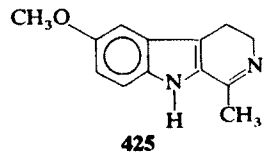
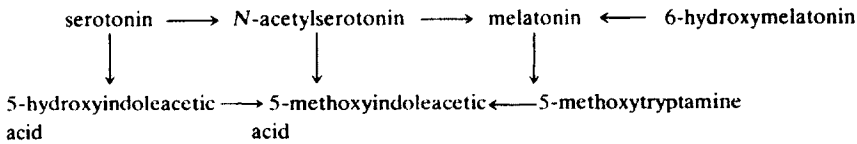
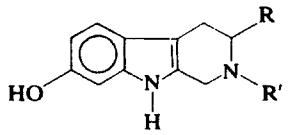


425

Other substances which have been isolated from the pineal gland, such as 5-hydroxy- and 5-methoxyindole-3-acetic acid[436] and 6-hydroxymelatonin,[15,497] as well as the demonstration of the rapid interconversion of serotonin and melatonin by methylation of *N*-acetylserotonin with *S*-adenosylmethionine,[497] have established, in mammals, the metabolic pathways below:



McIsaac has speculated[496] that abnormal melatonin metabolism could generate 5-methoxy analogues (e.g., **425**) of the known hallucinogen



426; R = C_2H_5, R′ = H
427; R = H, R′ = CH_3 or C_2H_5

harmaline, which might also be hallucinogenic. Eberts and Daniels, in a study of the metabolism of α-ethyltryptamine,[405] isolated as a minor metabolite the β-carboline **426**,[498] in addition to the major metabolites, the 6-hydroxytryptamine and various conjugates. This product of reaction with some source of formaldehyde, they feel, could account for the physiological activity of the tryptamine and may represent a general pathway in the metabolism of α-alkyl- or *N,N*-dialkyltryptamines, that is, tryptamines not deaminated by monoamine oxidase. With the latter tryptamines, a step of *N*-dealkylation would have to precede ring closure (→**427**).

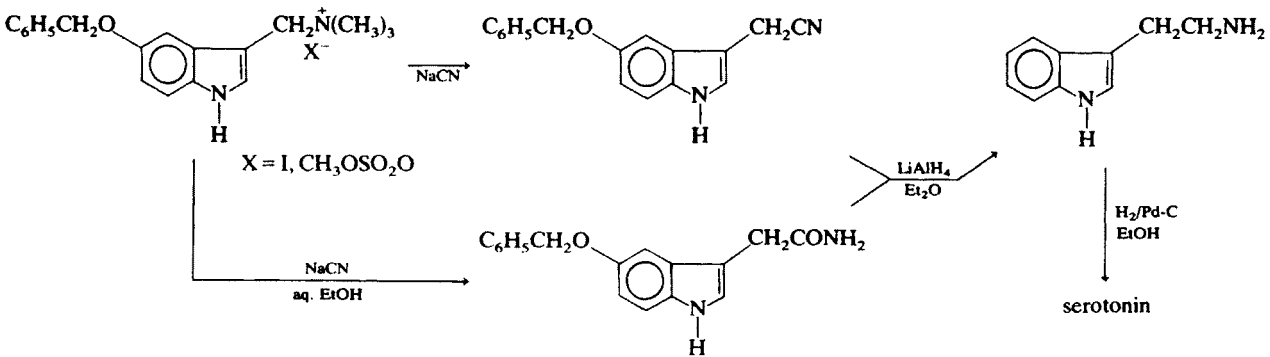
B. Synthesis from Alkoxyindoles

The syntheses of the alkoxy- or hydroxytryptamines can be conveniently divided into two main types according to whether indolic or non-indolic starting materials are employed. The majority of hydroxytryptamine syntheses are of the former type and for this reason much attention has been paid to the development of practical and high-yield syntheses of benzyloxy- and methoxyindoles as discussed in Section III. Synthetic schemes of both types will be illustrated, where possible, by their application to the synthesis of serotonin.

1. *Via Gramine Derivatives*

As mentioned in Section IV.B, one of the most versatile and widely applied procedures for the elaboration of the aminoethyl side chain at the 3-position of alkoxyindoles makes use of displacement of trimethylamine by cyanide ion from methylgramine salts. When sodium cyanide is employed in refluxing *aqueous* ethanol, an indole-3-acetamide results. Either the 3-acetonitrile or the 3-acetamide on reduction with lithium aluminum hydride affords the alkoxytryptamine. This route, employing 5-benzyloxyindole, was chosen for three of the earliest syntheses of serotonin [219a,b,236,85a,b] and a recent synthesis of ^{14}C-labeled serotonin where $^{14}CN^-$ was used[237] (Scheme 34).

The intermediate indole-3-acetonitriles have also been reduced with


C6H5CH2O
CH2N(CH3)3
X−
X = I, CH3OSO2O
NaCN
C6H5CH2O
CH2CN
LiAlH4
Et2O
CH2CH2NH2
H2/Pd-C
EtOH
serotonin
NaCN
aq. EtOH
C6H5CH2O
CH2CONH2
N
H

Scheme 34

hydrogen and Raney nickel catalysts in either ethanol containing hydrazine[90a,b,237] or methanol containing ammonia.[238a,b,c,88,98] A sodium–ethanol reduction has also been used.[152] Julia and co-workers[98] found lithium aluminum hydride reduction of 4-benzyloxy-5-methoxyindole-3-acetonitrile unsatisfactory; satisfactory results, however, were obtained with a Raney nickel hydrogenation.

In addition to serotonin, 4-hydroxy-,[80] 4-hydroxy-[α^{14}C], 6-hydroxy-,[80,86,239] and 7-hydroxytryptamine[85a,b] have been synthesized in essentially the same manner, as well as 5-hydroxy-7-methyltryptamine.[229]

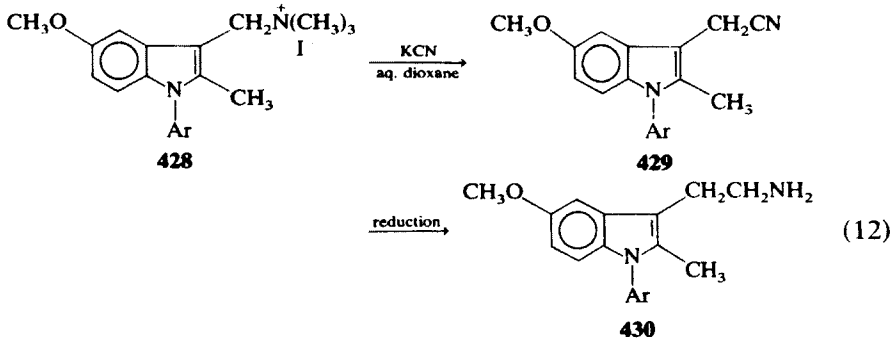
Methoxytryptamines that have been synthesized by means of the gramine–cyanide pathway are as follows: 4-methoxytryptamine,[71] 5-methoxytryptamine (used in the first synthesis of melatonin),[275] 6-methoxytryptamine,[223,241a,b] and 5-chloro-6-methoxytryptamine (used in the synthesis of modified reserpines).[238a,b,c] Kveder and McIsaac have reported, without details, the synthesis of ^{14}C-labeled melatonin from 5-methoxygramine and $^{14}CN^-$ followed by reduction and acetylation steps.[15] Dihydroxytryptamine derivatives synthesized in this manner are 5,6-dimethoxytryptamine,[88] 5-methoxy-6-benzyloxytryptamine,[98,242] 5-methoxy-6-hydroxytryptamine,[98,242] 4-hydroxy-5-methoxytryptamine,[98] 5,6-dibenzyloxytryptamine,[224a,b] and 5,6-dihydroxytryptamine.[224a,b]

Taborsky and co-workers have synthesized 6-hydroxymelatonin, a metabolite of melatonin, from 5-methoxy-6-benzyloxygramine methosulfate and sodium cyanide, followed by reduction, acetylation, and finally, debenzylation[242] (see also Ref. 277 for another approach to this compound).

A series of 1-aryl-2-methyl-5-methoxytryptamines, including the potent antiserotonin compound of Woolley and Shaw (**430**; Ar = $CH_2\varnothing$), has been prepared by Grinev, Terentév, and co-workers using the gramine–cyanide route. 1-Benzyl-2-methyl-5-methoxyindole-3-acetonitrile could be obtained in 72% overall yield from 1-benzyl-2-methyl-5-methoxyindole. Reduction to the tryptamine was effected with either sodium in ethanol,[152] hydrogen and Raney nickel in hydrazine,[153] or lithium aluminum hydride in ether[240] (eq. 12).

Julia and co-workers obtained *N,N*-dimethyl-4-benzyloxy-5-methoxytryptamine in 31% yield by the reduction of 4-benzyloxy-5-methoxyindole-3-acetonitrile with hydrogen and Raney nickel in the presence of dimethylamine.[98] The *N,N*-diethyl homologue was prepared in 29% yield. These transformations presumably proceed by aminolysis of an intermediate Schiff's base (Scheme 35). Catalytic debenzylation afforded the *N,N*-dialkyl-4-hydroxy-5-methoxytryptamines.

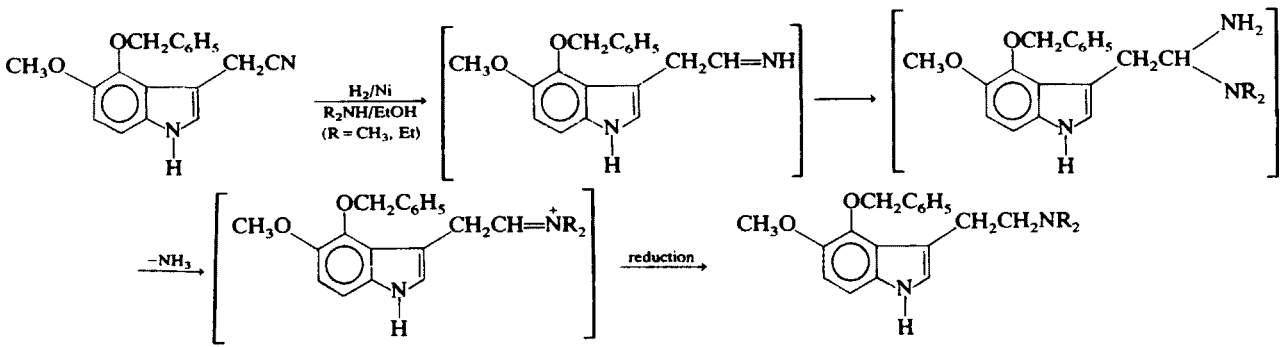
Three routes to alkoxytryptamines have been developed using alkoxyindole-3-acetic acids which are easily obtained by alkaline



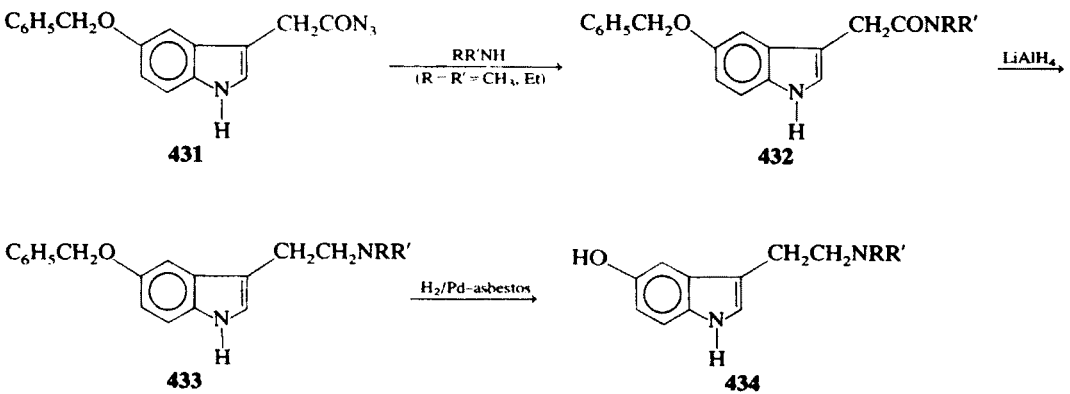
(12)

hydrolysis of the corresponding acetonitrile. Hoshina and Shimodaira, in the first synthesis of bufotenine, reduced 5-methoxyindole-3-acetic acid to the alcohol, converted this to the 2-bromoethylindole, thence to 5-methoxy-*N*,*N*-dimethyltryptamine with dimethylamine in methanol, and lastly, to bufotenine, by demethylation using aluminum chloride in benzene.[244a,b] A second route to bufotenine and to a number of *N*-mono- and *N*-dialkylated serotonin derivatives was developed by Hofmann and co-workers,[80] who employed the reaction of 5-benzyloxyindole-3-acetyl azide (**431**) with primary and secondary amines to produce a series of indole-3-acetamides.[432] Compound **431** was derived stepwise via the methyl ester and the hydrazide. The indoleacetamides were reduced to the tryptamines **433**, with lithium aluminum hydride in refluxing ether, ether–THF, or ether–ethylmorpholine mixtures. The benzyl group was removed by hydrogenation with a palladium–asbestos catalyst in methanol. In this manner, bufotenine, methyl-, ethyl-, and diethylserotonin **434**, were prepared (Scheme 36).

A third procedure featuring indole-3-acetic acids as tryptamine intermediates was first applied to the synthesis of *N*-methyl- and *N*-ethyl-4-hydroxytryptamines.[227a-f] 4-Benzyloxyindole-3-acetic acid was converted to the corresponding *N*-methyl- or *N*-ethylacetamides by the reaction of methyl- or ethylamine on the acid chloride, generated *in situ* with PCl_5. These primary indoleacetamides were reduced with excess lithium aluminum hydride in THF at 42–45° over an extended reaction period—conditions that proved critical for the success of this reaction. At room temperature, very little reduction occurred, whereas at reflux temperature, debenzylation resulted. The resulting 4-benzyloxytryptamines were debenzylated with hydrogen and a palladium on alumina catalyst. The acid chloride–amine route, via tertiary acetamides, has been used by two groups in the synthesis of labeled psilocins. Kalberer and co-workers have reported[490] the synthesis of [α-^{14}C] psilocin from 4-benzyloxyindole-3-acetic acid[$^{14}CO_2H$], prepared in turn from the gramine and labeled


CH3O
OCH2C6H5
CH2CN
H2/Ni
R2NH/EtOH
(R = CH3, Et)
CH2CH=NH
NH2
CH2CH
NR2
-NH3
CH2CH=N+R2
reduction
CH2CH2NR2
N
H

Scheme 35


C6H5CH2O
CH2CON3
RR'NH
(R = R' = CH3, Et)
C6H5CH2O
CH2CONRR'
LiAlH4
431
432
C6H5CH2O
CH2CH2NRR'
H2/Pd-asbestos
HO
CH2CH2NRR'
433
434

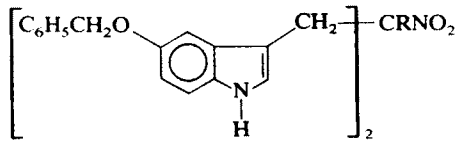
Scheme 36

cyanide. Agurell and Nilsson have described[408a,b] the preparation of [α-$^3H_2$] psilocin by lithium aluminum tritide reduction of 4-benzyloxyindole-3-dimethylacetamide, then catalytic (Pd/Al_2O_3) debenzylation. Although PCl_5 has generally been used to produce the reactive acyl chloride intermediate in these reactions, Unanyan and co-workers have used $SiCl_4$ for this purpose in their preparation[499] of 5-methoxyhomotryptamines, disubstituted on the amine nitrogen.

Although the yields of tryptamines from indole-3-acetic acids, via either the acyl azide or chloride are generally good to excellent, the oxalyl chloride procedure is usually chosen for the synthesis of N^{ω}-dialkyltryptamines. These procedures are still useful, however, in the preparation of N^{ω}-monoalkyltryptamines, whereas for some reason, the oxalyl chloride route often gives poor yields.

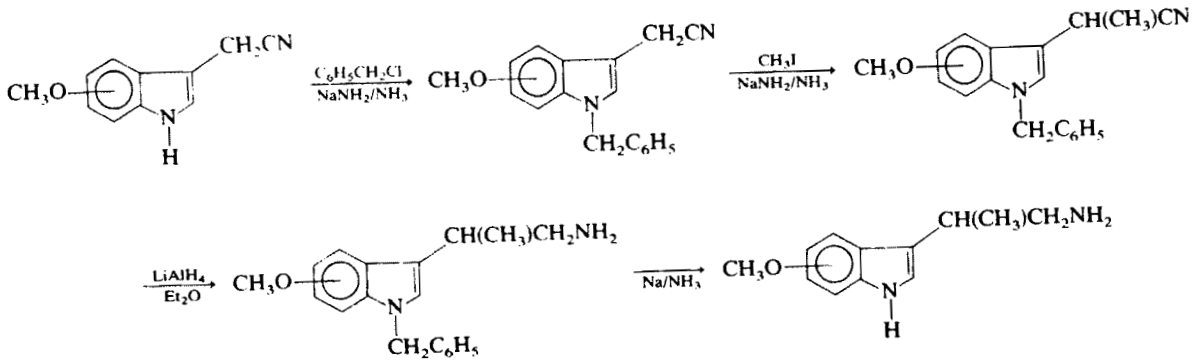
α-Methyl- or α-ethylalkoxytryptamines can be prepared from alkoxygramines and the sodium salts of nitroethane and 2-nitropropane, respectively. These nitroindoles can be reduced under a variety of conditions to the α-alkylalkoxytryptamines. For example, hydrogenation with a Raney nickel catalyst in ammonia–methanol containing chloroplatinic acid was employed by Troxler and co-workers[227] to reduce the reaction product from 4-benzyloxygramine and nitroethane. Catalytic debenzylation gave α-methyl-4-hydroxytryptamine. Raney nickel alone in ammonia–ethanol was used by Heath-Brown and Philpott to prepare α-methyl-6-methoxytryptamine and α-methyl-6-benzyloxytryptamine.[229] The reaction product from 2-nitropropane and 5- and 6-methoxygramine was similarly reduced, yielding the corresponding α,α-dimethyltryptamines. Reducing the reaction product from 1-nitropropane and either 5- or 6-methoxygramine with lithium aluminum hydride in refluxing THF afforded α-ethyl-5- and α-ethyl-6-methoxytryptamine.[228]*

The nitroethyl indoles can be reduced to the hydroxylamine stage using a platinum catalyst in methanol containing one equivalent of hydrochloric acid.[245a,b] In this way, Cohen and Heath-Brown obtained 5-methoxy-α,α-dimethyl-N^{ω}-hydroxytryptamine and 6-methoxy-α-methyl-N^{ω}-hydroxytryptamine (eq. 13).

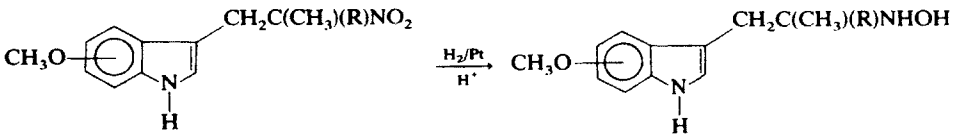


435: R = CH_3, C_2H_5

* Ash and Wragg have reported[64] that 5-benzyloxygramine with nitromethane or nitroethane and sodium hydroxide gave mainly the bis-substituted nitroalkanes **435**.


CH2CN
CH3O
N
H
C6H5CH2Cl
NaNH2/NH3
CH2CN
CH3O
N
CH2C6H5
CH3I
NaNH2/NH3
CH(CH3)CN
CH3O
N
CH2C6H5
LiAlH4
Et2O
CH(CH3)CH2NH2
CH3O
N
CH2C6H5
Na/NH3
CH(CH3)CH2NH2
CH3O
N
H

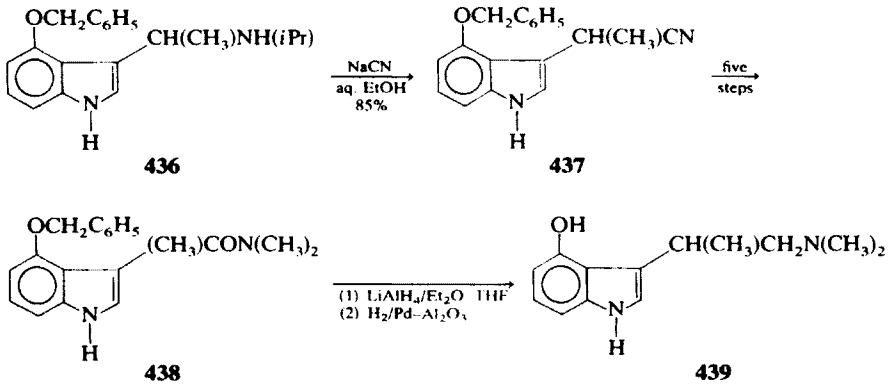
Scheme 37



R = H, CH_3 (13)

Meier has reported that β-substituted methoxytryptamines can be prepared from 1-benzyl-5- and -6-methoxyindole-3-acetonitrile by alkylation with methyl iodide in ammonia containing sodamide prior to hydride reduction. The benzyl protecting group was removed in a subsequent step using sodium in ammonia.[246a,b] These transformations are illustrated in Scheme 37.

Another route to a β-substituted hydroxytryptamine was reported by Troxler and co-workers[227a-f] (scheme 38). The Mannich-reaction product from 4-benzyloxyindole, acetaldehyde, and isopropylamine, **436**, formed in 39% yield, was treated directly with sodium cyanide to provide the 3-(2-propionitrile) derivative **437**. This was converted via the acyl hydrazide and acyl azide to the dimethylacetamide derivative **438**. Hydride reduction and catalytic debenzylation gave *N,N,*β-trimethyl-4-hydroxytryptamine (**439**).



436 **437** **438** **439**

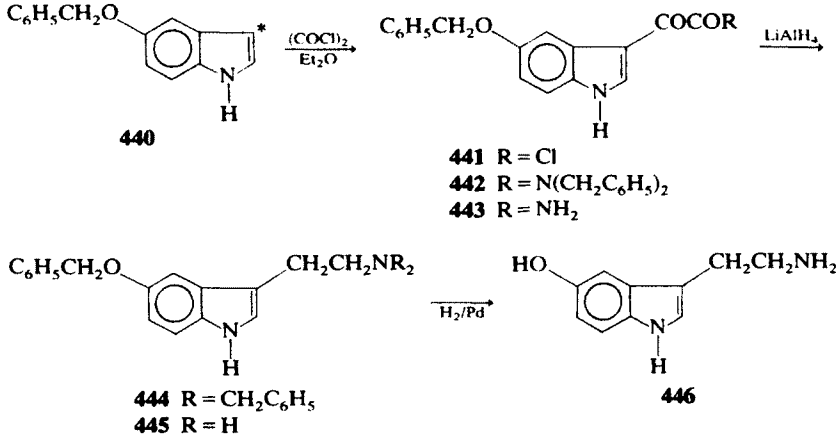
Scheme 38

2. *Oxalyl Chloride Procedure*

The most convenient method for synthesizing alkoxy- or hydroxytryptamines from alkoxyindoles is the procedure generally attributed to

Speeter and Anthony,* in which a slight excess of oxalyl chloride in ether is used to form the indole glyoxoyl chloride.[248] Reaction with ammonia[79,248] or with secondary amines[248] produces the glyoxylamides, for example, **443** and **444**. These can be reduced to the tryptamines in one step using lithium aluminum hydride in refluxing THF or dioxane.[227,256] Although Troxler and co-workers have reported[227a] that the synthesis is not applicable to monosubstituted tryptamines, a number of reports[61,62,251,256] do exist according to which *N*-alkylalkoxytryptamines have been successfully prepared by this route.

Speeter and Anthony found[248] that oxalyl chloride reacted with 5-benzyloxyindole (**440**) to give a nearly quantitative yield of the glyoxoyl chloride derivative **441**. When this was treated with dibenzylamine, the *N,N*-dibenzylglyoxamide, **442**, resulted which could be reduced to the dibenzyltryptamine **444** with lithium aluminum hydride. Debenzylation by hydrogenolysis with a palladium–carbon catalyst yielded serotonin (**446**) in an overall yield of better than 60%. This pathway would appear to be the most satisfactory route to serotonin at this time. Keglevic and Stancic reported[250] the preparation of serotonin (10% overall yield) labeled with ^{14}C in the 3-position starting with labeled pyruvate and *p*-benzyloxyphenylhydrazine. The labeled 5-benzyloxyindole thus obtained was treated by the Speeter–Anthony procedure as outlined above. Kondo and co-workers reacted[79] the glyoxoyl chloride **441** with aqueous ammonia to form the primary glyoxamide **443**, which was reduced (→**445**) and catalytically debenzylated to afford serotonin in a slight variation of



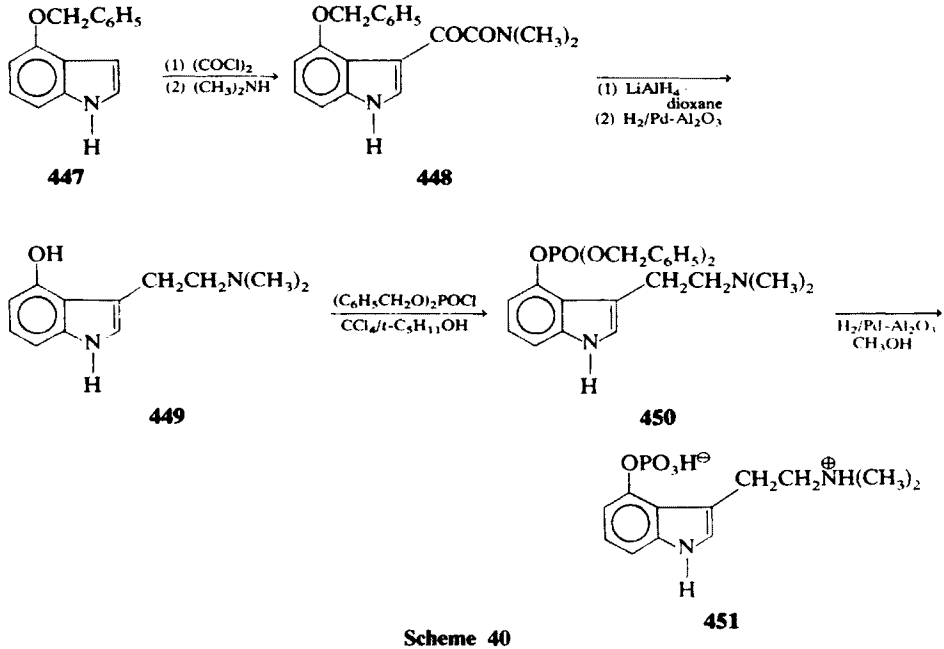
Scheme 39

* Kharash and co-workers seem to have recognized this reaction much earlier as a general reaction of 3-unsubstituted indoles, although they did little to exploit it.[249]

the Speeter–Anthony synthesis. In this manner the 6-hydroxy analogue of serotonin was also prepared.[79,89]

When 5-benzyloxyindole-3-glyoxoyl chloride was treated with dimethylamine, the *N,N*-dimethylglyoxamide resulted in good yield. Reduction and debenzylation afforded bufotenine.[248,79,251,253b] 1-Methylbufotenine could be obtained by methylating 5-benzyloxytryptamine with methyl iodide in ammonia–sodamide followed by debenzylation.[252] *N,N*-Diethyl and *N,N*-dipropyl serotonin,[253b] 3-pyrrolidinylethyl-5-hydroxyindole,[257] and the 2-methyl derivatives of *N,N*-dimethyl and *N,N*-diethyl serotonin[254] were synthesized starting with 5-benzyloxyindole or 2-methyl-5-benzyloxyindole.

The Speeter–Anthony procedure has been applied to the synthesis of psilocin by Hofmann and co-workers (Scheme 40).[259a,b] 4-Benzyloxyindole (**447**) on reaction with oxalyl chloride, then dimethylamine, gave the dimethylglyoxamide, **448**. Lithium aluminum hydride reduction in dioxane followed by hydrogenolysis in methanol gave psilocin (**449**). Psilocin was converted to psilocybin (**451**) by reaction with dibenzylphosphoryl chloride in *t*-amyl alcohol followed by catalytic debenzylation. Other psilocin esters (e.g., acetyl, tosyl, benzoyl, pivaloyl, sulfonyl) have also been prepared,[260a,b] as well as psilocin esters alkylated on the indole nitrogen.[260b]



447 **448** **449** **450** **451**

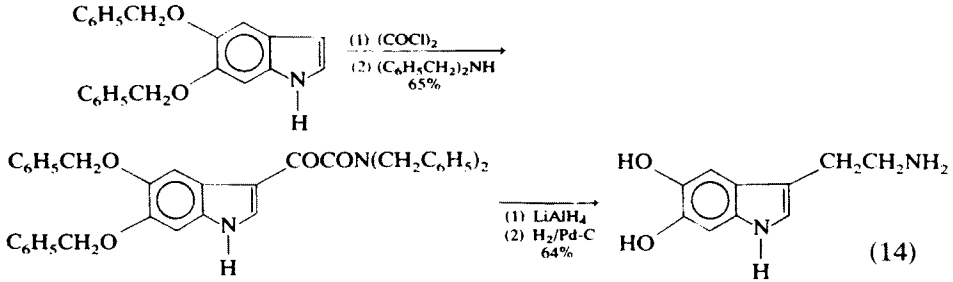
Scheme 40

Troxler and co-workers synthesized the *N,N*-diethyl and *N*-piperidinyl derivatives of 4-hydroxytryptamine as well as *N,N*-dimethyl-4-methoxytryptamine using the same route.[227a,b] The 1-methyl, 1-benzyl, and 1-acetyl derivatives of 4-benzyloxy-*N,N*-dimethyltryptamine and the three 1-substituted 4-hydroxytryptamines were also synthesized by this group. Starting with 6- or 7-benzyloxyindole, Troxler and co-workers achieved the synthesis of the 6- and 7-hydroxy analogues of psilocin and psilocybin.[227a,c,d] Kondo and co-workers have also reported the synthesis of the 6-hydroxy analogue of psilocin.[79]

Julia and co-workers found the Speeter–Anthony procedure unsatisfactory for the synthesis of tryptamines from 4-benzyloxy-5-methoxyindole, as only a 38% yield of the glyoxoyl chloride could be obtained.[98] However, the gramine–cyanide route did provide them with good yields of the tryptamines.

A number of methoxy- and ethoxytryptamines have been prepared using the Speeter–Anthony procedure. Among them are the following 5-methoxytryptamines: N^{ω}-methyl,[62,251,256] N^{ω}-ethyl,[62] N^{ω},N^{ω}-dimethyl,[252,256] N,N^{ω},N^{ω}-trimethyl,[252] N^{ω},N^{ω}-ethyl,[62] and N^{ω}-pyrrolidinyl.[257,258] Melatonin has been synthesized by Supniewski and Misztal by the action of ammonia on 5-methoxyindole-3 glyoxoyl chloride and subsequent reduction and acetylation.[255] 6-Alkoxytryptamines synthesized by the oxalyl chloride method include 6-methoxytryptamine[87] and its N^{ω}-methyl,[62] N^{ω}-ethyl,[62] N^{ω},N^{ω}-dimethyl,[62,264] N^{ω},N^{ω}-diethyl,[62] N^{ω}-pyrrolidinyl,[258] and higher[62] homologues, as well as 6-ethoxytryptamine[73a,b,d] and N^{ω}-ethyl-6-ethoxytryptamine.[61] The following 7-methoxytryptamines have also been prepared: N^{ω},N^{ω}-dimethyl,[91,194] N^{ω},N^{ω}-diethyl,[91] and N^{ω}-pyrrolidinyl.[258]

Schlossberger and Kuch have reported the synthesis of 5,6-dihydroxytryptamine as outlined in eq. 14.[82] This substance or an isomeric catecholamine has been implicated as a neurohormone in crustaceans.[265]



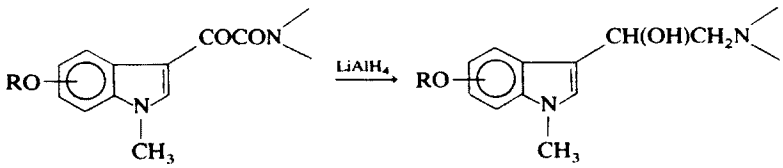
(14)

Other dihydroxytryptamines which have been prepared by means of the oxalyl chloride procedure are 5,6-methylenedioxytryptamine,[73a,b,d]

4,7-dimethoxytryptamine,[96] 5,7-dimethoxytryptamine,[378] *N*-methyl- and *N,N*-dimethyl-5,7-dimethoxytryptamine,[378] *N,N*-dimethyl-4-hydroxy-5-methoxytryptamine,[98] N^{ω}-methyl-5-methoxy-6-hydroxytryptamine,[98] *N,N*-diethyl-5-methoxy-6-hydroxytryptamine,[98] *N,N*-dimethyl-6-hydroxy-7-methoxytryptamine,[98] and *N,N*-diethyl-6-hydroxy-7-methoxytryptamine.[98] Brown and co-workers have noted[349] that 4,6-dimethoxyindole behaves abnormally in the oxalyl chloride synthesis, giving an indole-7-glyoxoyl chloride.

Hardegger and Corrodi have reported the successful synthesis of *N,N*-dimethyl-5,6,7-trimethoxytryptamine,[104] and Carlsson and co-workers,[189] the synthesis of *N,N*-dimethyl-4,5,6-trimethoxytryptamine by the glyoxoyl chloride route.

Glyoxamides are also produced in good yield when 1-alkyl-alkoxyindoles are employed in the Speeter–Anthony procedure. Reduction with lithium aluminum hydride in refluxing dioxane or THF does not yield simple tryptamines, however, but instead gives β-hydroxytryptamines (eq. 15).[227,266,267] Ames and co-workers prepared 1-methyl-2-phenyl-*N,N*-dimethyl-5-benzyloxy (and hydroxy)-β-hydroxytryptamine by lithium aluminum hydride reduction in benzene–ether.[268] In one instance, even an *N*-unsubstituted glyoxamide has yielded a β-hydroxytryptamine. Troxler and co-workers reported[227a] that the dimethylglyoxamide derived from 4-benzyloxyindole could be reduced with lithium aluminum hydride in refluxing THF to a mixture of the β-hydroxytryptamine and psilocin benzyl ether. When refluxing dioxane was employed in the reduction, only psilocin benzyl ether resulted. Taborsky and co-workers attempted, but could not achieve, partial reductions with 1-unsubstituted 5-methoxy- or 5-benzyloxy-indole-3-glyoxamides.[267]



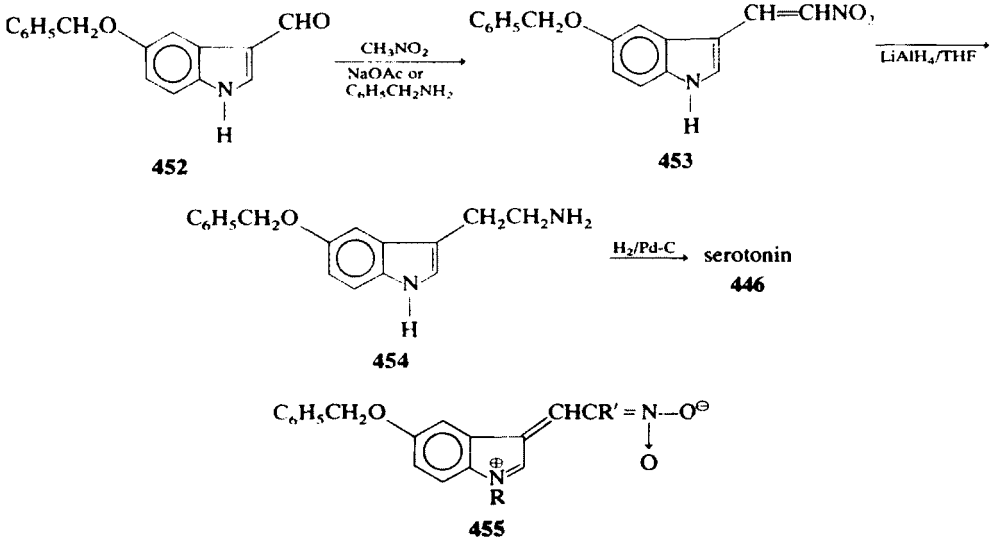
(15)

3. *Via Alkoxyindole-3-aldehydes and Nitroalkanes*

Another widely used method for introducing the 2-aminoethyl side chain at the 3-position of an alkoxyindole employs the condensation of nitromethane or its homologues with alkoxyindole-3-aldehydes, usually in the presence of sodium or ammonium acetate,[269a,b] although acetic anhydride–acetic acid containing sodium or ammonium acetate[222,275] or

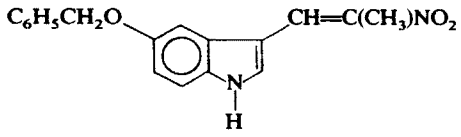
catalysis by neat benzylamine[64,270] and piperidine[273a–c,278a–d] have also been used. A 3-(2-nitrovinyl) alkoxyindole (e.g., **453**, **456**) results, which can be reduced in one step to the tryptamine using lithium aluminum hydride in ethers or hydrogen and a palladium–carbon catalyst. This synthesis is applicable only to tryptamines unsubstituted on the side-chain amino group. Two fairly early syntheses of serotonin employed this sequence.

Using the Vilsmeier–Haack formylation procedure ($POCl_3$–DMF), Young obtained[269a–e] 5-benzyloxyindole-3-aldehyde (**452**) in 86% yield. Heating the aldehyde with sodium acetate in an excess of nitromethane gave the nitrovinyl derivative **453** in 65% yield. Work by Heinzelman and co-workers[222] suggests that the zwitterionic structure **455** more correctly represents the properties of this and similar compounds. Lithium aluminum hydride reduction in THF gave 5-benzyloxytryptamine (**454**), which was debenzylated to serotonin (Pd/C–CH_3OH) in an overall yield of 34%. Ash and Wragg independently reported a similar synthesis of serotonin in an overall yield of 20%[64] using benzylamine catalysis in the nitromethane condensation step.

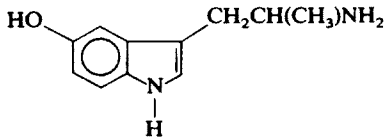


452 453 454 446 455

When homologues of nitromethane are employed in this synthesis, α-alkylated tryptamines result. Both Young[269a–e] and Ash and Wragg[64,270] prepared α-methyl- (**457**) and α-ethylserotonin using nitroethane and 3-nitropropane, respectively, on **452**. Heinzelman and co-workers have also prepared α-methyl serotonin in this way.[222]

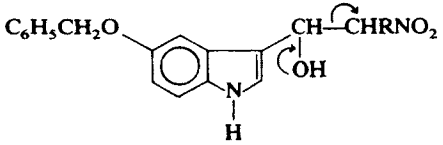


456

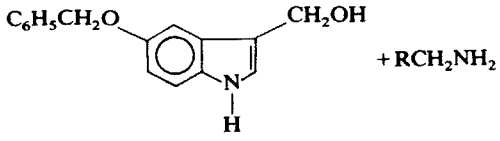


457

Ash and Wragg noted[64] that 5-benzyloxyindole-3-methanol (**459**) resulted as a by-product in the reduction of the nitropropenyl- and nitrobutenyl-5-benzyloxyindoles and suggested that this arose by hydride-induced cleavage of nitro alcohols **458**, contaminating these nitrovinyl preparations.



458; R = CH_3, Et



459

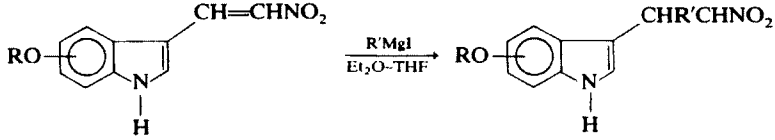
Other alkoxy- or hydroxytryptamines which have been synthesized by means of the aldehyde–nitroalkane route are α-ethyl-4-benzyloxytryptamine,[271] 5-methoxytryptamine,[272,275] α-methyl-5-methoxytryptamine,[269a] α-ethyl-5-methoxytryptamine,[229] 6-benzyloxy- and 6-hydroxytryptamine,[269a] α-methyl-6-methoxytryptamine,[273a–c] α-ethyl-6-methoxytryptamine,[229] 7-methoxytryptamine,[91] α-methyl-7-methoxytryptamine,[91,274] and 4,5,6-trimethoxytryptamine.[189]

For their second synthesis of melatonin, Szmuszkovicz and co-workers prepared 5-methoxytryptamine using the aldehyde–nitroalkane procedure with ammonium acetate in a mixture of acetic anhydride and acetic acid.[275] Melatonin was obtained by Kralt and co-workers in a similar manner; it was then reduced to *N*-ethyl-5-methoxytryptamine with

lithium aluminum hydride.[61] Starting with 1-methyl-5-benzyloxyindole-3-aldehyde, Heinzelman and co-workers successfully synthesized 1,α-dimethyl-5-hydroxytryptamine. The condensation step proceeded in 40% yield with ammonium acetate in acetic anhydride–acetic acid. The starting material was prepared in 76% yield by methylation of 5-benzyloxyindole-3-aldehyde with methyl iodide and potassium carbonate in carbitol.[222]

Hall and Jackson found the Speeter–Anthony synthesis unsatisfactory for their purpose and turned to the aldehyde–nitromethane method for a successful synthesis of 6-hydroxymelatonin, a mammalian metabolite of melatonin.[277] Starting with 5-methoxy-6-benzyloxyindole-3-aldehyde, they obtained 6-hydroxymelatonin in an overall yield of 19%. Another important alkoxytryptamine, the serotonin antagonist 1-benzyl-2-methyl-5-methoxytryptamine, was synthesized by Domschke and Mueller by means of the aldehyde–nitromethane route.[276]

β-Alkyl-alkoxytryptamines, **461** have been prepared by alkylation of 5- and 6-methoxy-3-(2-nitroethylene)indoles (**460**) with methyl- or ethylmagnesium iodide prior to the reduction step. In this way, β-methyl-5-methoxytryptamine,[278a,b] and β-methyl-[278c] and β-ethyl-6-methoxytryptamine[278c,d] have been prepared.

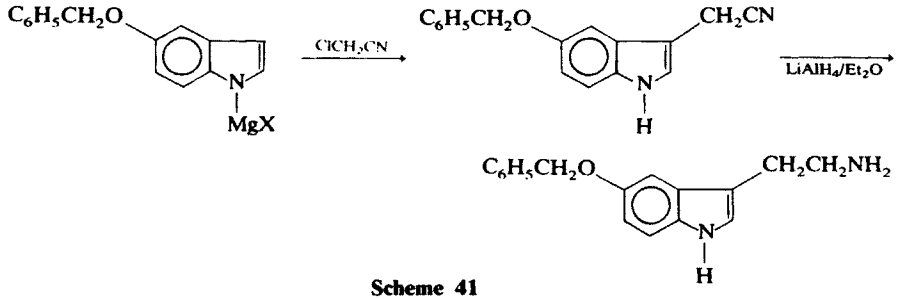


460; R = 5- or 6-CH_3O **461**; R' = CH_3 or Et

4. *Via Alkoxyindolemagnesium Halides*

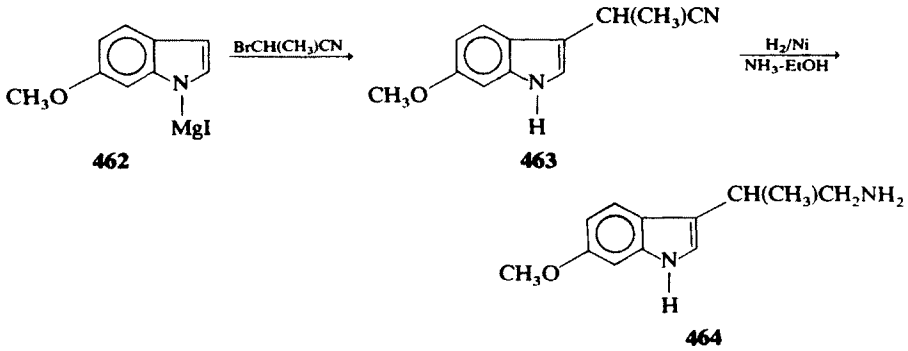
A number of practical syntheses of alkoxytryptamines, including several of the earliest, feature the use of alkoxyindole Grignard derivatives.

a. Coupling with α-Haloacetonitriles. The first syntheses of 5-methoxytryptamine by Wieland and co-workers[279] and of 6-methoxytryptamine by Akabori and Saito,[280] as well as an early synthesis of 5-ethoxytryptamine by Hoshino and Kotake,[281] utilized the reaction between chloroacetonitrile and the appropriate alkoxyindolemagnesium halide. The intermediate alkoxyindole-3-acetonitriles were reduced to tryptamines with sodium in alcohol. More recent syntheses, by this route, of 5-benzyloxytryptamine,[282,283] substituted 5-benzyloxytryptamines[283] and substituted 5-benzhydryloxytryptamines,[283] and 5-benzhydryloxytryptamine[283] employ lithium aluminum hydride in the reduction step. Serotonin has been obtained[282] by the pathway shown in Scheme 41.



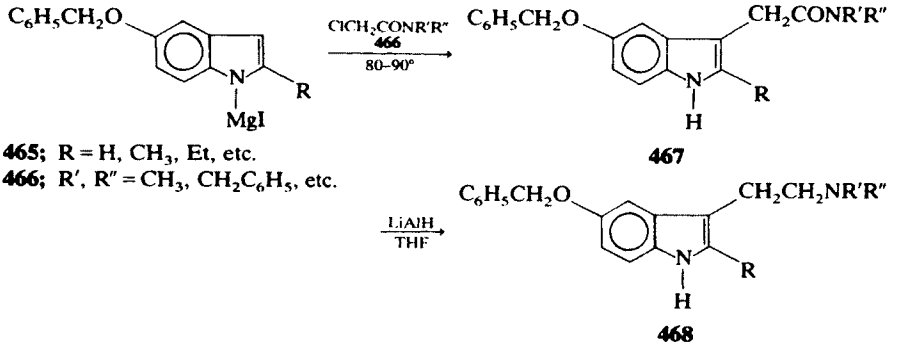
Scheme 41

The Grignard derivative of 6-methoxyindole **462** has been coupled with 2-bromopropionitrile to provide the indolepropionitrile derivative, **463**. Reduction of this nitrile with Raney nickel in ammoniacal ethanol afforded 6-methoxy-β-methyltryptamine[284a–d] (**464**).



462 **463** **464**

b. COUPLING WITH α-CHLOROACETAMIDES. 5-Benzyloxyindole and its 2-alkyl derivatives, **465**, have been converted into tryptamines by reaction of their magnesium iodide derivatives with tertiary chloroacetamides

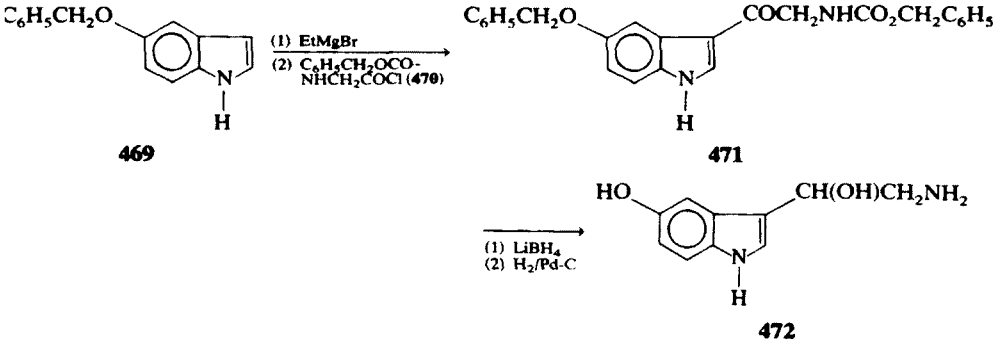


465; R = H, CH_3, Et, etc.
466; R′, R″ = CH_3, $CH_2C_6H_5$, etc.

467 **468**

466 in the absence of a solvent.[285a,b] The reaction is less successful with secondary acetamides and fails with chloroacetamide.[286] Lithium aluminum hydride reduction of **467** in THF affords the *N,N*-dialkyltryptamines, **468**, usually in good yield.[285b]

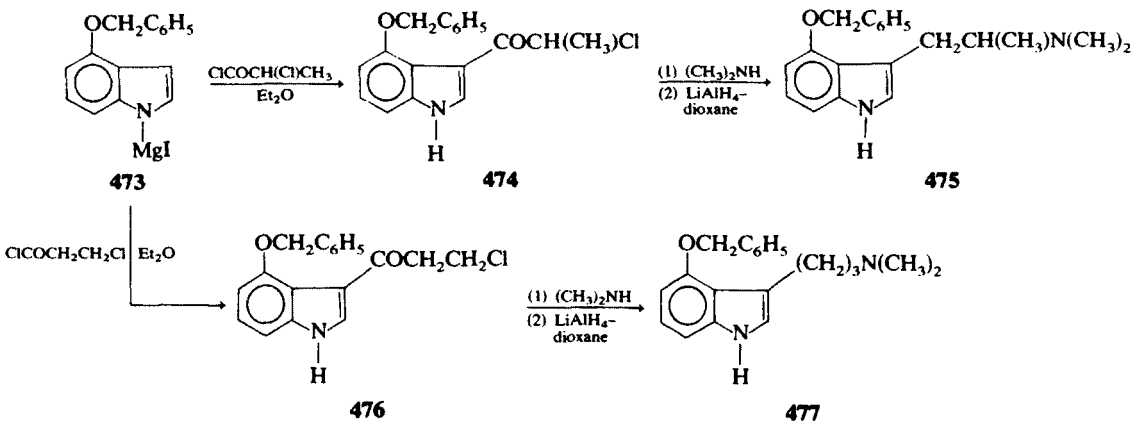
c. Reaction with Acyl Chlorides. Ames and co-workers have reported[644] the synthesis of 5,β-dihydroxytryptamine (**472**) using the reaction between the Grignard derivative of 5-benzyloxyindole and *N*-carbobenzyloxyglycyl chloride (**470**). The intermediate carbobenzyloxyglycyloylindole, **471** was reduced to the carbinol with lithium borohydride; the carbobenzyloxy group was then removed by hydrogenolysis.



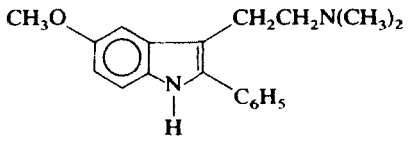
Troxler and co-workers have coupled 4-benzyloxyindolemagnesiumiodide (**473**) with α- and β-chloropropionyl chloride to give the chloroacyl intermediates **474** and **476** (Scheme 42). Treatment with dimethylamine and lithium aluminum hydride reduction afforded the α-methyl tryptamine **475** and the indole-3-propylamine **477**. A final debenzylation (H_2/Pd/Al_2O_3) gave the two hydroxyindoles. Interestingly, some hydrogenolysis of the benzyl group was also noted during the hydride reduction.[227a]

d. Reaction with Amines. When 2-chloro-*N,N*-dimethylethylamine was coupled with the Grignard derivative of 2-phenyl-5-methoxyindole in anisole at -5°, the tryptamine **478** resulted, although in very poor yield. In this reaction, the aziridinium salt **479** is probably the actual reactant.[287]

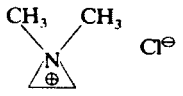
Bucourt and co-workers have developed a very promising tryptamine synthesis using indole Grignard derivatives with aziridine in an ether–xylene mixture.[288] Tryptamines result directly in good yield (eq. 16). 5-Methoxy-, 5-benzyloxy-, 6-methoxy-, and 5,6-methylenedioxytryptamines have been synthesized in this manner.


OCH2C6H5
MgI
473
ClCOCH(Cl)CH3
Et2O
COCH(CH3)Cl
474
(1) (CH3)2NH
(2) LiAlH4–
dioxane
CH2CH(CH3)N(CH3)2
475
ClCOCH2CH2Cl
Et2O
COCH2CH2Cl
476
(CH2)3N(CH3)2
477

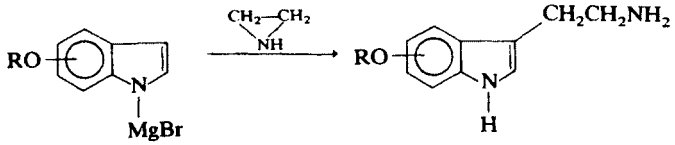
Scheme 42



478

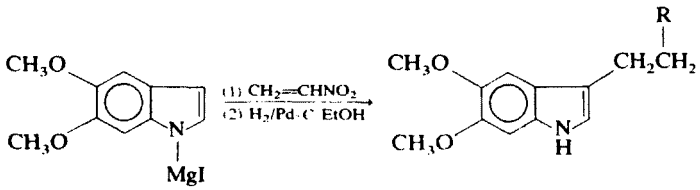


479



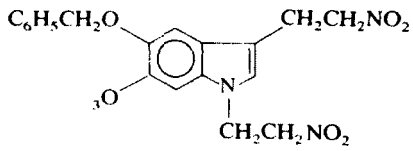
(16)

e. OTHER. 5,6-Dimethoxytryptamine (**482**) has been synthesized in 10% yield using the Grignard derivative of 5,6-dimethoxyindole, **480**, and nitroethylene followed by reduction of the intermediate nitroindole **481**. When this procedure was applied to 5-benzyloxyindole, only the disubstituted nitroethylene product **483** could be obtained.[289] Noland's direct nitroethylation procedure[290] obviates the use of the indole Grignard derivative, and has supplanted this route to alkoxytryptamines (see Section V.B.6).



480

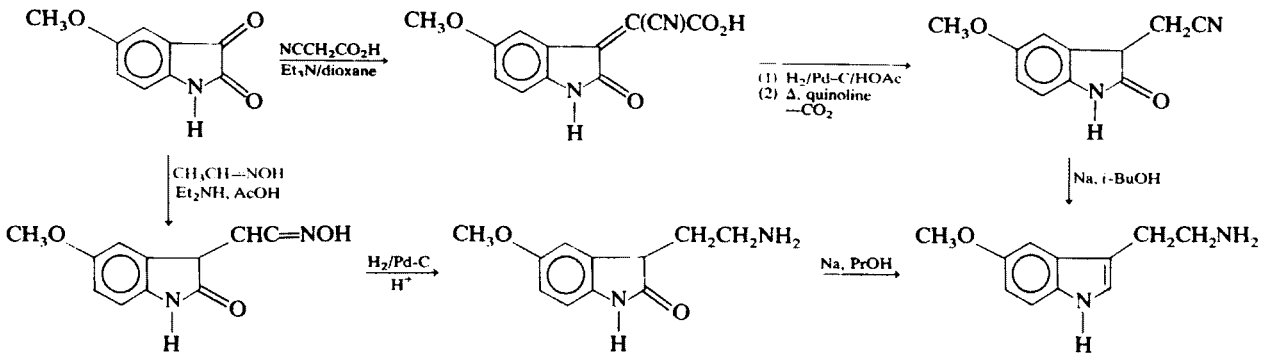
481; R = NO_2
482; R = NH_2



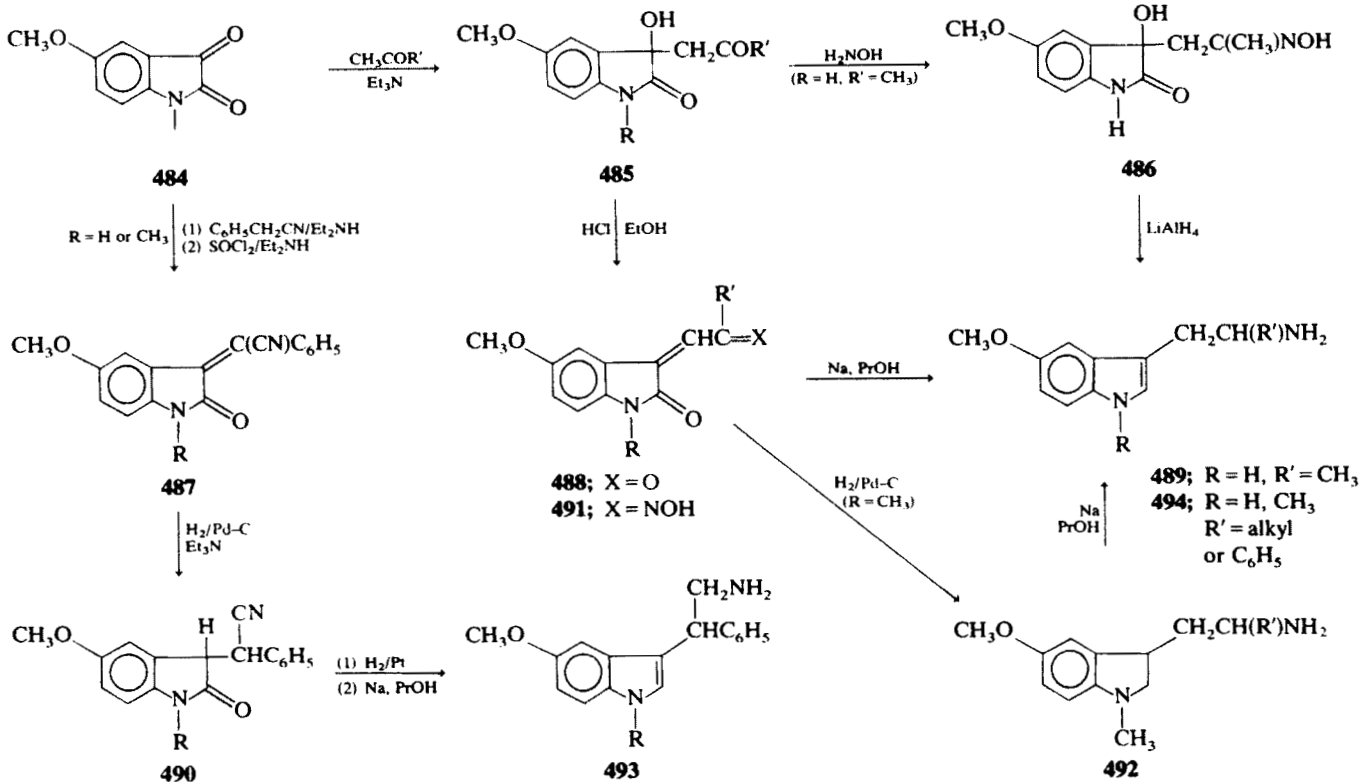
483

5. *Alkoxytryptamines from Isatin or Indoxyl Derivatives*

Pietra and Tacconi have each devised a synthesis of 5-methoxytryptamine utilizing 5-methoxyisatin as a starting material. Pietra's synthesis[291] employed amine-catalyzed condensation with cyanoacetic acid, decarboxylation, and two reduction steps as outlined in


CH3O
O
O
N
H
NCCH2CO2H
Et3N/dioxane
C(CN)CO2H
(1) H2/Pd–C/HOAc
(2) Δ, quinoline
–CO2
CH2CN
CH3CH=NOH
Et2NH, AcOH
Na, t-BuOH
CHC=NOH
H2/Pd-C
H+
CH2CH2NH2
Na, PrOH

Scheme 43


CH3O
O
O
N
484
CH2COR'
Et3N
OH
CH2COR'
485
H2NOH
(R = H, R' = CH3)
CH2C(CH3)NOH
486
R = H or CH3
(1) C6H5CH2CN/Et2NH
(2) SOCl2/Et2NH
HCl
EtOH
LiAlH4
C(CN)C6H5
487
R'
CHC=X
488; X = O
491; X = NOH
Na, PrOH
CH2CH(R')NH2
489; R = H, R' = CH3
494; R = H, CH3
R' = alkyl
or C6H5
Na
PrOH
H2/Pd-C
Et3N
H2/Pd-C
(R = CH3)
CN
H
CHC6H5
490
(1) H2/Pt
(2) Na, PrOH
CH2NH2
CHC6H5
493
CH3
492

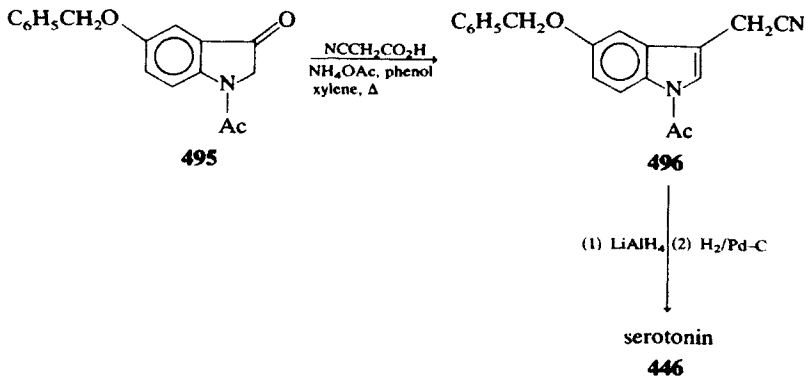
Scheme 44

Scheme 43. Tacconi's synthesis featured a condensation with acetaldehyde oxime and subsequent reduction steps.[292]

Since Asero and co-workers[293] had effected the demethylation of 5-methoxytryptamine with aluminum chloride in boiling benzene, the above and any other synthesis of 5-methoxytryptamine (see Section V.C.2) can be considered equivalent to a serotonin synthesis.

Using 5-methoxyisatin[295,296] or 1-methyl-5-methoxyisatin[296,297] (**484**) and amine catalyzed condensations with various methyl ketones[295,297] or phenylacetonitrile,[296] Pietra and Tacconi, in collaboration, have synthesized a number of 5-methoxytryptamine derivatives including the α-methyl, α-phenyl, and β-phenyl derivatives (**493**, **494**, Scheme 44). The α,β-unsaturated ketones **488** were converted to oximes **491** and reduced to the tryptamine, **494**, in either one step (R = H) or two steps ($R = CH_3$). Franklin and White reported[298a,b] that the dioxindole oxime **486** could be reduced directly to the indole with lithium aluminum hydride in refluxing THF or with a mixture of $NaBH_4$ and $AlCl_3$ in diglyme.

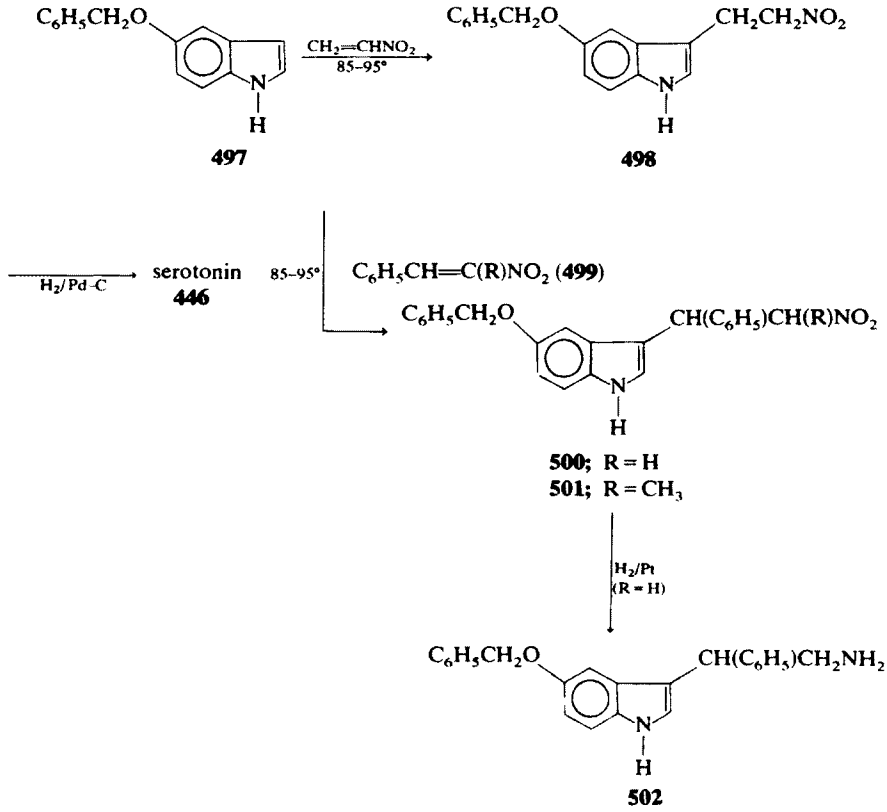
In a related condensation, Nenitzescu and Raileanu have described[299] the reaction of 1-acetyl-5-benzyloxyindoxyl (**495**) with cyanoacetic acid to give the indole-3-acetonitrile derivative **496**. This was converted to serotonin by a two-step reduction.



6. *Miscellaneous*

Noland and Hovden[290] have devised a novel serotonin synthesis based upon the reaction of nitroethylene with molten 5-benzyloxyindole (Scheme 45). The resulting 5-benzyloxy-3-(2-nitroethyl) indole (**498**), produced in 45% yield, was reduced with hydrogen and a platinum catalyst to 5-benzyloxytryptamine or, using a palladium catalyst, directly

to serotonin, in an impressive 31% overall yield. These authors also described the reaction of 5-benzyloxyindole with the β-nitrostyrenes, **499**, to give the nitroethylindoles **500** and **501** in yields of 72 and 37%, respectively. Kondo and co-workers have described[300] the reduction of the β-nitrostyrene adducts from 5- and 6-benzyloxyindole to give 5- (**502**) and 6-benzyloxy-β-phenyltryptamine.



Scheme 45

Although the nitroethylation of 5,6-dibenzyloxyindole proceeded normally, Acheson and Hands have reported[289] their failure to reduce the adduct to a tryptamine derivative by hydrogenation with either Raney nickel or palladium catalysts.

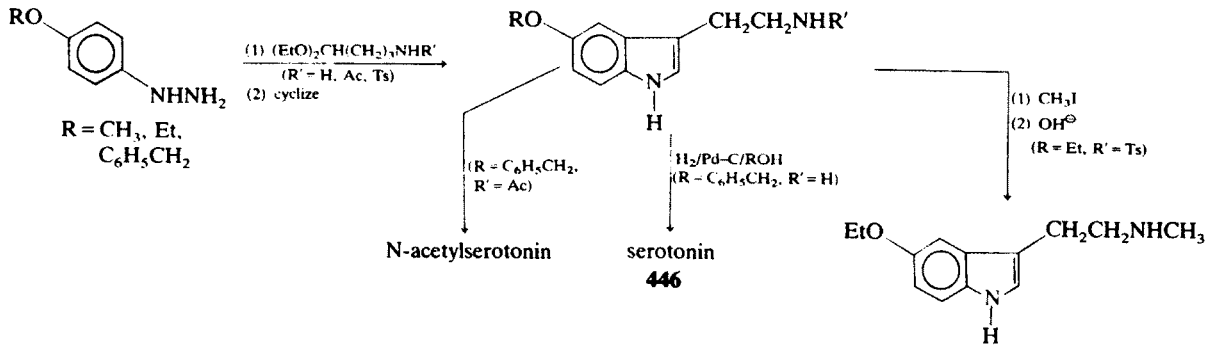
C. Alkoxy- or Hydroxytryptamines from Non-Indolic Precursors

This synthetic concept, obviously desirable because of its simplicity, was used in many of the early syntheses of methoxy- and ethoxytryptamines. In some instances good yields were obtained, although modest yields were generally the case. With the development of such refinements as the Abramovitch–Shapiro and Grandberg schemes, and the replacement of the traditional zinc chloride catalysts by homogeneous catalyst systems such as the dilute acetic acid system used by Keglevic and co-workers,[34] the Fischer cyclization has enjoyed a resurgence in popularity as a method for the synthesis of alkoxytryptamines. Several practical syntheses of serotonin utilize these modifications.

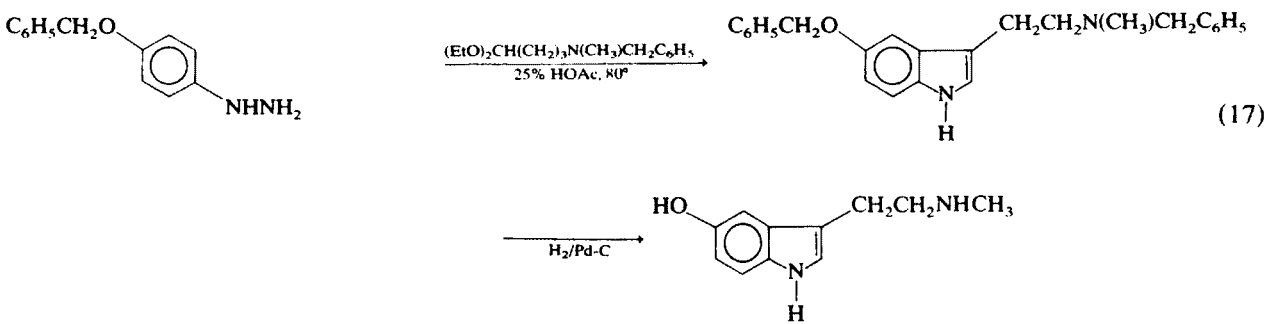
1. *Fischer Cyclization of Alkoxyphenylhydrazones*

a. FROM ALDEHYDES. Alkoxyphenylhydrazones of γ-aminobutyraldehyde on Fischer cyclization afford alkoxytryptamines directly. Späth and Lederer cyclized such *o*- and *p*-methoxyphenylhydrazones with $ZnCl_2$ and obtained 7- and 5-methoxytryptamine, respectively[301] (Scheme 46). Under similar conditions, the *m*-methoxy isomer afforded a mixture of 4- and 6-methoxytryptamine.[302] Hoshino and co-workers employed this reaction in their preparation of 5-methoxy- and 5-ethoxytryptamine.[303] Hoshino and Kobayashi synthesized the N^{ω}-tosyl derivative of 5-ethoxytryptamine[304] by cyclizing the phenylhydrazone from *p*-ethoxyphenylhydrazine and *N*-tosly-γ-aminobutyraldehyde diethyl acetal. This was then methylated and detosylated to give N^{ω}-methyl-5-ethoxytryptamine. Bernini has described[305] the synthesis of 5-benzyloxytryptamine in 45% yield on cyclization of the *p*-benzyloxybenzylhydrazone of γ-aminobutyraldehyde with zinc chloride in hot xylene. Hydrogenolysis afforded serotonin in 36% overall yield. Desaty and co-workers have reported[306] the synthesis of *N*-acetylserotonin in 41% overall yield by a similar pathway (Scheme 46), employing 25% aqueous acetic acid at 80° in the cyclization step.

Keglevic's group has also reported[34] the synthesis in good yield of 5-methoxytryptamine, melatonin, and 5-benzyloxytryptamine by cyclizing the *p*-methoxy-or *p*-benzyloxyphenylhydrazones of either γ-aminobutyraldehyde or its *N*-acetyl derivative in 25% acetic acid. For some reason the *m*-benzyloxyphenylhydrazone of γ-aminobutyraldehyde fails to cyclize. Using the same catalyst system and a series of *p*-alkoxyphenylhydrazones of *N,N*-dialkyl-γ-aminobutyraldehydes, they obtained


RO
NHNH2
R = CH3, Et, C6H5CH2
(1) (EtO)2CH(CH2)3NHR'
(R' = H, Ac, Ts)
(2) cyclize
RO
CH2CH2NHR'
N
H
(R = C6H5CH2, R' = Ac)
H2/Pd-C/ROH
(R = C6H5CH2, R' = H)
N-acetylserotonin
serotonin
446
(1) CH3I
(2) OH⊖
(R = Et, R' = Ts)
EtO
CH2CH2NHCH3
N
H

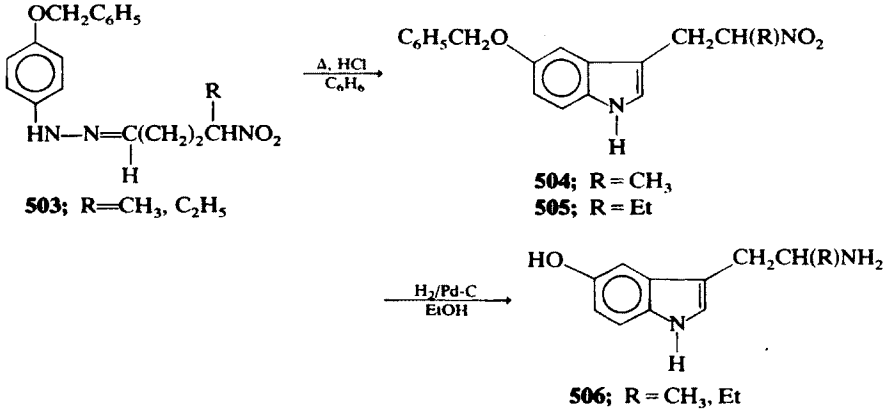
Scheme 46


C6H5CH2O
NHNH2
(EtO)2CH(CH2)3N(CH3)CH2C6H5
25% HOAc, 80°
C6H5CH2O
CH2CH2N(CH3)CH2C6H5
N
H
H2/Pd-C
HO
CH2CH2NHCH3
N
H

(17)

generally good yields (50–80%) of 5-alkoxy-*N*,*N*-dialkyltryptamines.[307] *N*-Methylserotonin was obtained as shown in eq. 17. The synthesis of 1-*p*-chloro- or 1-*p*-methylbenzoyl-5-methoxy-*N*,*N*-diethyltryptamine from the hydrochlorides of the hydrazines and γ-diethylaminobutyraldehyde in ethanol has recently appeared.[500]

In a related Fischer synthesis, α-methyl- and α-ethylserotonin, **506**, resulted on reduction of the nitroindole derivatives **504** and **505**, obtained by cyclization of the *p*-benzyloxyphenylhydrazones of 3-nitropentanal and 3-nitrohexanal (**503**), respectively.[308]



503; R=CH_3, C_2H_5

504; R = CH_3

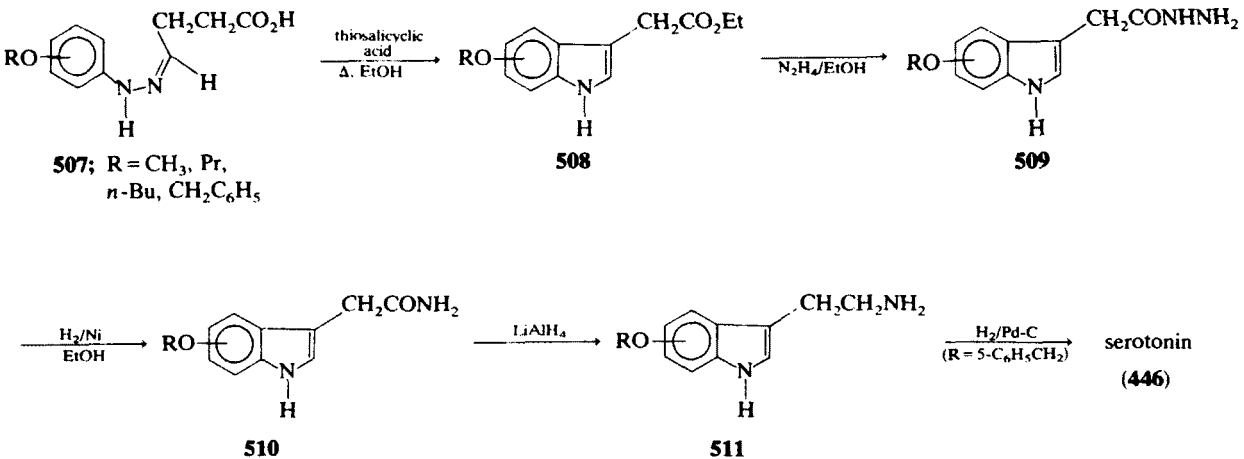
505; R = Et

506; R = CH_3, Et

Shaw has condensed[65a,b] succinaldehydic acid with *as*-methyl- or *as*-benzyl-*p*-methoxyphenylhydrazine in ethanolic hydrochloric acid to give 1-methyl- and 1-benzyl-5-methoxyindole-3-acetic acid in 71 and 51% yield after saponification. These acids could be converted into the corresponding amides and reduced to tryptamines as described in the following section.

Suvorov and Murasheva have also described a Fischer cyclization of the *o*- and *p*-alkoxyphenylhydrazones of succinaldehydic acid (**507**), using, in this case, thiosalicylic acid in ethanol as the catalyst (Scheme 47). The resulting ethyl esters, **508**, were converted into the hydrazides (**509**) with hydrazine in alcohol, thence to indoleacetamides (**510**) by Raney nickel reduction and finally to the tryptamines, **511**, using lithium aluminum hydride. 5-Ethoxy-, 5-propoxy-, and 5-butyloxytryptamine as well as 7-methoxytryptamine were synthesized in this manner.[309,310] 5-Benzyloxytryptamine prepared by this route, on catalytic debenzylation, gave serotonin in an overall yield of 14%.

b. From Ketones. Fischer cyclization of alkoxyphenylhydrazones of



507; R = CH_3, Pr, *n*-Bu, $CH_2C_6H_5$

508

509

510

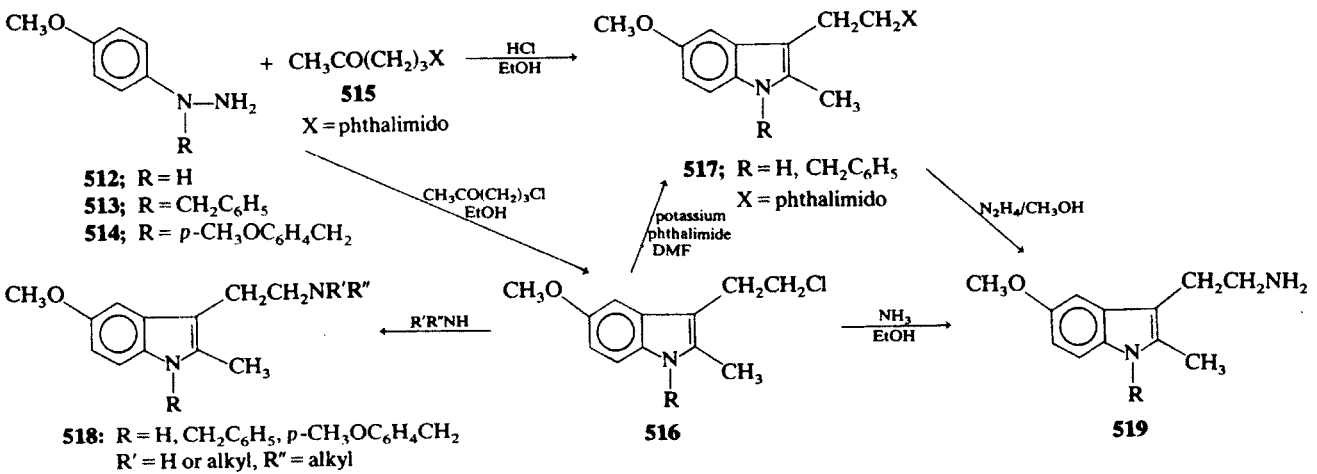
511

Scheme 47

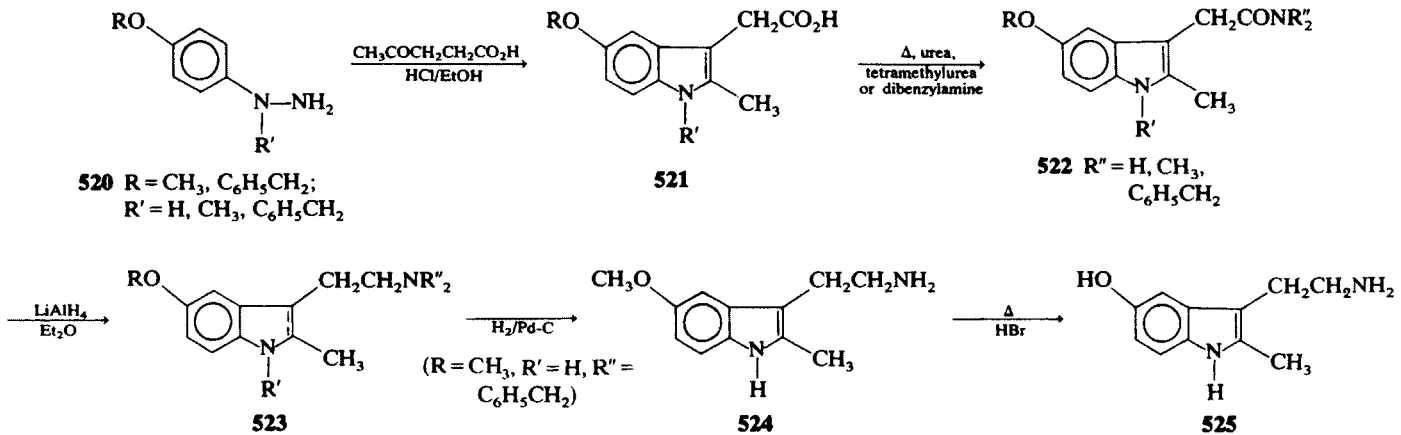
5-substituted pentan-2-ones has led to a number of 2-methyl-alkoxytryptamines (Scheme 48). In 1930, Eisleb reported that 2-methyl-5-butyloxy-*N*,*N*-diethyltryptamine results on cyclization of the *p*-butyloxyphenylhydrazone of *N*,*N*-diethyl-5-aminopentan-2-one.[311] Sletzinger and co-workers cyclized the phenylhydrazone from *N*-benzyl-*N*-*p*-methoxyphenylhydrazine (**513**) and 5-phthalimidopentan-2-one (**515**) and obtained the *N*-phthalimidotryptamine **517** (R = C_7H_7), which could be converted to the antiserotonin compound **519** (R = C_7H_7) (BAS) of Woolley and Shaw using hydrazine in methanol.[312a,b] Phenylhydrazone **514** afforded the *p*-methoxy analogue. When the *p*-methoxyphenylhydrazone **512** was employed, subsequent alkylation of the indole nitrogen of **517** (R = H) with benzyl chloride derivatives permitted the synthesis of a number of other serotonin antagonists.[312b] Another route to these compounds was devised using phenylhydrazones of 5-chloropentan-2-one and subsequent reaction of the chloroethylindole derivatives **516** with ammonia or amines.[312a-d] A reaction of **516** with potassium phthalimide followed by hydrazinolysis provided another route to BAS.[312c] *N*-ethyl-α-methyl BAS resulted when the phenylhydrazone from **512** and 5-chlorohexan-2-one was cyclized and then reacted with ethylamine.[312c,d] When *p*-benzyloxyphenylhydrazones were employed in these sequences, 5-hydroxytryptamines could be obtained by hydrogenolysis of the intermediate 5-benzyloxytryptamines.[312c]

2-Phenyl-substituted 5-methoxytryptamines have been synthesized in good yield (ca. 65%) by Julia and co-workers,[313] who cyclized the *p*-methoxyphenylhydrazone of γ-chlorobutyrophenone with polyphosphoric acid, then reacted the resulting chloroethyl indole with ammonia or dimethyl- or diethylamine. Demethylation with HBr afforded the corresponding 5-hydroxytryptamine.

Shaw has described[65a,b] the cyclization of the *p*-methoxy- and *p*-benzyloxyphenylhydrazones of methyl levulinate to give, after saponification, 2-methyl-5-methoxy- and 2-methyl-5-benzyloxyindole-3-acetic acid (**521**, R′ = H) in 70 and 84% yield (Scheme 49). With *N*-methyl- or *N*-benzyl-*N*-*p*-alkoxyphenylhydrazines, good yields of the 1-methyl or 1-benzyl derivatives of these acids could be obtained. Fusion of the acids with urea at 190° furnished the acetamide derivatives in 50–60% yield and a subsequent hydride reduction provided the tryptamines, which are potent antiserotonin drugs. The use of tetramethylurea in the above sequence permitted the preparation of *N*,*N*-dimethyltryptamine derivatives, although the yield was lower because of some decarboxylation. The fusion of the dibenzylamine salt of **521** (R = CH_3, R′ = H) at 220° gave the *N*,*N*-dibenzylacetamide derivative, **522**, which could be reduced with lithium aluminum hydride to the tryptamine, **523**, then debenzylated to


CH3O
N—NH2
R
+ CH3CO(CH2)3X
515
X = phthalimido
HCl
EtOH
CH3O
CH2CH2X
N
CH3
R
512; R = H
513; R = CH2C6H5
514; R = p-CH3OC6H4CH2
517; R = H, CH2C6H5
X = phthalimido
CH3CO(CH2)3Cl
EtOH
potassium
phthalimide
DMF
N2H4/CH3OH
CH3O
CH2CH2NR'R"
N
CH3
R
R'R"NH
CH3O
CH2CH2Cl
N
CH3
R
NH3
EtOH
CH3O
CH2CH2NH2
N
CH3
R
518: R = H, CH2C6H5, p-CH3OC6H4CH2
R' = H or alkyl, R" = alkyl
516
519

Scheme 48



520 $R = CH_3, C_6H_5CH_2$; $R' = H, CH_3, C_6H_5CH_2$

521

522 $R'' = H, CH_3, C_6H_5CH_2$

523

($R = CH_3$, $R' = H$, $R'' = C_6H_5CH_2$)

524

525

Scheme 49

2-methyl-5-methoxytryptamine (**524**). This could be demethylated to 2-methylserotonin (**525**) in 74% yield with HBr, although a similar attempt to demethylate 1-methyl-5-methoxytryptamine gave only an 8% yield of 1-methylserotonin.

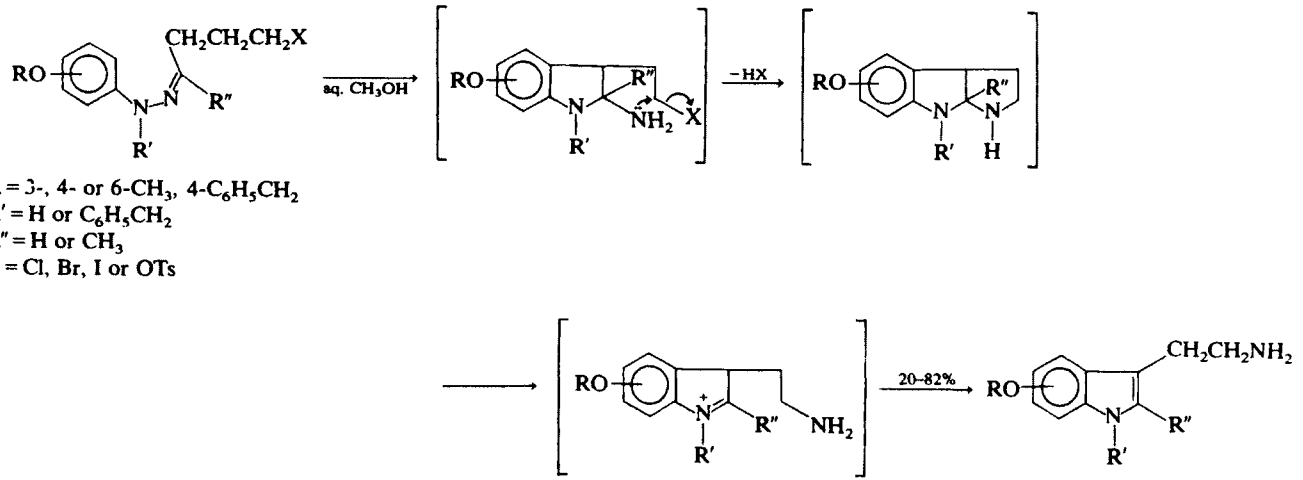
Grandberg and co-workers have introduced[314a–e] an important variation of the Fischer cyclization which allows the direct synthesis of tryptamines, including derivatives alkylated at the 1- and 2-positions, by cyclizing 5-halo- or 5-tosyloxypentan-2-one alkoxyphenylhydrazones in 50% aqueous methanol (Scheme 50). Yields ranged from 20 to 80% for the tryptamines shown. The reaction has also been applied to γ-chlorobutyraldehyde *p*-methoxyphenylhydrazone and its *N*-benzyl derivative, where 5-methoxytryptamine and its 1-benzyl derivative result in 45 and 70% yield.[314a,c] The reaction may proceed via pyrrolo(2,3-*b*)indole intermediates as shown.

c. From α-Acyl Esters and Alkoxybenzenediazonium Salts. Two groups have reported serotonin syntheses based on the reaction of *p*-benzyloxybenzenediazonium chloride (**526**) and active methylene compounds (Scheme 51). Justoni and Pessina used 2-carbethoxycyclopentanone (**527**) to produce the *p*-benzyloxyphenylhydrazone of α-oxoadipic acid. On cyclization, the dicarboxylic acid, **528**, resulted. This was transformed to 5-benzyloxytryptamine and thence serotonin by a lengthy pathway featuring a Curtius rearrangement.[315a–d]

Wragg and co-workers have reported[316a,b] a simpler route to serotonin which also exploits the Japp–Klingemann reaction (Scheme 52). Using **526** and ethyl α-acetyl-ε-phthalimidovalerate (**529**), they obtained serotonin by the route shown. Excellent yields are obtained in each step and the procedure is claimed to be suitable for large-scale operations. Similar procedures afforded 6-benzyloxytryptamine, 6-hydroxytryptamine, and 4,5,6-trimethoxytryptamine.[316b]

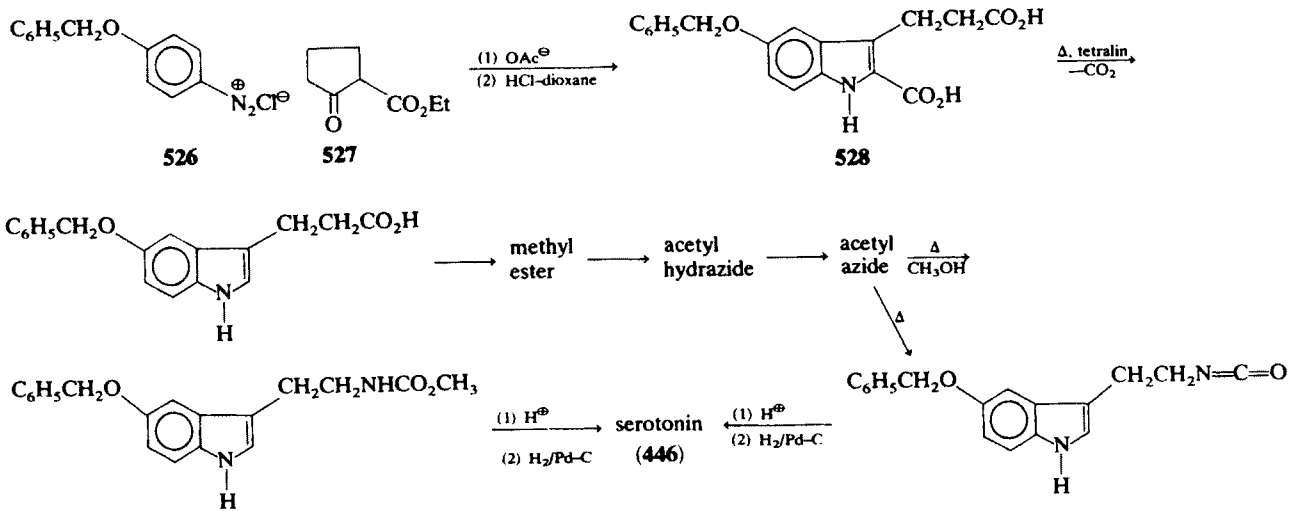
2. *Abramovitch–Shapiro Reaction*

In 1955, Abramovitch and Shapiro described[294a] a variation on the Japp–Klingemann reaction which permits a more direct and practical route to alkoxytryptamines than the procedures above. They coupled *p*-methoxybenzenediazonium chloride (**530**) with 2-piperidone-3-carboxylic acid (**531**), then rearranged the resulting phenylhydrazone **532** with 70% formic acid to the 1-oxo-tetrahydro-β-carboline derivative **533** (Scheme 53). Alkaline hydrolysis to the tryptamine-2-carboxylic acid, **534**, and a final decarboxylation afforded 5-methoxytryptamine[294a,b] (**535**). Although they were unable to obtain 5-benzyloxytryptamine by this route, Suvorov

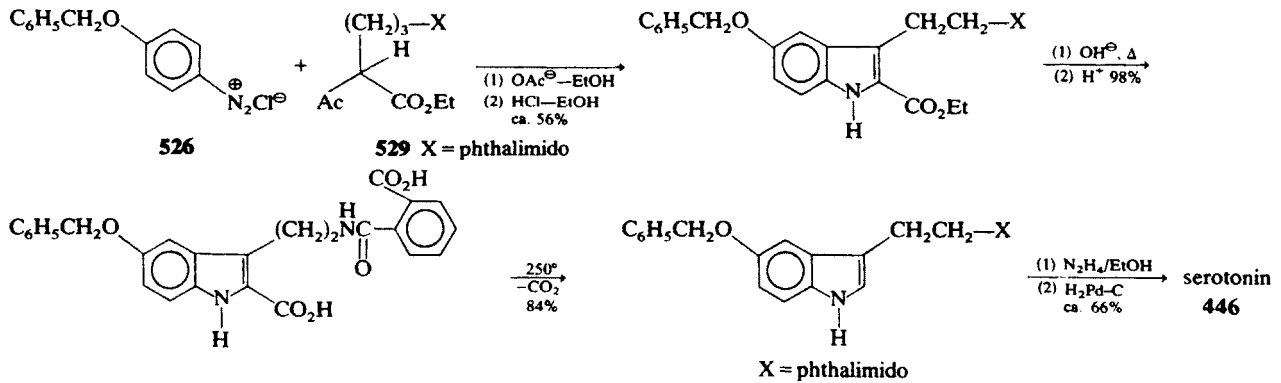


R = 3-, 4- or 6-CH_3, 4-$C_6H_5CH_2$
R′ = H or $C_6H_5CH_2$
R″ = H or CH_3
X = Cl, Br, I or OTs

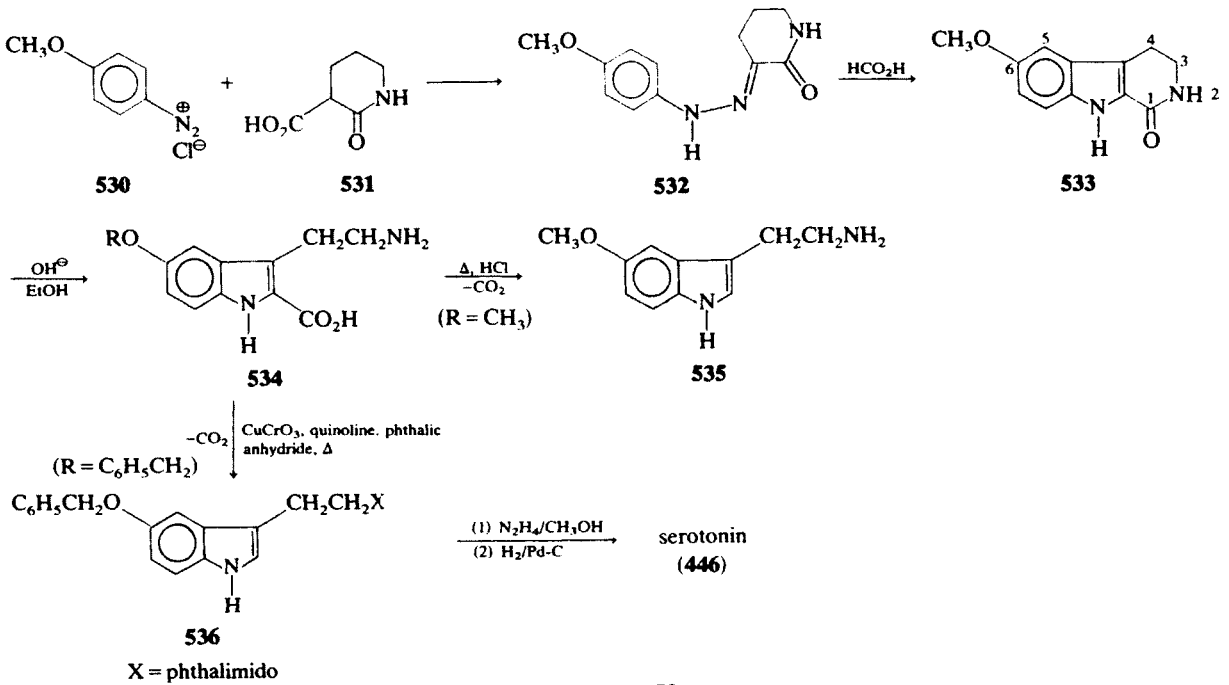
Scheme 50


C6H5CH2O
N2Cl⊖
CO2Et
O
526
527
(1) OAc⊖
(2) HCl-dioxane
CH2CH2CO2H
CO2H
528
Δ, tetralin
−CO2
methyl ester
acetyl hydrazide
acetyl azide
Δ
CH3OH
CH2CH2NHCO2CH3
(1) H⊕
(2) H2/Pd-C
serotonin (446)
CH2CH2N=C=O

Scheme 51


C6H5CH2O
N2Cl⊖
(CH2)3—X
H
Ac
CO2Et
(1) OAc⊖—EtOH
(2) HCl—EtOH
ca. 56%
CH2CH2—X
(1) OH⊖, Δ
(2) H+ 98%
CO2Et
526
529 X = phthalimido
CO2H
(CH2)2NC
250°
−CO2
84%
(1) N2H4/EtOH
(2) H2Pd–C
ca. 66%
serotonin
446
X = phthalimido

Scheme 52


CH3O
N2 Cl⊖
HO2C
NH
O
530
531
532
HCO2H
533
OH⊖ EtOH
RO
CH2CH2NH2
CO2H
534
Δ, HCl −CO2
(R = CH3)
535
−CO2
CuCrO3, quinoline, phthalic anhydride, Δ
(R = C6H5CH2)
C6H5CH2O
CH2CH2X
536
X = phthalimido
(1) N2H4/CH3OH
(2) H2/Pd-C
serotonin
(446)

Scheme 53

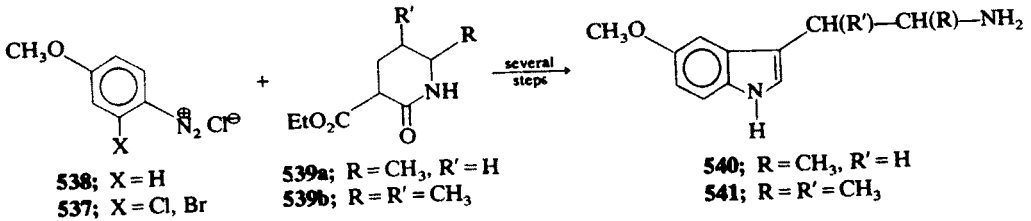
and co-workers did succeed, apparently by virtue of a modified decarboxylation procedure. They employed copper chromite in quinoline containing added phthalic anhydride to form, *in situ*, the *N*-phthaloyl derivative of 5-benzyloxytryptamine, **536**. Removal of the phthaloyl protecting group with hydrazine and catalytic debenzylation made serotonin accessible by the Abramovitch–Shapiro route. In general, however, the procedure has been applied to the synthesis of methoxy- or ethoxytryptamines.

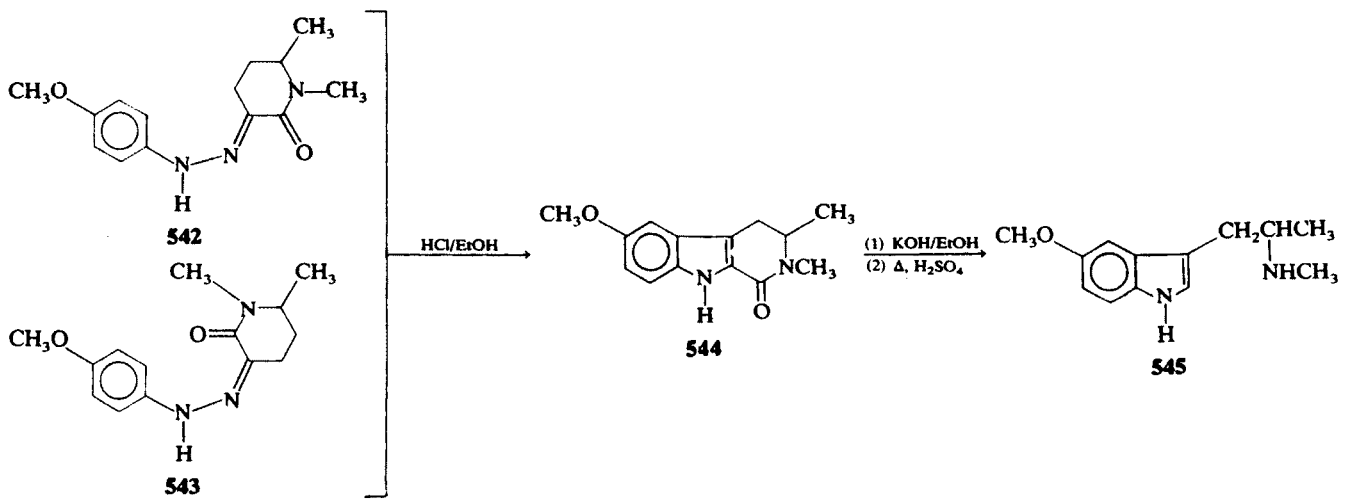
Abramovitch reported the synthesis of 6-methoxytryptamine in poor yield from *m*-methoxybenzenediazonium chloride.[318] When the Fischer cyclization was conducted with the usual 70% formic acid, a mixture of the 5- and 7-methoxy-β-carbolines resulted, whereas the use of ethanolic hydrogen chloride gave only the 7-methoxy compound, but in poor yield. Other catalyst systems employed in the cyclization step are 70% acetic acid,[319] 85% formic acid,[329] and HCl in alcohols[229,321a–e] or in acetic acid.[86] 5–10% hydrochloric acid is usually employed in the decarboxylation step.

Chloromethoxybenzenediazonium chlorides have been employed in the Abramovitch–Shapiro procedure to prepare the following chloromethoxytryptamines: 4-chloro-7-methoxytryptamine,[321a–e] 6-chloro-7-methoxytryptamine,[321a,c–f] 6-methoxy-7-chlorotryptamine,[321a,c,e,f] 5-methoxy-7-chlorotryptamine,[322] and 5-chloro-6-methoxytryptamine.[312a,c] Suvorov's group utilized the halogen atom in 2-chloro- or 2-bromo-5-methoxybenzenediazonium chloride (**537**) as a blocking group in their synthesis of 4-methoxytryptamine.[86,501] After cyclization of the 2-oxopiperidone hydrazone to the β-carboline with HCl in acetic acid, they removed the bromine atom using a Raney nickel reduction in ethanol[86]; dechlorination was effected with Pd/C in aqueous hydrazine.[501] Alkaline hydrolysis and decarboxylation with 7% hydrochloric acid gave the tryptamine.

The following alkoxytryptamines have been synthesized using the original Abramovitch–Shapiro procedure: 5-methoxy-7-methyltryptamine,[324] 4,5,6-trimethoxytryptamine,[321c,e,325a,b] 5-methoxytryptamine,[73a–c] and 5-ethoxytryptamine.[73a–c]

Side-chain-substituted tryptamines result when alkyl-substituted 2-oxopiperidine-3-carboxylic acids are employed in the Abramovitch–Shapiro tryptamine synthesis. Two groups have reported the synthesis of 5-methoxy-α-methyltryptamine (**540**) from **538** and 3-carbethoxy-6-methyl-2-piperidone (**539a**).[319,326] Mkhitaryan and co-workers have described[320] the preparation of 5-methoxy-α,β-dimethyltryptamine (**541**) starting with the appropriate dimethylpiperidone (**539b**). Good yields were reported in the individual steps of these syntheses.


CH3O
N2 Cl⊖
X
538; X = H
537; X = Cl, Br
+
R'
R
NH
EtO2C
O
539a; R = CH3, R' = H
539b; R = R' = CH3
several steps
CH3O
CH(R')—CH(R)—NH2
N
H
540; R = CH3, R' = H
541; R = R' = CH3


CH3
CH3O
N—CH3
N
N
O
H
542
CH3
CH3
CH3O
N
O
N
N
H
543
HCl/EtOH
CH3O
CH3
N
NCH3
H
O
544
(1) KOH/EtOH
(2) Δ, H2SO4
CH3O
CH2CHCH3
NHCH3
N
H
545

Heath-Brown and Philpott coupled *p*-methoxybenzenediazonium chloride with 1,6-dimethyl-2-oxo-3-carbethoxypiperidone and obtained a mixture of the two isomeric phenylhydrazones **542** and **543**. These were cyclized to the same 1-oxo-β-carboline, **544**, the lactam ring hydrolyzed with ethanolic potassium hydroxide, and the resulting *N*-methyltryptamine-2-carboxylic acid decarboxylated with 4.5–5.0 *N* sulfuric acid to give α,*N*-dimethyl-5-methoxytryptamine (**545**) in overall yields of 22–37%. When more concentrated sulfuric acid was employed in the decarboxylation, some *O*-demethylation resulted.[229].

It has been reported that the Abramovitch–Shapiro procedure failed in an attempted synthesis of 4,6-dimethoxytryptamine.[349]

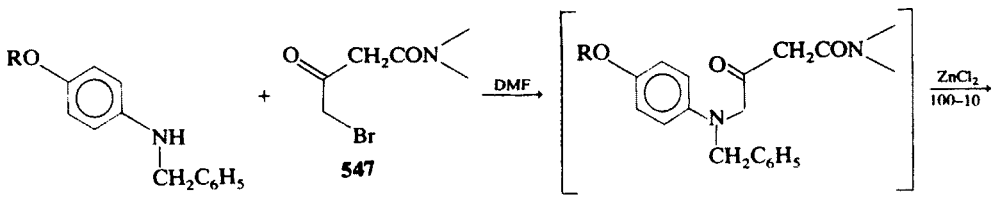
3. *Bischler Synthesis*

Julia and his co-workers have successfully applied this reaction to a large number of alkoxytryptamine syntheses. One route employed the reaction between the *N*-benzyl-*p*-hydroxyaniline derivatives **546** and secondary or tertiary 4-bromoacetoacetamides, **547**, to produce the alkoxyindole-3-acetamides **548**, which could be reduced to tryptamines, **549**, with lithium aluminum hydride (Scheme 54). 1-Benzyl-5-benzyloxy-*N*-phenyltryptamine and 1-benzyl-5-methoxy-*N*,*N*-diethyltryptamine were prepared in this manner.[327]

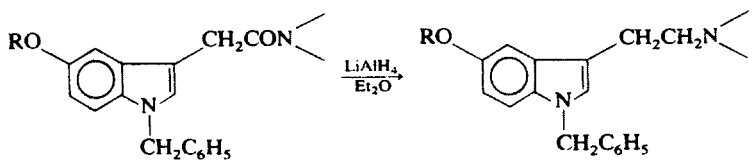
Another procedure employed ethyl 4-bromoacetoacetate and various *N*-aryl mono- and dihydroxylated aniline derivatives to yield ethyl esters of either 1-aryl-5-methoxyindole-3-acetic acid or 1-aryl-5,6-dimethoxyindole-3-acetic acids (Scheme 55). These could be reduced to tryptophols, converted to the corresponding bromides, and treated with amines to produce the desired tryptamines. Alternatively, the esters could be hydrolyzed to acids and converted to amides by heating with urea or by reaction with ethyl chloroformate followed by ammonia or amines. Some amides were also prepared by ammonolysis of the esters with ammonia-saturated methanol in a sealed tube.[328,329]

Julia and Manoury have described[62] the synthesis of 5-methoxytryptamine from *N*-benzyl-*p*-anisole and ethyl 4-bromoacetoacetate (using the ethyl chloroformate procedure and a final debenzylation with sodium in ammonia.

The above procedure was applied[349] successfully to the synthesis of 4,6-dimethoxy-*N*,*N*-dimethyltryptamine by Brown and co-workers. 3,5-Dimethoxy-*N*-benzylaniline was reacted with ethyl 4-bromoacetoacetate and the resulting 4,6-dimethoxyindole-3-acetic acid ester debenzylated with sodium in ammonia, then converted into the amide, and finally

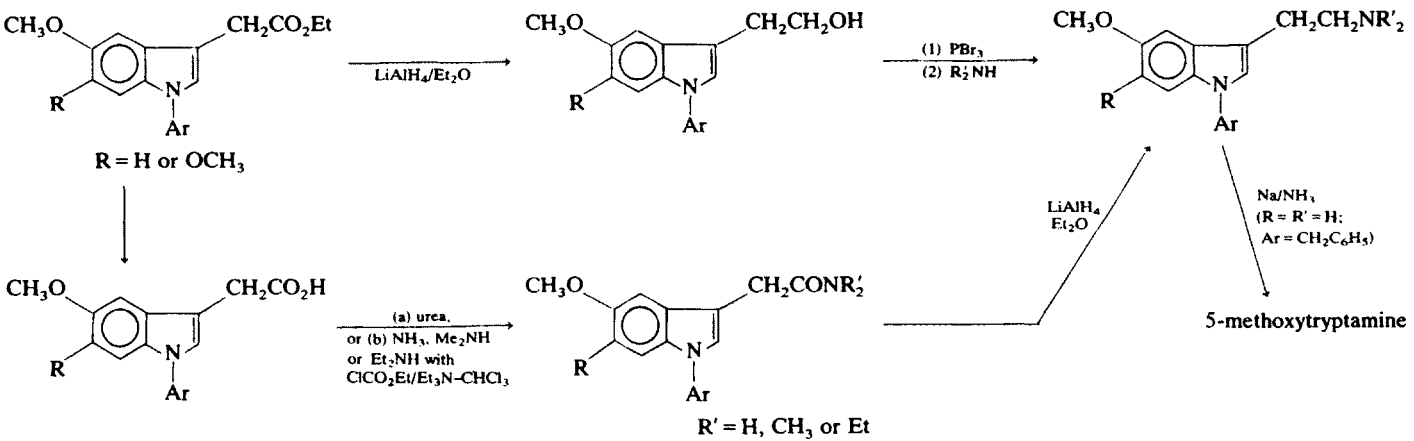


546 $R = CH_3$ or $C_6H_5CH_2$



548 **549**

Scheme 54

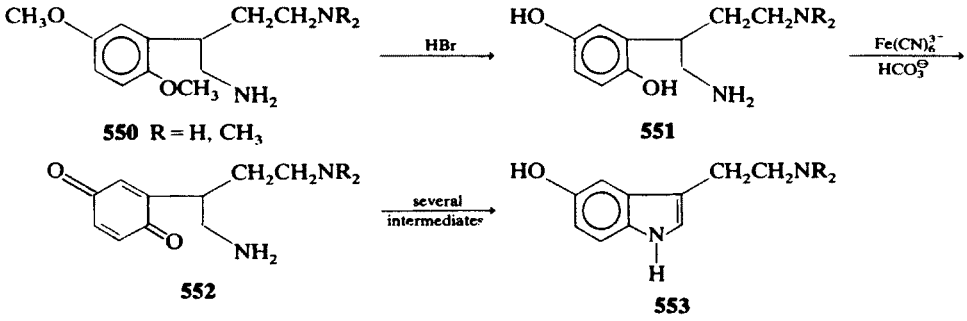

CH3O
CH2CO2Et
R
N
Ar
R = H or OCH3
LiAlH4/Et2O
CH2CH2OH
(1) PBr3
(2) R'2NH
CH2CH2NR'2
LiAlH4
Et2O
Na/NH3
(R = R' = H;
Ar = CH2C6H5)
5-methoxytryptamine
CH2CO2H
(a) urea,
or (b) NH3, Me2NH
or Et2NH with
ClCO2Et/Et3N–CHCl3
CH2CONR'2
R' = H, CH3 or Et

Scheme 55

reduced to the tryptamine with diborane. Three conventional tryptamine syntheses—the gramine, oxalyl chloride, and aldehyde–nitromethane routes—failed when applied to 4,6-dimethoxyindole.[349]

4. *Miscellaneous Syntheses*

A variation on the Nenitzescu synthesis provided Harley-Mason and Jackson with a novel synthesis of bufotenine (**553**; R = CH_3) and serotonin (**553**; R = H) (Scheme 56). Their procedure employed ferricyanide oxidation of the appropriately substituted hydroquinones **551** to the *p*-benzoquinones **552**. The hydroquinones were obtained by demethylation of the dimethyl ether **550** with HBr. Serotonin resulted in an overall yield of 25% starting with 2,5-dimethoxybenzaldehyde. This procedure afforded 6-hydroxybufotenine in poor yield.

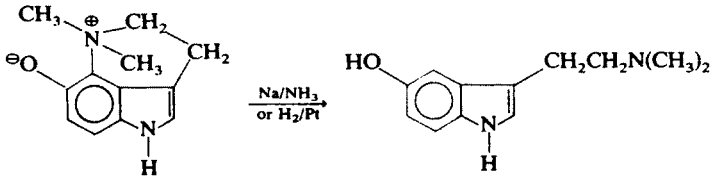


550 R = H, CH_3 **551** **552** **553**

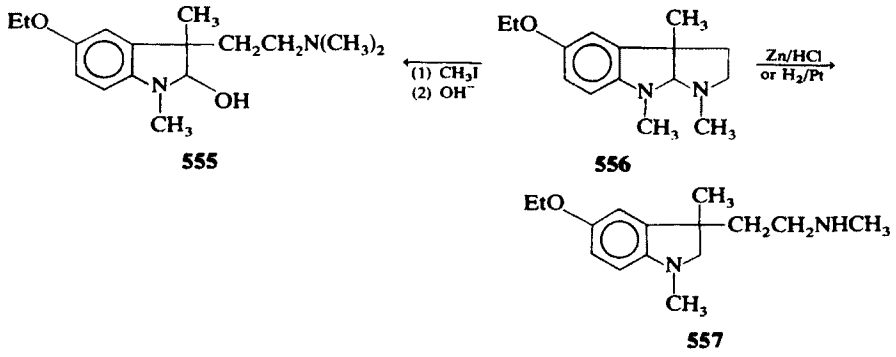
Scheme 56

Bufotenine is produced in nearly quantitative yield by an Emde-type fission (eq. 18) of dehydrobufotenine (**554**), the major indole alkaloid from the parotid glands of the South American toad *Bufo marinus* and found also in the toad *Bufo vulgaris*.[411] The same transformation can be effected by hydrogenation.[410]

Stedman and Barger, in another tricyclic scission reaction, converted[751]

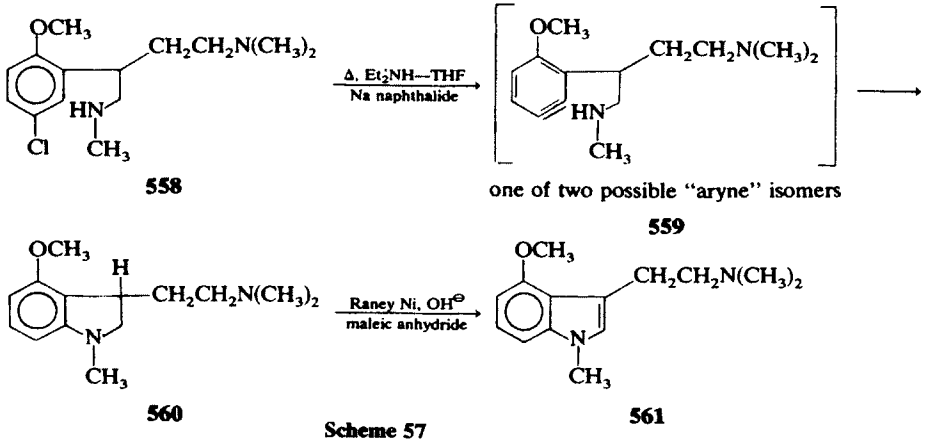


554 (18)



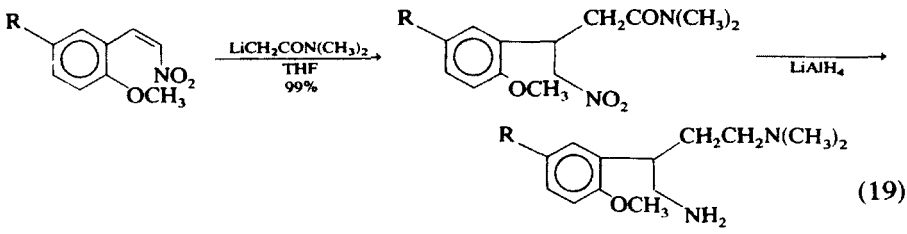
eserethole (**556**) to the 5-ethoxydihydrotryptamine derivative **557** with either zinc dust in HCl or catalytic hydrogenation. The action of hydroxide ion on eserethole methiodide gave the ring-cleaved pseudo-base **555**.

Julia and Gaston-Breton have described[211] a novel synthesis of 1-methyl-4-methoxy-*N*,*N*-dimethyltryptamine (**561**) by ring closure of the *p*-chloroanisole derivative, **558** via the "aryne" intermediate **559** (Scheme 57). The indoline **560**, produced in 31% yield, was dehydrogenated to the indole in 60% yield with Raney nickel.



Scheme 57

Seebach and Leitz have recently reported[502] improved procedures for the preparation of the key intermediates of the Harley-Mason and Julia alkoxytryptamine syntheses. They utilized the addition of lithium *N*,*N*-dimethylacetamide in THF to the appropriate nitrostyrenes. A subsequent lithium aluminum hydride reduction afforded the tryptamine precursor **561a** (eq. 19). Other tertiary acetamide or propionamide derivatives can also be used.



(19)

561a; R = OCH_3 or Cl

D. Hydroxytryptamine Reactions

1. *O-Alkylation or O-Acylation*

Wieland and co-workers have reported the methylation of 6-hydroxytryptamine with methyl iodide and thallium hydroxide,[279] although the use of diazomethane as used to methylate serotonin[256,539] and bufotenine[413a,434] would now seem preferable, in general, for such methylations. Suvorov and co-workers have prepared a number of *O*-acyl derivatives of serotonin as well as its *O*-phosphate by first protecting the side-chain amine function of 5-benzyloxytryptamine with the trityl group, catalytically removing the benzyl group, and acylating the resultant 5-hydroxyl group with a variety of acid chlorides in triethylamine–benzene.[540–542] The sodium salt of *N*-trityl serotonin has been reacted with dibenzylchlorophosphate to produce the corresponding serotonin *O,O*-dibenzylphosphate ester, which can be hydrogenated to the *N*-trityl serotonin *O*-phosphate.[543] Detritylation of the *N*-trityl serotonin carboxylic[540–542] or phosphoric acid[543] esters is accomplished using 50% acetic acid. Woolley has reported[544] the synthesis of a number of 1-benzyl-2-methylserotonin ethers by alkylation of the N^{ω}-phthalimido-blocked serotonin; the protecting group can be removed with hydrazine.

2. *N-Alkylation or N-Acylation*

The indole nitrogen of 5-methoxy- or 5-benzyloxytryptamine and 5-methoxytryptophol has been selectively methylated with methyl tosylate in refluxing xylene containing potassium carbonate.[361] In the case of melatonin, methylation of the side-chain amide nitrogen resulted instead.[361]

A number of procedures have appeared in the literature for the

monoalkylation of the side-chain nitrogen in alkoxytryptamines. *N*-methylation has been accomplished by methylation of the N^{ω}-tosylate, followed by removal of the tosyl group[433] or by lithium aluminum hydride reduction of the *N*-formyl[545] or *N*-ethylcarbamyl[319] groups.

N-Ethyl-5-methoxytryptamine results when melatonin is reduced with lithium aluminum hydride.[61,546] Stauffer noted that when *N*-formyl-5-benzyloxytryptamine was reduced with lithium aluminum hydride, and the reaction worked up by the addition of ethyl acetate, the *N*-methyl-*N*-ethyltryptamine resulted, presumably from hydride reduction of an intermediary $N(CH_3)Ac$ group.[545] *N*-Alkylation of 5-hydroxytryptamines by reduction (Pt/H_2) of Schiff bases resulting from reaction with various methyl, ethyl, propyl, or butyl ketones has been reported.[547] Earlier,[548] Speeter had employed a similar route to *N*-alkyl derivatives of 5-benzyloxytryptamine. Kalberer and co-workers prepared *N*-methyl [^{14}C]-psilocin by methylation of *N*-methyl-*N*-benzyl-4-benzyloxytryptamine with $^{14}CH_3I$, treatment with AgCl, then debenzylation of the methochloride salt by hydrogenolysis (Pd/Al_2O_3).[490]

α-Haloacyl analogues of melatonin have been prepared by acylating 5-methoxytryptamine with various α-halo esters.[549] Melatonin and its N^{ω}-methyl analogue result on acetylation of the methoxytryptamines with phenyl acetate and phenol.[550] *N*-acetylserotonin results when serotonin is *O*,*N*-diacetylated (Ac_2O/Et_3N) and then the *O*-acetyl group selectively hydrolyzed in bicarbonate.[497] The N^{ω}-formylation of 6-methoxytryptamine by solvent DMF has been reported.[223]

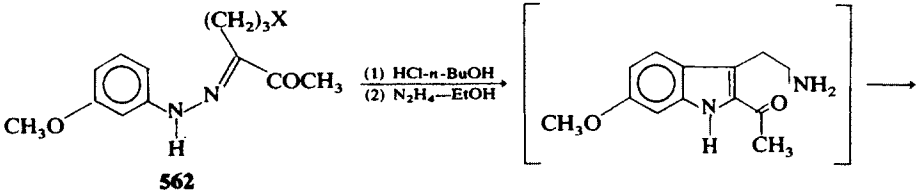
3. *Salt Formation*

Taborsky has reported[551] the purification of 5-methoxytryptamine as salts with indoleacetic acid, octanoic acid, and stearic acid. Joly and Bucourt have described the purification of 5-, 6-, and 7-methoxytryptamine via their *N*-carbonates; the tryptamines are regenerated by decomposing the carbonates in refluxing toluene under nitrogen.[552,878a,b]

4. *Formation of β-Carbolines*

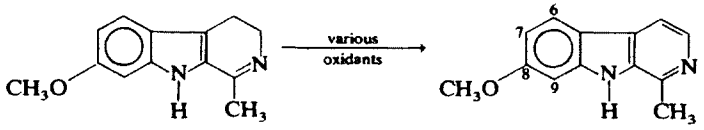
a. Cyclization of *N*-Acetyltryptamines or -tryptophans. Späth and Lederer reported[302] the synthesis of harmaline (**563**) in 78% yield by cyclization (P_2O_5/xylene) of *N*-acetyl-6-methoxytryptamine, a much simpler route to this natural product than the ingenious first synthesis of Robinson and co-workers[553] from the Fischer cyclization of the phenylhydrazone **562**, followed by concomitant hydrazinolysis of the

phthalimido group and a second cyclization. Späth and Lederer also introduced the catalytic dehydrogenation of harmaline with a palladium catalyst at 200°, a much more successful route to harmine (**564**) than the wasteful chromic acid oxidation employed by Robinson's group.[553] Shortly thereafter, Späth and Lederer also reported[301] the synthesis of the harmaline analogues **565** and **566** by cyclization of *N*-acetyl-5- and -7-methoxytryptamines by the same method. The *N*-formyl derivatives of these tryptamines could also be similarly cyclized, although in poor yield; the resulting 7- and 9-methoxy-4,5-dihydro-β-carbolines were dehydrogenated in tetralin, again in poor yields. More recently, the cyclization

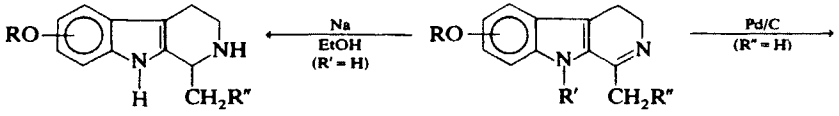


562

X = phthalimido

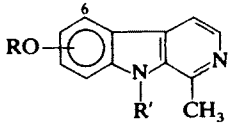


563 harmaline **564** harmine



570; R = 7, 8-CH_3, R" = H
571; R = 7-CH_3, R" = C_6H_5
572; R = 9-CH_3, R" = C_6H_5

565; R = 7-CH_3, R" = H
566; R = 9-CH_3, R" = H
567; R = 7, 8-CH_3, R" = H
568; R = 7-CH_3, R" = C_6H_5
569; R = 9-CH_3, R" = C_6H_5

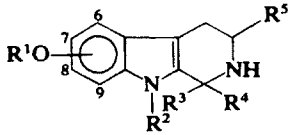


573; R = 6-CH_3, R' = CH_3
574; R = 7-CH_3, R' = CH_3
575; R = 7, 8-CH_3, R' = H
576; R = 9-CH_3, R' = CH_3
577; R = 7-CH_3, R' = H
578; R = 9-CH_3, R' = H

procedure of Späth and Lederer has been applied to the synthesis of 7,8-dimethoxy-4,5-dihydroharmane **567** using 5,6-dimethoxytryptamine[88] and a redundant synthesis of 7-methoxy-4,5-dihydroharmane **565**.[539] The former has been reduced to the tetrahydro-β-carbazole, **570**, and both compounds have been dehydrogenated with a palladium catalyst to the alkoxyharmanes **574** and **575**. Protiva and co-workers have cyclized[554] the *N*-phenylacetyl derivatives of 5- and 7-methoxytryptamines with phosphorus oxychloride in benzene to the 7- and 9-methoxy-dihydroharmanes **568** and **569**, which could be reduced with sodium–alcohol to the tetrahydro-β-carbolines **571** and **572**.

b. Cyclization of Tryptamines or Tryptophans with Aldehydes or Ketones. Methoxytryptophans can be cyclized easily to tetrahydro-β-carboline-4-carboxylic acids **579–584** with aqueous acetaldehyde; these have been converted with potassium dichromate oxidation in acetic acid to methoxyharmane derivatives. 1-Methyl-4-methoxy-,[26,220] 1-methyl-5-methoxy-,[49] 1-methyl-7-methoxy-,[220] 5-methoxy-,[49,70] and 7-methoxytryptophan[70,220] have been converted to methoxyharmanes **573–578**, respectively, following Harvey and Robson's procedure[69] for 6-methoxytryptophan. **573** was shown to be identical to the zinc dust distillation product of mitragynine.[26]

Hester (see Ref. 286, p. 104) has reported the facile cyclization of α-ethyl-6-hydroxytryptamine or 6-hydroxy- or 6-methoxytryptamine in aqueous acetone at pH 4.7 to give the tetrahydro-β-carbolines **585–587**. The reaction fails with 5-methoxytryptamine. An early route to harmine



	R^1	R^2	R^3	R^4	R^5
579	6-CH_3	CH_3	H	CH_3	CO_2H
580	7-CH_3	CH_3	H	CH_3	CO_2H
581	7-CH_3	H	H	CH_3	CO_2H
582	8-CH_3	H	H	CH_3	CO_2H
583	9-CH_3	CH_3	H	CH_3	CO_2H
584	9-CH_3	H	H	CH_3	CO_2H
585	8-CH_3	H	CH_3	CH_3	C_2H_5
586	8-H	H	CH_3	CH_3	H
587	8-CH_3	H	CH_3	CH_3	H
588	8-CH_3	H	H	CH_3	H
589	7-CH_3	H	H	H	H
590	9-CH_3	H	H	H	H

employed the reaction of 6-methoxytryptamine with acetaldehyde in dilute acid at 110° to give a tetrahydroharmine **588** (85%), which could be dehydrogenated to harmine (70%) with palladium on carbon in aqueous sodium hydroxide containing maleic acid.[280]

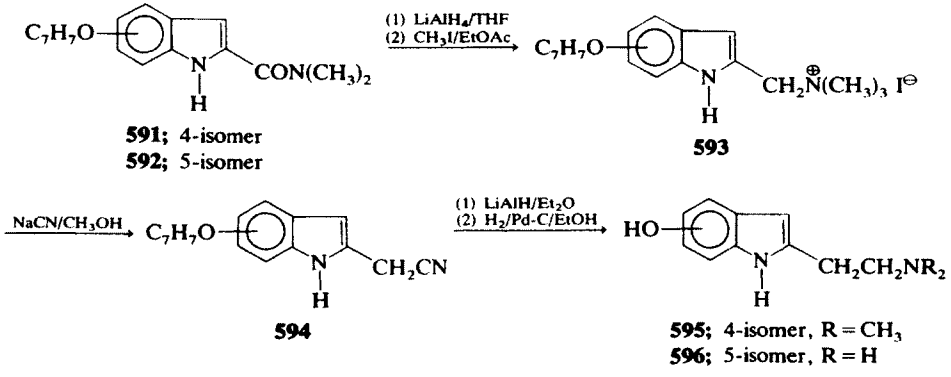
Späth and Lederer have described[301] the preparation of tetrahydro-β-carbolines **589** and **590** from 5- and 7-methoxytryptamines with formaldehyde in sulfuric acid in 24 and 53% yields, respectively.

VI. Other Alkoxyindolealkylamines

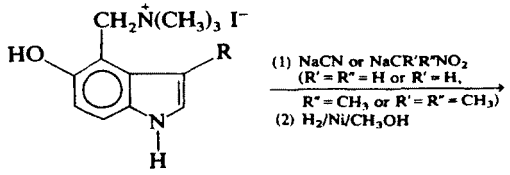
A. Hydroxyisotryptamines

Serotonin analogues with the ethylamine side chain in position 2[389a,b] or 4,[390] a psilocin analogue with the side chain in position 2,[227a] as well as 6-hydroxyindole-7-ethylamine derivatives,[390] have been synthesized from the appropriate isogramines. Schindler prepared the first of the isoserotonins, **596**, from the 5-benzyloxyisogramine methiodide **593**, using the classical cyanide ion displacement—reduction sequence.[389a,b] The methiodide was prepared by lithium aluminum hydride reduction of 5-benzyloxyindole-2-carboxylic acid dimethylamide (**592**) followed by methylation with methyl iodide. The action of diethyl *N*-formylaminomalonate on **593** led to 5-hydroxyisotryptophan.[389a,b] Troxler and co-workers prepared 4-benzyloxyindole-2-acetonitrile **594** following Schindler's procedure and hydrolyzed this to the 2-acetic acid derivative. Conversion to the dimethylamide and two steps of reduction provided them with the isopsilocin **595**.[227a]

A number of 5-methoxyisogramine analogues have been synthesized following Schindler's procedure.[391]

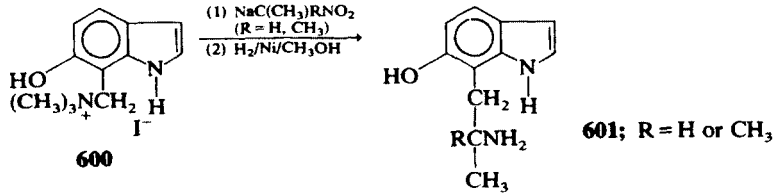


Troxler has employed the reaction of sodium salts of cyanide, nitromethane, nitroethane, or 2-nitropropane directly upon the hydroxyisogramine derivatives **597**, **598**, and **600** to afford, after Raney nickel reduction, the hydroxyisotryptamines **599** or **601**. The use of formamidomalonate or ethyl 2-nitropropionate led to a number of hydroxyisotryptophans.[390]



597; R = H
598; R = CH_3

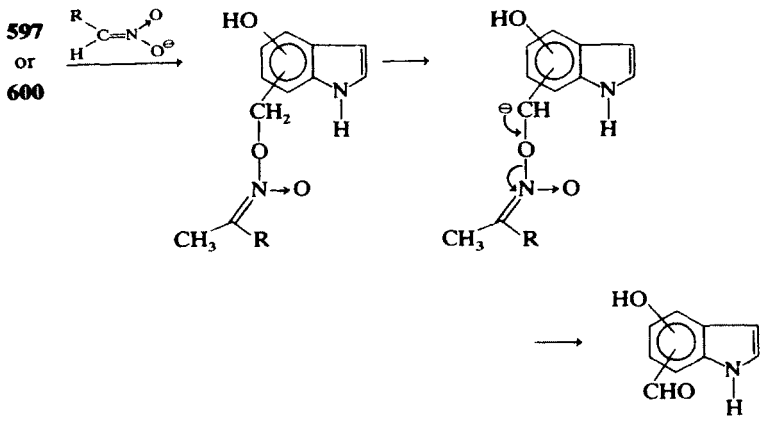
599; R = H, R′ = R″ = H
or R = H or CH_3, R′ = H, R″ = CH_3
or R = H, R′ = R″ = CH_3



600

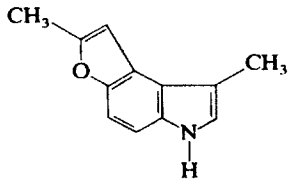
601; R = H or CH_3

The hydroxyaldehydes **602** and **603** were detected as very minor by-products in the reactions of **597** or **600** with nitroethane or 2-nitropropane and probably arise by the mechanism shown (eq. 20).



(20)

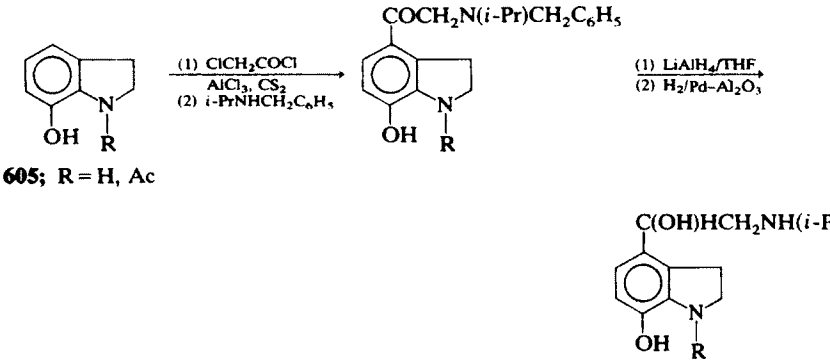
602; 5-OH, 4-CHO
603; 6-OH, 7-CHO



604 (30%)

Another interesting by-product **604** arose from **598** and nitroethane. This furoindole, surprisingly, was not produced from **597**.[390]

The Friedel–Crafts reaction of chloroacetyl chloride with the 7-hydroxyindolines **605** has been used to prepare the β-hydroxyethylamine derivatives **606**[392] in the manner given in Scheme 58.



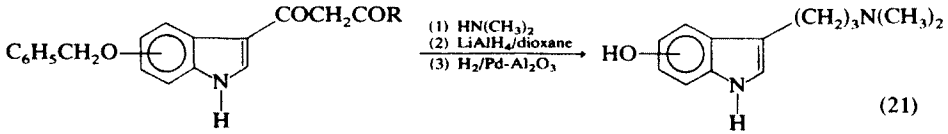
605; R = H, Ac

606; R = H, C_2H_5

Scheme 58

B. Hydroxyhomotryptamines

The 4-[227a,f] and 5-hydroxyhomotryptamines[393] **609** (eq. 21), have been prepared by Troxler and co-workers using the reaction of 4- or 5-benzyloxyindolemagnesium iodide with β-chloropropionyl chloride, treatment



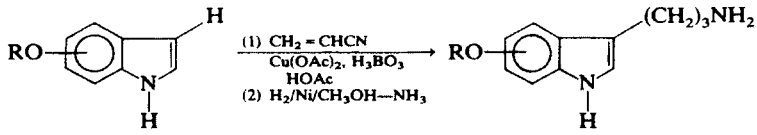
(21)

607; 4- or 5-, R = Cl
608; 4- or 5-, R = $N(CH_3)_2$

609; 4- or 5-

of the resultant **607** with dimethylamine to give **608**, and successive steps of hydride and catalytic reduction.

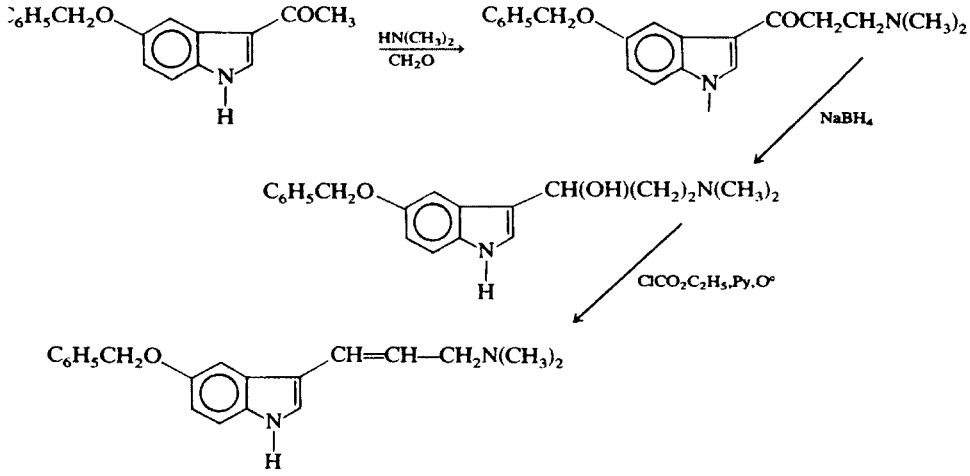
5-Ethoxy-[394] and 6-methoxy-homotryptamine[395] **612** have been produced from the indoles **610** or **611** and acrylonitrile in an autoclave, followed by a high-pressure Raney nickel reduction.



610; R = 5-C_2H_5
611; R = 6-CH_3

612

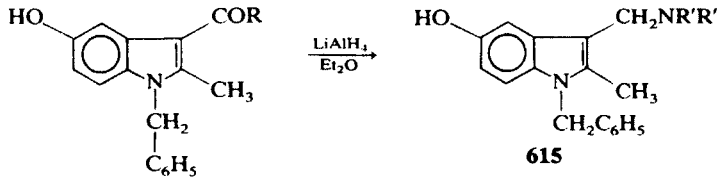
A benzyloxyhomotryptamine with unsaturation in the side chain has been synthesized using the Mannich reaction with 3-acetyl-5-benzyloxyindole and steps of reduction and dehydration as shown in Scheme 59.[397a,b]



Scheme 59

C. 3-Aminomethyl Derivatives of Hydroxyindoles

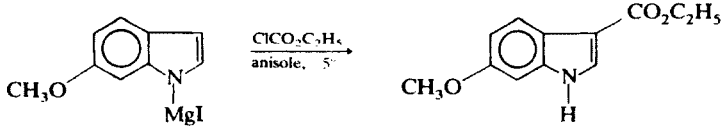
Two routes to these gramine analogues have featured starting materials derived from the Nenitzescu reaction. Domschke and Fürst have prepared a large series of 5-hydroxygramine analogues using the reaction of 1-benzyl-2-methyl-5-hydroxyindole-3-carboxylic acid chloride (**613**) and



613; R = Cl
614; R = NRR'
615

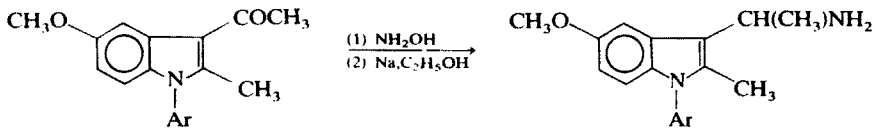
amines, either neat or in pyridine or dioxane. The resulting indole-3-formamides **614** are reduced with lithium aluminum hydride to the 3-aminomethyl derivatives **615**. In the case of the *N,N*-diphenylformamide, cleavage occurred to give the 3-methanol instead.[398]

A recent patent describes the synthesis of 6-methoxyindole-3-carboxylic acid derivative, **617**, based on the reaction of the Grignard derivative **616** and ethyl chloroformate. This route would seem to provide a useful route to alkoxyindole-3-carboxylic acid esters in general.[399] Marchelli and co-workers have prepared the four hydroxyindole-3-carboxylic acids from the benzyloxyindoles using this method.[402]



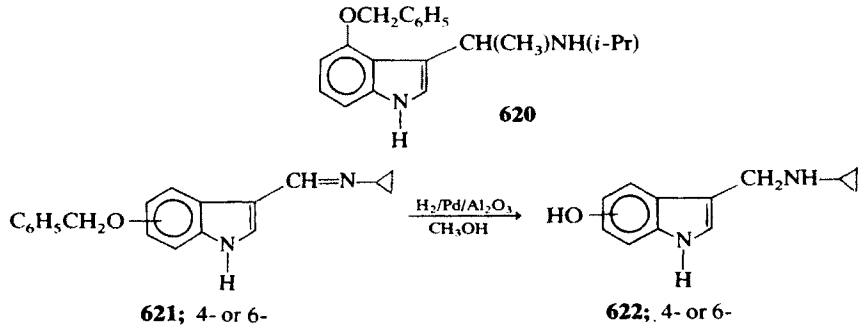
616 **617**

Grinev and co-workers have reduced the oximes of the methylated Nenitzescu reaction products **618** to the 3-aminomethylindoles **619**.[400]



618 **619**

Troxler and co-workers have reported the synthesis of a gramine analogue **620** substituted with a side-chain methyl group, using the Mannich reaction with 4-benzyloxyindole, isopropylamine, and acetaldehyde.[227a] Hydroxygramine analogues with a cyclopropane ring replacing the methyl groups, **622**, have been prepared by reduction of the Schiff's base derivatives **621**, in turn obtained from the benzyloxyindole-3-carboxyaldehydes.[401]



VII. Reactions of Hydroxyindoles

A. Chromogenic Reactions

The color-producing reactions which have seen the most application in the characterization of hydroxyindoles are the van Urk–Ehrlich reaction with *p*-dimethylaminobenzaldehyde or -cinnamaldehyde,[137,330b] the reaction with ferric chloride in ethanol,[25,92b,93] water,[137] or acetic acid–sulfuric acid (the Keller reaction),[80,227,384] and the reaction with various diazonium salts in acids or alkali.[10,13,137,330b,416] Troxler and co-workers, in particular, have made use of the van Urk–Ehrlich and Keller reagents to distinguish between various 4-, 5-, 6-, and 7-hydroxyindoles,[384] monomethylated in the benzene ring, the four hydroxytryptamines,[80] their *N,N*-dimethyl derivatives,[227] *N,N*-dimethyl *O*-phosphates,[227] as well as many *N*-mono and *N*-dialkyl, 1-alkyl, and side-chain-substituted 4-hydroxy-, 4-methoxy-, and 4-benzyloxytryptamines.[227] The Keller reaction proved useful in the isolation of psilocin and psilocybin (see Table XVII).[259b,482] Jepson and co-workers have also reported that the *p*-dimethylaminobenzaldehyde and -cinnamaldehyde reagents are useful in characterizing the four hydroxytryptamines.[330b] The van Urk–Ehrlich reagent,[42,67,82,92b,93,137,185,277,510] *p*-dimethylaminocinnamaldehyde,[137] and the ferric chloride systems[67,82,92b,217] are less useful when applied to the 5,6-dihydroxyindole system, where these reagents usually give rise to blue-gray, blue, or violet colors, even in the case of 2,3-dihydro-5,6-dihydroxyindole[217] or 5,6-dihydroxyindole-2-carboxylic acid derivatives.[67] 5,6-Dimethoxyindole is reported to give a blue-green color with the Ehrlich reagent[42] and a green color with ferric chloride.[75,88,107] 5,6-Dihydroxyindoles can, however, be distinguished using a number of other chromogenic reactions,[137] and distinctive colors are produced with the

Ehrlich and ferric chloride reagents when applied to monomethyl ethers of 5,6- and 6,7-dihydroxyindole.[93] Jepson and co-workers and Stowe and Thimann[505] have reported distinctive Ehrlich color reactions with 5-,[330b,505] 6-,[330b] and 7-hydroxyindole-3-acetic acid.[330b,505] Positive Ehrlich reactions have been reported for the following methoxyindole derivatives: 4-, 5-, and 6-methoxyindole,[52] 1-methyl-5-alkoxyindoles,[361] 5- and 7-methoxy skatole,[52] and 2-methyl-[26] and 1,3-dimethyl-7-methoxyindole.[191] 2-Substituted monohydroxyindoles generally give a positive Ehrlich test.[25,93,510] Table XVII in the Appendix of Tables includes van Urk–Ehrlich and ferric chloride color reactions of the more common hydroxyindoles.

Jepson and co-workers have reported that diazotized sulfanilic acid or *p*-nitroaniline in either acid or alkali can conveniently distinguish the four hydroxytryptamines. Their reactions are particularly sensitive and characteristic in the case of 6-hydroxytryptamines, which produce immediate red or purple colors in acid or alkali, respectively.[330b] Psilocin gives with diazotized sulfanilic acid a red-orange color useful in detection on paper chromatograms.[484] It has been reported that this reagent is also useful in distinguishing the four hydroxyskatoles.[13] Stowe and Thimann have indicated[505] the usefulness of the two reagents in the detection and characterization of 5-hydroxytryptamine and -tryptophan, where red colors are produced. Ichihara and co-workers claim[503,504] that these reagents are useful in distinguishing between 5- and 7-hydroxy-substituted indole-3-acetic acids and tryptophans, where the 7-isomers react immediately to give orange-red colors but the 5-isomers react more slowly (see also Ref. 14).

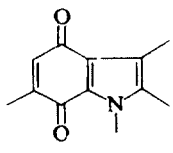
Other chromogenic reactions which have been applied to hydroxyindoles are those from sodium nitroprusside,[92b,433] α-nitroso-β-naphthol,[330b,438] the Hopkins–Cole reagent,[137] the Gibbs reagent,[137] the Folin–Ciocalteu reagent,[137] the Salkowski reagent,[137,505] ammoniacal silver nitrate,[137] potassium persulfate in acid,[137] ferric chloride–potassium ferricyanide,[137] xanthydrol,[137,435,361] and the Folin–Denis reagent.[413a]

B. Oxidation

1. *Simple Hydroxyindoles*

Substitution of the indole benzene ring with a hydroxyl group has long been known to make the resulting hydroxyindole more prone to autoxidation. The early literature in particular contains many references to the

instability of solutions of the hydroxyindoles.[25,68,342] Beer and co-workers observed[37] that a 5-methoxy substituent in 2,3-substituted indoles facilitated the formation of indolenine 3-hydroperoxides, although in the hydroxyindoles themselves, the site of autoxidation is probably the benzene ring. Serotonin is easily oxidized by silver nitrate—the basis of the so-called argentochromaffin test in histochemistry. In this case a quinone imine system may be first produced. Fremy's salt (potassium nitrosodisulfonate) oxidations have been reported for 4-, 5-, and 6-hydroxyindoles where indoloquinones result, often in good yields.[23a,b,508] In the oxidation of 1-ethyl-2-methyl-,[506] 1-ethyl-2,6-dimethyl-,[507] and 2,3-diphenyl-4-hydroxyindole,[33] mainly the 4,7-indoloquinone system **623** results with some orthoquinone also detected in the oxidation of the 6-substituted indole; with 2-phenyl-,[23a,b,508] 3-methyl-,[23a,b] or 3-carbethoxy-5-hydroxyindole,[157] a 4,5-indoloquinone **624** is produced, whereas the 6,7-indoloquinone **625** is thought to be the oxidation product from 2,3-diphenyl-6-hydroxyindole.[33] 2,3-Dimethyl-4,7-dihydroxyindole on oxidation with potassium dichromate affords the 4,7-indoloquinone in 79% yield.[339] Amorphous polymers are reported[66] to result on treatment of 3-phenyl-6-hydroxyindole-2-carboxylic acid and its 5-methyl analogue with oxidizing agents. The preparation and reactions of indoloquinones are covered in greater detail in Chapter IX.



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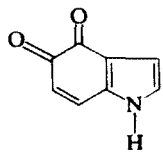

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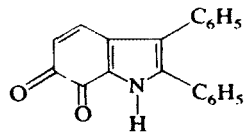
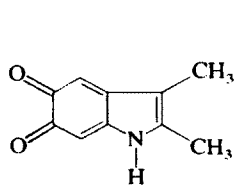


625

2. *5,6-Dihydroxyindoles and Melanin Formation*

Raper's discovery[509] in 1927, that 5,6-hydroxyindole-2-carboxylic acid and 5,6-dihydroxyindole were the immediate precursors of melanin, the skin pigment resulting from the enzymatic oxidation of tyrosine, has provided the stimulus for the synthesis and study of a host of 5,6-dihydroxyindoles[135a,b,146] under conditions of autoxidation or oxidation. Beer and co-workers have reported the most extensive studies on the autoxidation of 5,6-dihydroxyindoles. On the basis of the length of time required to form deeply colored solutions in aqueous sodium bicarbonate and whether or not melanin-like precipitates formed, they were able to judge whether a particular substituent in the parent 5,6-dihydroxyindole

facilitated or retarded melanin production. In addition, they were able to demonstrate spectroscopically the intermediacy of 5,6-indoloquinones in a number of oxidations[510] using as a model the fairly stable (ca. 30 minutes) orthoquinone **626** produced from 2,3-dimethyl-5,6-dihydroxyindole and silver oxide. They observed that 5,6-dihydroxyindole[92b] and its 2-methyl,[92b] 3-methyl,[42] and 2,3-dimethyl[42] derivatives are all very rapidly autoxidized. True melanins appeared to form only from 5,6-dihydroxyindole and 2-methyl-5,6-dihydroxyindole and suggested that the 3-position was involved in melanin formation. 5,6-Dihydroxyindole is so unstable that even in the crystalline state in a sealed vessel, it blackens within two weeks. Burton and co-workers have noted[334b] the effect of ether peroxides in further hastening its polymerization. 5,6-Dihydroxyindole with *N*-methyl[511,512] or 2-methyl[512] substituents earlier had been observed as good "methyl melanin" precursors by Burton, who suggested a melanin structure **627** based on 4'-7, 4'-4, or 7'-7 "dehydrogenative" coupling of 5,6-dihydroxyindole units, followed by their oxidation to indoxyls.



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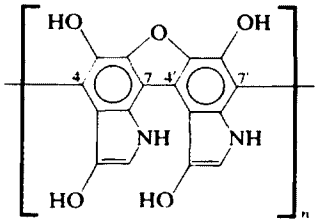


627

Lending support to coupling adjacent to the 5- and 6-hydroxyl positions are the observations[67] of Beer and co-workers that 5,6-dihydroxyindoles with 4- or 7-alkyl substituents are fairly stable in dilute alkali and are even more stabilized by additional 2-[93] or 3-methyl[67] substituents.

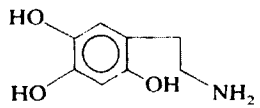
Beer and co-workers, on the basis of quantitative studies[510] which measured the rate of oxygen uptake and hydrogen peroxide production by a series of 5,6-dihydroxyindoles, proposed the following general mechanism for melanin production:

5,6-dihydroxyindole $\xrightarrow[O_2 \rightarrow H_2O_2]{}$ 5,6-indoloquinone ⟶ soluble melanochrome oligomer

⟶ insoluble melanin polymer $(C_8H_3NO_2)_n$

Swan has ruled out[513] the dopamine metabolite **628** (see Section III.G.6) as a normal melanin precursor and has suggested that the dihydro-5,6-quinone **629** may be the reactive intermediate in the formation of melanin from dopamine.

The mono- and dimethyl ethers of 5,6-dihydroxyindole are also prone



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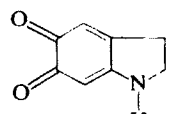
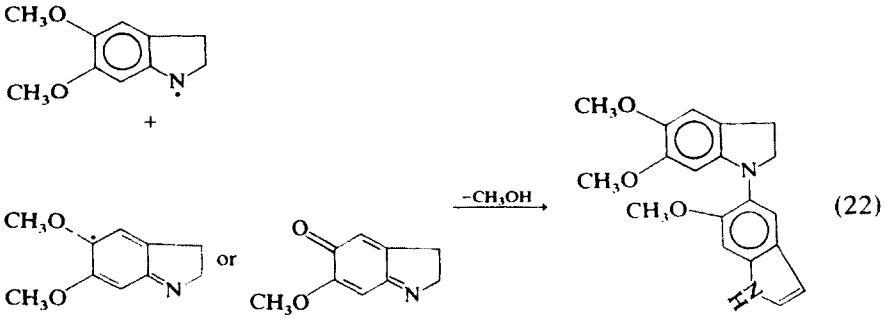


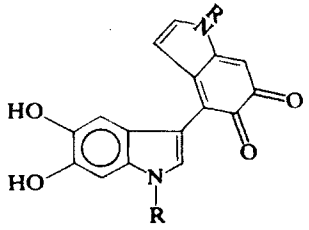
629

to autoxidation. 5-Hydroxy-6-methoxy- and 5-methoxy-6-hydroxyindole form deeply colored solutions within 35 and 3 minutes, respectively,[92b] and 5,6-dimethoxyindole[75] and 5,6-dimethoxytryptamine[88] are reported to yield rapidly, brown and blue solutions, respectively. 7,8-dimethoxytetrahydrocarbazole is so easily autoxidized that a hydroperoxide forms during recrystallization from petroleum ether–ethyl acetate.[42]

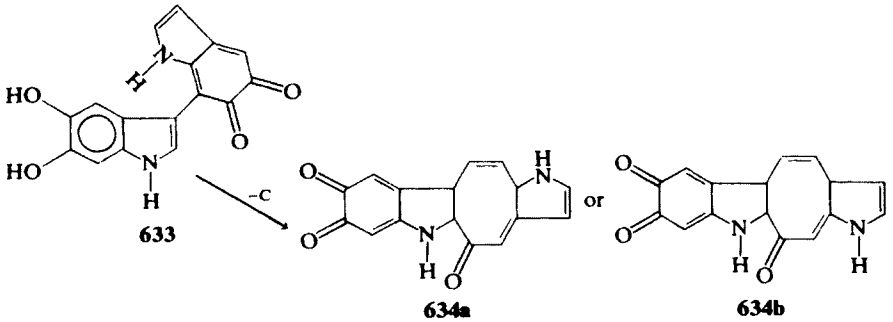
Mishra and Swan have described an interesting "dimer," **631**, which forms on oxidation of 5,6-dimethoxyindoline with silver oxide in ether or with sodium methoxide and air in methanol.[97] It may arise by the radical-coupling mechanism shown (eq. 22) or by the addition of the indoline to the quinone imine **630**. The easy formation of this dimer under mildly oxidative conditions suggests that such a process might intervene, at least to some extent, in the formation of melanin—leading to indole units linked with C–N bonds. Bu'Lock has reported spectroscopic evidence for another dimer (possible structure **632**) as a reactive intermediate in the formation of melanin from 5,6-dihydroxyindole and adrenochrome.[514,515] Another hypothetical melanin intermediate, chiefly of historical interest, is the dimer proposed by Bruce,[518,519] who postulated a purpurogallin-type oxidative condensation of the quinone **633**, related to Bu'Lock's intermediate, which loses one carbon unit to form the condensed orthoquinone **634a** or **634b**, either or both of which are polymerized to melanin. The carbon loss on melanization has been shown by Swan's[513] and Beer's[510] groups to be artifactural—caused by some oxidative destruction of the polymer by the hydrogen peroxide produced.



630 631 (22)



632; R = H or CH_3



633 **634a** **634b**

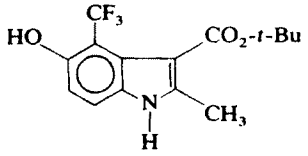
Swan has recently reviewed[513,516] structural evidence for melanin and concludes that the structure (**7b**) put forward[6] by Bu'Lock and Harley-Mason on the basis of reactions of indole with model *o*- and *p*-quinones, modified by the inclusion of some 2,3-dihydroindole units, most satisfactorily fits the available data. A comprehensive review on melanin and melanin-like pigments has recently appeared.[517]

Related to the melanin problem is the observation that both 5,6-dihydroxyindole and the 2-carboxylic acid, monomethylated in either the 5- or 6-positions, are detected in the urine of melanoma patients[520–522] (see also Ref. 523). Catechol *O*-methyl transferase is known to methylate these compounds, mainly in the 6-position, whereas hydroxyindole *O*-methyl transferase gives mainly 5-methylation.[524] 5,6-Dihydroxyindole has been detected in the urine of a mentally retarded child.[525]

C. Alkylation

Methylation of the phenolic group of hydroxyindoles is usually accomplished with dimethyl sulfate in aqueous alkali[252] or in acetone containing potassium carbonate[155] or hydroxide[33]; hydroxyindole sodium salts have also been methylated in benzene.[234a] Grinev and co-workers have reported[152,163,164,166,168,169,171,173,174] the methylation of a large number of

Nenitzescu reaction products in excellent yields using the original procedure of Nenitzescu.[154] Alkylations with chloroacetic acid,[175] ethyl bromoacetate,[175] allyl bromide,[225] and benzyl bromide have been reported. Little and Allen have described the methylation of **635** with dimethyl sulfate in acetone containing potassium carbonate; the 4-trifluoromethyl group apparently offers little hindrance.[155] 7-Hydroxytryptamine, however, fails in methylation attempts with either diazomethane or dimethyl sulfate.[193]



635

The four hydroxy-1-acetylindolines,[193] 6-hydroxy-5-methoxy-,[196] and 5-hydroxy-6-methoxy-1-acetylindoline[196] have been methylated with dimethyl sulfate, although the reaction proceeds poorly—probably for steric reasons—with the 7-hydroxy-1-acetylindoline.[193] A similar methylation of a mixture of 4- and 7-hydroxy-1-methyloxindoles is reported to proceed satisfactorily.[191] 2,3-diphenyl-6-hydroxyindole,[125] 5,6-dihydroxyindole,[92b] and 2-methyl-5,6-dihydroxy-7-iodoindole[99] have been methylated with dimethyl sulfate.

D. Dealkylation

1. *Aluminum Halides*

Until the introduction of the catalytic debenzylation procedure[78] much effort was invested in developing satisfactory procedures for the demethylation of methoxyindoles or for methylene removal from methylenedioxyindoles. In some instances surprisingly good yields were obtained, although in general yields tended to be discouragingly low. The most commonly used and generally most consistently successful procedure was the use of aluminum chloride or bromide in refluxing benzene under nitrogen. Using the former catalyst, 5-hydroxyindole[25] and its 2-methyl derivative[25] were obtained from the corresponding methyl ethers in 6 and 14% yield, respectively. 2,3-Diphenyl-4- (ca. 25%)[33] and -6-hydroxyindole,[126] 1-methyl-2,3-diphenyl-6-hydroxyindole,[33,126] 3-phenyl-5,6-dihydroxyindole (75%),[42] and 2,3-dimethyl-4,7-dihydroxyindole

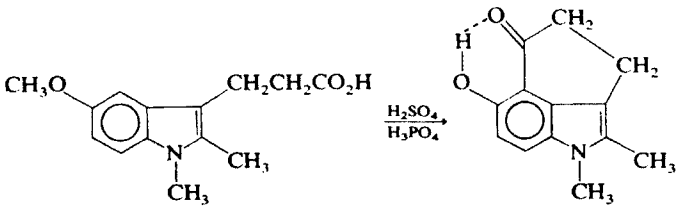
(54%)[339] were similarly obtained. Aluminum bromide has been successfully employed to demethylate 2,3-dimethyl-5,6-dimethoxyindole (78%)[42] and a number of 5,6-dimethoxyindoles substituted with *n*-propyl groups in positions 4 or 7 and either unsubstituted or carrying a methyl group at position 3.[67] Bufotenine ethyl[244a] and methyl[244b] ethers and serotonin methyl ether[293] were dealkylated with aluminum chloride in two early routes to bufotenine (see also Ref. 425) and serotonin; N^{ω}-benzyl-6-hydroxytryptamine has been similarly produced.[263] Aluminum chloride has also been employed to debenzylate two 6-benzyloxyindole-2-carboxylic acid esters.[66]

2. *Acids*

Acids have been less commonly used to dealkylate hydroxyindole ethers, although in some instances their use is indicated as preferable to the aluminum halides.[3,25,94] Clemo and Weiss successfully dealkylated 2,3-dimethyl-5,6-methylenedioxyindole with 75% sulfuric acid[41]; Harley-Mason, 2-methyl- (50%) and 2,3-dimethyl-5,6-dimethoxyindole with HBr[94]; and Mishra and Swan, 5,6-dimethoxyindoline (ca. 60%) with HCl in a sealed tube.[217] HBr is reported to give a quantitative yield of hydroxyindole from 1-methyl-2-phenyl-5-methoxyindole[268] and a good yield from 1,2-dimethyl-3-ethyl-5-methoxyindole.[3] Shaw has reported[65a] the successful demethylation of 2-methyl-5-methoxytryptamine (74%) with HBr, although the 1-methyl isomer gave only an 8% yield of the 5-hydroxytryptamine.[65a] Julia and co-workers also reported[313] an excellent yield (70%) in the demethylation of 2-phenyl-5-methoxytryptamine with HBr and the production of 1-methyl- (71%) and 1-ethyl(68%)-4-hydroxyindoline.[211] *N*-Methylaniline hydrobromide was found superior to aluminum chloride in the demethylation of 5-methoxyindole (16%), 1- (15%) and 2-methyl-5-methoxyindole (21%), and 7-methoxyindole (3%).[25] Pyridine hydrochloride has been applied less successfully in the demethyleneation of 5,6-methylenedioxyindole[339b] and its 2-methyl derivative[339b,511]; failure was reported with 1,2-dimethyl-3-ethyl-5-methoxyindole.[3]

A number of other failures to effect satisfactory dealkylations with acid have been reported. Hydrochloric acid or sulfuric acid was unsuccessful when applied to 6-methoxytryptophan,[69] HI failed with 5-benzyloxyindole,[77] HBr or HI failed to debenzylate 6-benzyloxyindole,[77] and all three halogen acids were unsuccessful in the demethylation of 4,7-dimethoxyindole.[96]

An interesting, very facile demethylation (32%) occurred unexpectedly in an acid-catalyzed cyclization of the 5-methoxyindole acid, **636**. In this



636 **637**

case, the driving force may be the formation of a strong intramolecular hydrogen bond in the product, **637**.[39]

E. Reduction

1. *Dissolving Metals in Hydrochloric Acid*

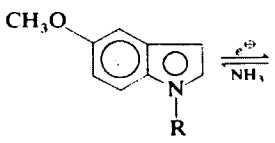
Späth and Brunner reduced 2-methyl-5-methoxy- and -6-methoxyindole as well as 1,3-dimethyl-5-methoxyindole and 3-methyl-5-methoxyindole to the indolines using a tin in hydrochloric acid reduction.[27] Gardner and Stevens reduced 1,2,3-trimethyl-5-hydroxyindole to the indoline in 50% yield by the same method.[38] Kolosov and Preobrazhenskaya, using zinc amalgam and HCl on 1-methyl-5-ethoxyindole and 1,3-dimethyl-5-methoxyindole, prepared 1-methyl- and 1,3-dimethyl-5-hydroxyindoline in 39 and 51% yield, respectively.[50] Under these conditions both reduction and dealkylation occur.

2. *Catalytic Hydrogenation and Dehydrogenation*

5-Methoxyindole,[97] 5,6-diacetoxyindole,[217] 5,6-dimethoxyindole,[217] 5-ethoxy-6-methoxyindole,[97] and 5-methoxy-6-ethoxyindole[97] have been reduced to the indolines by hydrogenation with a platinum oxide catalyst in acetic acid. Hydrogenation of 5-methoxyindole with a ruthenium dioxide catalyst led to the octahydroindole (86%).[358] 4- and 6-Benzyloxygramine on reduction with a palladium catalyst afford 4- and 6-hydroxy-2,3-dihydroskatole by-products[234]; 6-benzyloxyskatole, likewise, yields some 2,3-dihydro-6-hydroxyskatole.[234] 5,6-Dimethoxyindoline has been dehydrogenated to the indole in 60% yield with a palladium–carbon catalyst[217]—a reaction successful also with 2,3-dihydro-6-hydroxyindole.[234a] See Section III.H.2.a for a number of dehydrogenations of alkoxyindolines.

3. *Birch Reduction*

Remers and co-workers have described[526,527] the Birch reduction of 5-methoxyindole and its 1-methyl derivative with lithium in ammonia–THF containing methanol to 4,7-dihydroindoles in 82 and 60% yield, respectively. In the absence of methanol 1-methyl-5-methoxyindole was reduced instead to the indoline in 70% yield. Teuber and Schmitt have reported an 84% yield of 4,7-dihydro-5-methoxyindole when ethanol is employed in Remer's procedure.[358] 6-Methoxyindole is also reported[527] to yield a 4,7-dihydroindole. In these reductions the role of the alcohol proton donors is thought[526] to be that of intercepting the initially formed radical anion **638** to form the 4,7-dihydro product; in the absence of alcohols, a slower second step of reduction occurs to give the dianion **639** in equilibrium with **638**. This is sufficiently basic to remove protons from ammonia to form the indoline. Remers and Weiss have reported[528] that Birch reduction without methanol of 1-methyl-*N*,*N*-dimethyl-5-methoxytryptamine methiodide (**640**) gives the spiroindoline **641**. The methiodide of *N*,*N*-dimethyl-5-methoxytryptamine undergoes demethylation only. When the reductions are conducted in the presence of methanol, the 4,7-dihydrotryptamines result[527,528] in approximately 50% yields. 4,7-Dihydrotryptamines also result from *N*,*N*-dimethyl-5-methoxytryptamine and 2,7,*N*,*N*-tetramethyl-5-methoxytryptamine.[527]



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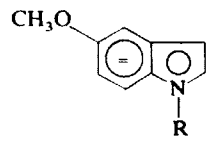

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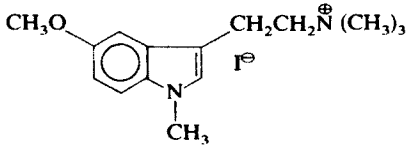

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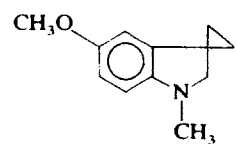

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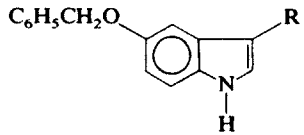
4. *Miscellaneous Reductions*

A number of methoxyindolines have been prepared using sodium–alcohol[357] or lithium aluminum hydride[26,49,186,191] reduction of oxindoles, the reduction of indolenine salts, either catalytically with palladium in

methanol[359] or with sodium borohydride,[356] and the reduction of thioxindoles at a lead cathode.[215]

F. Electrophilic Substitution

Very few studies deal with the substitution of hydroxy- or alkoxyindoles using electrophilic reagents; of the limited number which do exist, most treat the 5-hydroxyindole system. Both 5-hydroxy- and 5-benzyloxyindoles appear to exhibit maximum reactivity toward electrophiles at the 4-position. Remers and co-workers have reported[529] that **642** on nitration gives four times as much 4-nitro derivative as 6-, and Benigni and co-workers that nitration of **643** leads to the 4-nitro derivative in 70% yield.[396] At variance with these results is the report[386] that bromination in acetic acid of ethyl 2-methyl-5-hydroxyindole-3-carboxylate gives an 80% yield of the 6-bromo derivative. Similar results were obtained with the *O*-acetate and *O*-benzyl derivatives.

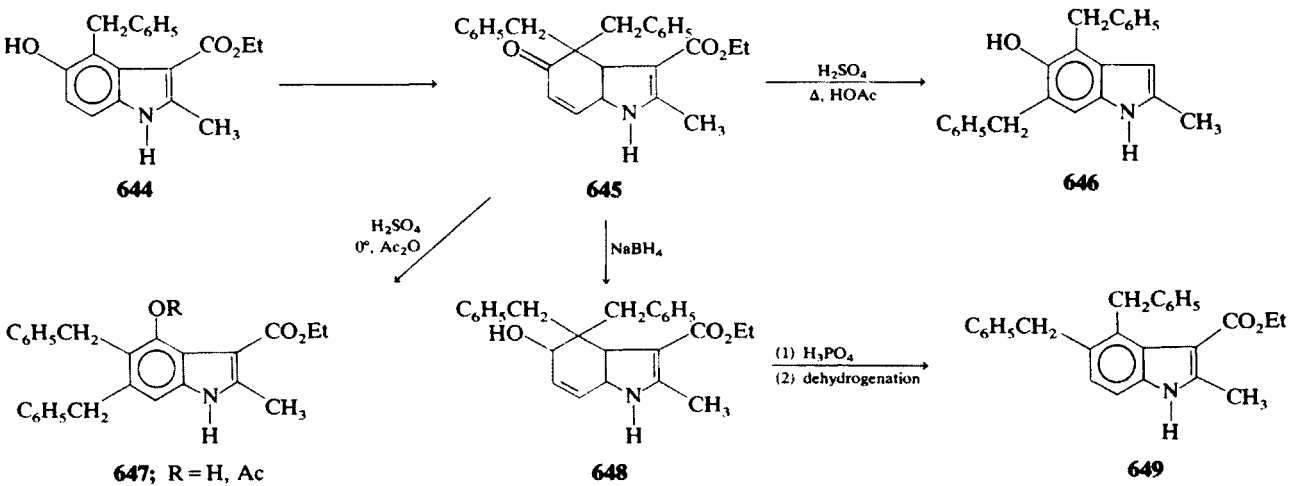


642; R = $COCO_2Et$
643; R = $CH_2N(CH_3)_2$

Kirby and co-workers have determined that the relative rate of deuterium exchange in 1*M* DCl at the following positions in 5-hydroxytryptophan is 4 > 6 > 2 > 7,[530]

A number of studies on the course of the Mannich reaction with 5-hydroxyindoles have indicated that the sole product is the 4-aminomethylisogramine (see Section IV.B).

Julia and Lallemand have showed that reaction of ethyl 5-hydroxyindole-2-carboxylate with oxalyl chloride and acetyl chloride also gives 4-substitution.[225] Formylation with the Vilsmeier–Haack reagent ($POCl_3$–DMF) gave the 3-formyl-5-formate derivative, however.[225] 4-Benzyloxyindole-2-carboxylic acid or its esters undergo formylation in the 7-position, providing a convenient route, through decarboxylation and Wolff–Kishner reduction, to 4-hydroxy-7-methylindole. With 4-Benzyloxyindole-2-carboxylic acid dimethylamide, however, the formyl group enters the 3-position.[750] The action of allyl bromide on 5-hydroxyindole led to 5-allyloxyindole in 65% yield accompanied by 10–15%


HO
CH2C6H5
CO2Et
CH3
N
H
644
C6H5CH2
O
645
H2SO4
Δ, HOAc
646
H2SO4
0°, Ac2O
NaBH4
OR
647; R = H, Ac
648
(1) H3PO4
(2) dehydrogenation
649

Scheme 60

of 4-allyl-5-hydroxyindole. Claisen rearrangement of the *O*-allyl product gave the 4-allyl product in 80% yield.[225]

Oxalylation of 4,6-dimethoxyindole is reported[349] to give 7-substitution. Troxler and co-workers have shown that 4-hydroxyindole is aminomethylated in the 5-position, 6-hydroxyindole in the 7-position, and 7-hydroxyindole in the 6-position.[384] When the 4-position of 5-hydroxyindole is blocked by a methyl group, aminomethylation gives mainly the 3-aminoethyl derivative with minor amounts of the 6-aminomethyl isomer. Similarly 6-hydroxy-7-methylindole gave the gramine as the major product with lesser amounts of the 5-aminomethylisogramine.[384]

The stepwise benzylation of ethyl 2-methyl-5-hydroxyindole-3-carboxylate with benzyl chlodine in xylene under alkaline conditions has been described by Suehiro[531] (Scheme 60). Both mono- (**644**) and dibenzylated (**645**) products can be isolated. The latter enone on refluxing with H_2SO_4 in acetic acid undergoes a dienone–phenol rearrangement and decarboxylation to 2-methyl-4,6-dibenzyl-5-hydroxyindole (**646**).[532] On acid treatment in acetic anhydride at 0°, however, **645** gave the 5,6-dibenzyl-4-hydroxyindole mixture, **647**, by an alternative dienone–phenol pathway.[533] When **645** was reduced, dehydrated, and dehydrogenated, the 4,5-dibenzylindole **649** resulted.[534] Suehiro and Sugimori have also reported similar selective 4-alkylations with vinyl chloride and cinnamoyl chloride.[535]

G. Miscellaneous Reactions

The carbonation of alkali metal salts of 2,3-diphenyl-6-hydroxyindole at elevated temperature and pressure is reported to give the 5-carbonates.[536a–c]

Heacock and Scott have noted that addition complexes result when 5,6-dihydroxyindole and its 1-methyl derivative are treated with sulfite or dithionite.[537]

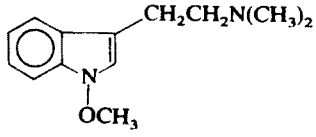
Robinson and Slaytor have reported the replacement of chlorine in 4-chloro-5-benzyloxyindole with the cyano group using cuprous cyanide in refluxing quinoline.[83]

O-Sulfation of the four hydroxyskatoles has been effected with chlorosulfonic acid or sulfur trioxide in pyridine.[363,538]

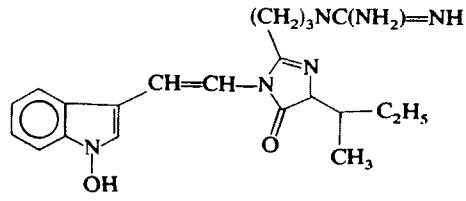
VIII. 1-Hydroxyindole and Derivatives

A. Introduction

The recent isolation of the 1-hydroxyindole derivatives, lespedamine (**650**) from *Lespedeza bicolor* var *japonica*,[437] 1,5-dimethoxygramine from



650



651

Gymnacranthera paniculata var *zippeliana*,[555] neoglucobrassicin (**869**) from mustard,[556] and the luciferin from *Cypridina hilgendorfi*[557a,b] (provisional structure, **651**); the frequent encountering of 1-hydroxyindole-2-carboxylic acids as main or by-products in modified Reissert reductions and the production of 1-hydroxyindoles in a number of cyclizations of nitrostilbenes[558]; as well as the recent observations of Mousseron–Canet and co-workers on the presence of the nitrone tautomer in solutions ($CHCl_3$, CH_3CN, etc.) of 1-hydroxyindoles[559,588,589] all have stimulated new interest in this uncommon but venerable indole system.

1-Hydroxyindoles are characterized by solubility in alkali,[566,570,574] by blue,[560,592,606] green,[562,564] or red-brown[574] colors with ferric chloride (see, however, Ref. 574), colors with triphenyltetrazolium chloride,[563] a bathochromic shift with alkali in the uv,[561,562,572] and an *O*-acetate with an unusually high frequency (ca. 1800 cm^{-1}) in the ir.[561,564,574,594,606] The N–O bond is easily cleaved as indicated by the loss of OH in the mass spectrometer[573] (*O*-acetates, however, undergo *O*-acyl cleavage[573,606]), the loss of OCH_3 from 1-methoxyindole-2-carboxylic acids on attempted decarboxylation,[562,565] the loss of OH from 1-hydroxy-2-phenylindole on heating[565,574] in alkali or from 1-hydroxy-2-phenyl-3-nitrosoindole on heating with ethanol in a sealed tube,[568a,b] and the facile rearrangement of certain N–O derivatives to indolenin-3-ols.[570,571] 1-Hydroxyindoles undergo easy reduction to indoles with zinc dust,[560,564,566,568b,574] ammonium sulfide,[568a,b] HI in acetic acid,[560] and triphenyl-phosphite[570] or phosphine.[606] In addition, reductions have been effected with hydroxylamine and hydrazine,[568a,b] by hydrogenolysis (Pd/C) of *O*-acetates[564,574] or *O*-benzoates,[574] and by the action of sodium amalgam on 1-methoxyindole-2-carboxylic acid.[560]

1-Hydroxyindoles will, however, withstand rather severe alkaline[560,569,574] or acidic[566] conditions and the 1-methoxy group is stable to lithium aluminum hydride.[562]

In general, the chemistry of the 1-hydroxy group resembles an aromatic hydroxylamine group rather than a phenol. It can be methylated with methyl iodide[43,560,569,591] and alkali or diazomethane in the case of the

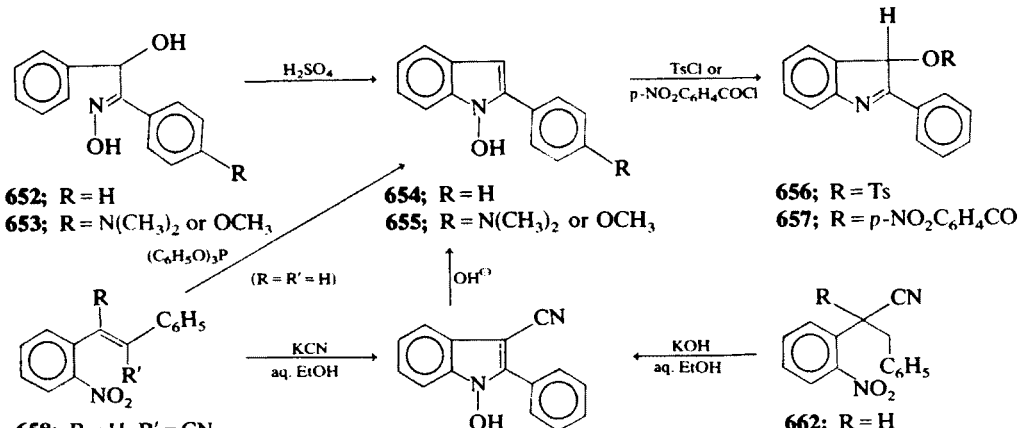
more acidic[557b,573] 1-hydroxyindole-2-carboxylic acid.[561,572] The easy oxidative dimerization of 1-hydroxyindoles with an unsubstituted 3-position is perhaps the most unique property of this system.[569,570,576,577]

B. 1-Hydroxy-2-Phenylindole

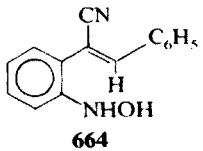
The oldest and most thoroughly investigated 1-hydroxyindole **654** was synthesized (80%) in 1895 by Fischer and Hütz,[566] who used a sulfuric acid cyclization of the oxime of benzoin (see also Refs. 557b, 570, 571, and 589) (Scheme 61). Although an indoxyl structure was originally proposed, this was corrected in a paper of the following year.[567] Kawana has recently synthesized *p*-dimethylamino and *p*-methoxy analogues **655** by the same procedure.[562] Fischer showed that 2-phenylindole resulted after reduction with zinc dust in acetic acid; Angeli and Angelico obtained the same material on heating the ethyl ether of **654** with ethanol in a sealed tube.[568a,b] Mousseron–Canet and Boca have recently reported[589] an alternative synthesis of **654** using a zinc dust reduction of *o*-nitrodeoxybenzoin (see the following section) **654** also results on vigorous alkaline hydrolysis of the nitrile **661** produced (24–30%) in an unusual reaction of potassium cyanide on 2-nitro-α-phenylcinnamonitrile (**658**) or the nitro β-cyanostilbene **659** (60%) and surprisingly even with the action of alkali on the saturated α-benzyl-2-nitrophenylacetonitriles **662** or **663**.[574] In the latter reactions, an intramolecular hydrogen transfer (→ **664**) may precede ring closure.[558] Analogues, **665–669**, have been prepared in a similar manner.[574,601]

Sundberg has recently shown that 1-hydroxy-2-phenylindole is probably an intermediate in the triphenyl phosphite cyclization of *o*-nitrostilbene (**660**) to 2-phenylindole by demonstrating that the reagent very effectively deoxygenates **654** (79%).[570] The tosylate[570] and *p*-nitrobenzoate[571] derivatives of **654** have been shown to rearrange with great ease to 3-hydroxyindolenine derivatives **656** and **657**, most probably by heterolytic scission of the N–O bond.[570]

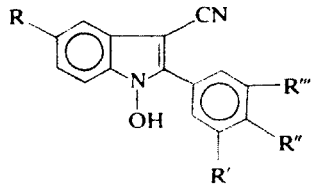
Colonna and his co-workers have described the facile dimerization of 1-hydroxy-2-phenylindole (**654**) to the bis-nitrone **668** using a number of mild oxidants, among them *p*-benzoquinone,[577,578] *N*-nitrosodiphenylamine,[576] *t*-butylhydroperoxide,[578] diethyl azodicarboxylate,[577,578] 4,4′-azopyridine,[581] and *N*,*N*-diphenyltriazene[576] (Scheme 62). Metal ion-catalyzed autoxidation at neutrality[579] or photooxidation in benzene[577] also produced **668**. The esr spectrum of **668** indicates some biradical **669** contribution.[575,576] On acid treatment in dioxane, 2-phenylisatogen (**674**) and 2,2′-diphenyl-3,3′-diindole (**676**) result.[575] When **654** is autoxidized in alcohol with Cu^{2+} present,[579] the 1-hydroxyindole dimer **675**


OH
N
OH
R
H2SO4
652; R = H
653; R = N(CH3)2 or OCH3
654; R = H
655; R = N(CH3)2 or OCH3
TsCl or
p-NO2C6H4COCl
H
OR
N
656; R = Ts
657; R = p-NO2C6H4CO
(C6H5O)3P
(R = R' = H)
OH⊖
R
C6H5
R'
NO2
KCN
aq. EtOH
CN
658; R = H, R' = CN
659; R = CN, R' = H
660; R = R' = H
661
KOH
aq. EtOH
C6H5
662; R = H
663; R = CO2C2H5

Scheme 61

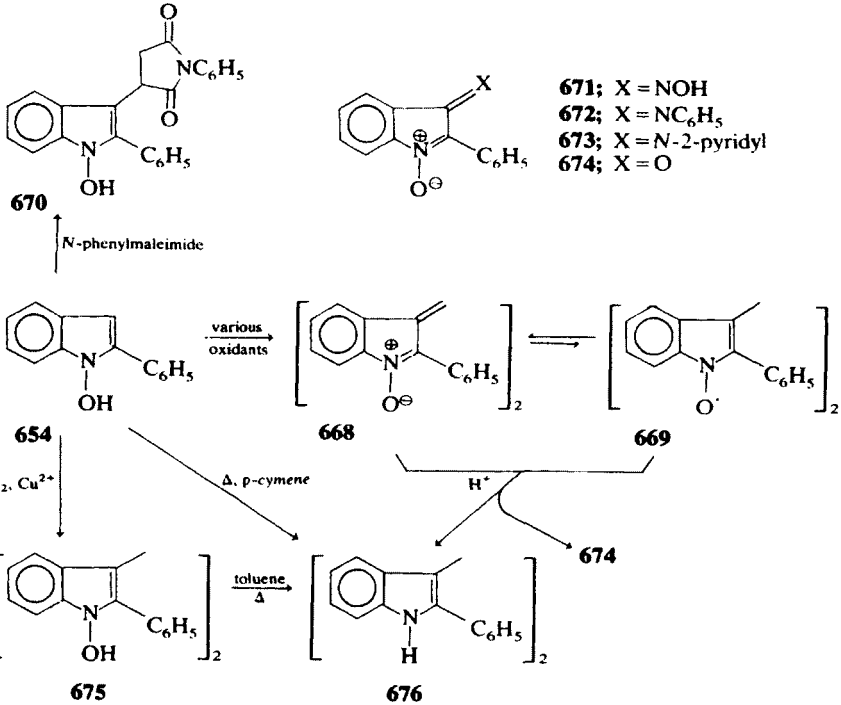


664



665; R = OCH_3, R′ = R″ = R‴ = H
666; R = R′ = R″ = R‴ = OCH_3
667; R = R′ = R‴ = H, R″ = OCH_3

results in addition to the bis-nitrone; the esr spectrum of **675** also indicates[585] some biradical content. On refluxing **675** in toluene, the indole dimer **676** results, and benzyl alcohol and benzaldehyde are formed by reaction of hydroxyl radicals with the solvent.[584,585] Sundberg has observed[570] the direct formation of **676** by refluxing 1-hydroxy-2-phenylindole in *p*-cymene. Greci and Padovana obtained **676** and



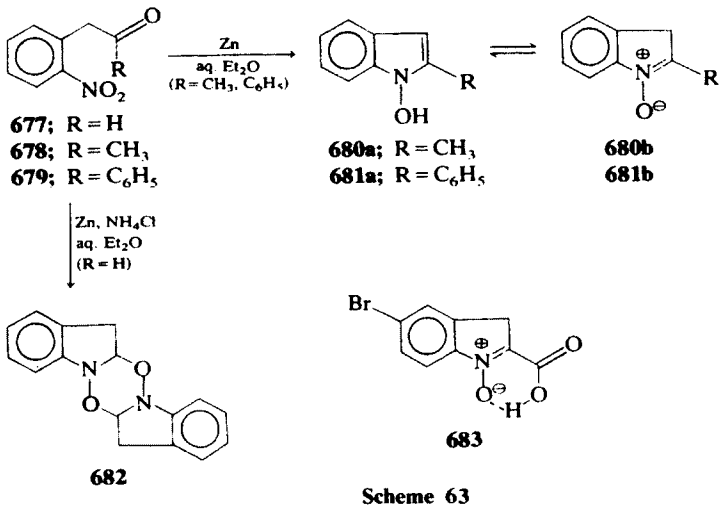
Scheme 62

2-phenylisatogen **674** when **654** was oxidized with *N*-chlorobenzotriazole.[587] Nitrosobenzene or certain of its derivatives[582] and 2,2′-azopyridine[581] are reported to convert **654** to the imino isatogens, for example, **672** and **673**. Under neutral conditions, nitrosobenzene gives rise to 1-hydroxy-2-phenylindole radicals.[580] **672** has been reduced with hydrazobenzene to 2-phenyl-3-anilinoindole.[583]

Angeli and Angelico, in 1904, reported[568a] that the reaction of 1-hydroxy-2-phenylindole with amyl nitrite and sodium ethoxide gave **671**; the tautomeric 1-hydroxy-2-phenyl-3-nitrosoindole is also possible. **671** could be reduced with hydroxylamine or hydrazine to 2-phenyl-3-nitrosoindole or with zinc in acetic acid to 2-phenyl-3-aminoindole.[568a,b] Colonna and Monti have reported[586] that 1-hydroxy-2-phenylindole adds—not on the hydroxyl group but rather at the 3-position—to, *N*-phenylmaleimide (forming **670**), as well as certain quinones.

C. 1-Hydroxy-2-Methylindole and Analogues

Mousseron–Canet and Boca have reported the synthesis of this compound[588,598] and the attempted synthesis of the parent 1-hydroxyindole by zinc dust reductions of 2-nitrophenylacetone (**678**) or -acetaldehyde (**677**), the latter reduction effected in the presence of ammonium chloride (Scheme 63). 1-Hydroxyindole is apparently inherently unstable and dimerizes spontaneously to **682**.[588,589] Nmr studies have indicated that **680a** and **681a** exist in equilibrium with the nitrones **680b** and **681b**.[559,588,589] The nitrone form is favored in donor solvents such as phenol whereas the hydroxylamine predominates in acceptor solvents such as pyridine.[588] Acheson and co-workers have reported[572] that 1-hydroxy-5-bromoindole-2-carboxylic acid is exclusively in the form of the nitrone **683** even in chloroform; in this case the nitrone form is stabilized by an intramolecular hydrogen bond. Interestingly, De Stevens and co-workers have reported[600] that superior *O*-alkylations of 1-hydroxy-2-phenylindole are effected in pyridine. Sundberg has reported that the triphenyl phosphite reduction of 2-nitro-β-propylstyrene gives 3% 1-ethoxy-2-propylindole as a by-product.[570] In this case, the reagent must effect alkylation of the intermediate 1-hydroxy-2-propylindole. Acheson and co-workers observed[573] that the hydroxyl group of 1-hydroxy-2-methylindole does not exchange with D_2O in pyridine and cannot be methylated with diazomethane and BF_3–Et_2O, indicating a very weakly acidic hydroxyl group in this compound.



677; R = H
678; R = CH_3
679; R = C_6H_5

680a; R = CH_3
681a; R = C_6H_5

680b
681b

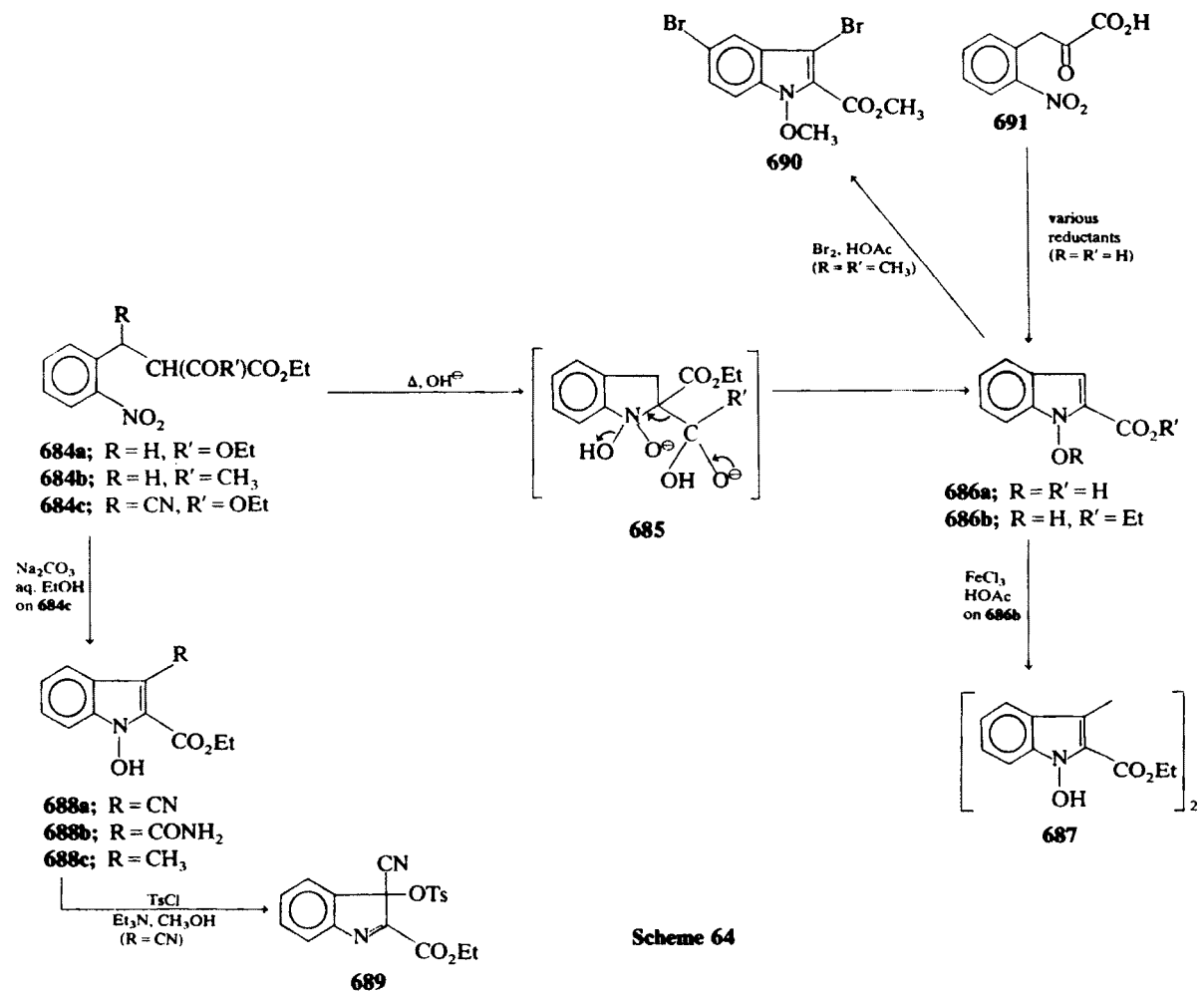
682

683

Scheme 63

D. 1-Hydroxyindole-2-Carboxylic Acid and Derivatives

Shortly after Fischer's synthesis of 1-hydroxy-2-phenylindole, Reissert reported[560] the synthesis of 1-hydroxyindole-2-carboxylic acid (**686a**) (Scheme 64) in better than 80% yield using an alkaline cyclization of the *o*-nitrobenzylmalonate **684a**. A decade later, Gabriel and co-workers prepared[569] this acid together with the ethyl ester using an alkaline ring closure of the *o*-nitrobenzylacetoacetate **684b**. These reactions probably proceed via the intermediates **685** (R′ = OC_2H_5 or CH_3) which suffer decarboxylation or deacetylation with the loss of hydroxide ion.[558,564] Reissert showed[560] that **686a** reduces hot Fehling's solution and can be *O*-acetylated and methylated. Gabriel and co-workers, working with the ester **686b**, extended the derivatives to the preparation of *O*-ethyl, *O*-benzyl, *O*-benzoyl, dichloro, and mono- and tribromo compounds.[569] Reduction to the known indole-2-carboxylic acid or ester was achieved with zinc in acetic acid, PH_4I in HI, or $SnCl_2$ in HCl.[569] Gabriel and co-workers also reported the oxidative dimerization to **687** with ferric chloride in HOAc, and Reissert described the preparation of indigo by sulfuric acid treatment of **686a** for several days followed by basification with ammonia.[560] The latter reaction could proceed through an N- to C_3-shift of hydroxyl; decarboxylation would then produce indoxyl. Reissert also prepared *N*-nitroso derivatives from both **686a** and **686b** by the action of nitrous acid. The pK_a of methyl-1-hydroxyindole-2-carboxylate has been reported[557b] as 8.7; it is considerably more acidic than 1-hydroxy-2-phenylindole (pK_a 10.3).


Br
Br
CO2CH3
N
OCH3
690
CO2H
O
NO2
691
various
reductants
(R = R' = H)
Br2, HOAc
(R = R' = CH3)
R
CH(COR')CO2Et
NO2
684a; R = H, R' = OEt
684b; R = H, R' = CH3
684c; R = CN, R' = OEt
Δ, OH⊖
CO2Et
R'
N
C
HO
O⊖
OH
O⊖
685
CO2R'
N
OR
686a; R = R' = H
686b; R = H, R' = Et
Na2CO3
aq. EtOH
on 684c
FeCl3
HOAc
on 686b
R
N
CO2Et
OH
688a; R = CN
688b; R = CONH2
688c; R = CH3
CO2Et
N
OH
2
687
TsCl
Et3N, CH3OH
(R = CN)
CN
OTs
N
CO2Et
689

Scheme 64

The 3-cyano derivative of Gabriel's ester **688a** was obtained by Loudon and Wellings,[564] who cyclized the benzylmalonate derivative **684c** with sodium carbonate; the 3-carboxamide results by a similar route[564] (see, however, Ref. 572, in which Acheson claims the former reaction gives the 3-acid). Gassman and co-workers have recently shown[571] that an attempted *O*-tosylation of this compound gives instead the rearranged indolenin-3-ol tosylate **689**. Acheson and co-workers have reported[572] that bromination of methyl 1-methoxyindole-2-carboxylate affords the 3,5-dibromo derivative **690**; in Reissert's hands[560] the 1-methoxy acid gave the 3-bromo derivative. When 1-hydroxy-3-cyanoindole-2-carboxylic acid is brominated, the 5-bromo derivative results.[572]

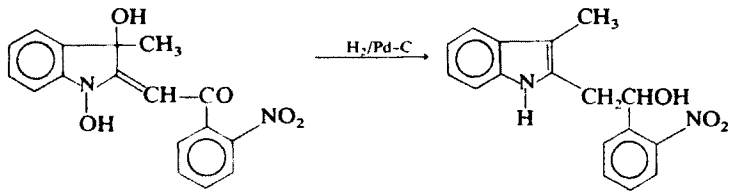
An early report[595] that sulfuryl chloride with ethyl 3-methylindole-2-carboxylate in acetic acid led to the 1-hydroxyindole derivative **688c** should be confirmed.

Currently the method of choice for the preparation of 1-hydroxyindole-2-carboxylic acid is the chemical or catalytic reduction of 2-nitrophenylpyruvic acid **691** or its esters. Reissert introduced[590] the use of sodium amalgam for the reduction of 2-nitro- and 2-nitro-4-methylphenylpyruvic acids and obtained 1-hydroxyindole-2-carboxylic acid (60%) and its 6-methyl analogue. Two other groups have reported yields of 40% in the former reduction.[43,591] Recently Acheson employed[572] a magnesium amalgam reduction of **691**, and its 5- and 4-bromo derivatives to prepare **686a** (54%) and 5- (40%) and 6-bromo-1-hydroxyindole-2-carboxylic acids (32%), respectively. Troxler and co-workers[392] reported that a dithionite reduction of 2-nitro-4-bromo-6-methylphenylpyruvic acid ethyl ester with sodium dithionite gives a mixture of ethyl 1-hydroxy-4-methyl-6-bromoindole-2-carboxylic acid and the 1-hydrogen indole. Omote and co-workers reduced methyl- or ethyl- substituted 2-nitrophenylpyruvic acid bisulfite addition complexes with sodium amalgam to 1-hydroxy-3-methyl- or 1-hydroxy-3-ethyl-indole-2-carboxylic acids.[591] Coutts and Wibberly[592] reduced 2-nitrophenylpyruvic acid and its ethyl ester to 40 and 64% yields, respectively, of **686a** using sodium borohydride in aqueous methanol containing palladium on charcoal, and Baxter and Swan[561] achieved a 50% yield of **686a** by hydrogenation of **691** with the Adams catalyst. Although indole-2-carboxylic acid is produced as a major by-product, the 1-hydroxy acid is recovered unchanged on additional hydrogenation. Baxter and Swan have postulated the initial formation of a hydroxylamine derivative which can cyclize to the 1-hydroxyindole or undergo further reduction to an amine which then cyclizes to the normal indole. A similar proposal has been advanced by Di Carlo to account for the production of 1-hydroxyoxindole and oxindole mixtures in the reduction of 2-nitrophenylacetic acid.[603] Baxter and Swan also reduced the

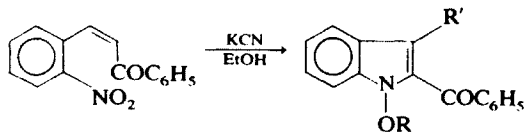
oxime, semicarbazone, and phenylhydrazones of 2-nitrophenylpyruvic acid to **686a**, although reduced yields were reported.[561] Coutts has reported that the reduction of **691** with a palladium–carbon catalyst and hydrazine hydrate in ethanol gave **686a** in 44% yield.[593]

E. Miscellaneous

Sakan and co-workers have described[594] an interesting base-catalyzed self-condensation of *o*-nitroacetophenone to the 1,3-dihydroxyindoline derivative **692**. Reduction afforded the indole **693**. Loudon and MacKay have reported[558] the synthesis of 1-hydroxy-2-benzoyl-3-cyanoindole (**695a**) by the action of cyanide ion upon **694**, and Sundberg, the formation of 1-ethoxy-2-benzoylindole (**695b**) (4%) as a by-product in the triphenyl phosphite cyclization of 2-nitrochalcone.[570]



692 **693**

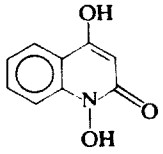


694

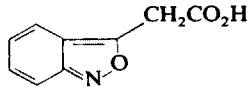
695a; R = H, R′ = CN
695b; R = Et, R′ = H

Ingraffia's claim[596] to have prepared 1-hydroxyindole and -skatole by action of hydrogen peroxide on the indole Grignard derivatives has been invalidated recently by Kawana and co-workers,[562] as has the claim[598] by Houff and co-workers to have prepared 1-hydroxyindole-3-acetic acid using ferric ion on indole-3-acetic acid in $HClO_4$–acetone. In this context, it should be noted that an attempt by Mousseron–Canet and Boca to prepare 1-hydroxy derivatives of indole and 2- and 3-methylindole using the reaction of their magnesium bromide derivatives with *p*-nitroperbenzoic acid led instead to 3-bromoindole, 2-methyl-3-bromoindole, and 2-bromo-3-methylindole, respectively.[597]

Acheson and co-workers have recently shown[573] that the mixture of 1-hydroxyindole-3-carboxylic acid and oxindole-3-acetic acid supposedly prepared by Askam and Deeks[599] by the action of fluorosulfonic acid on *o*-nitrophenylsuccinic anhydride is actually a mixture of 1,4-dihydroxy-2-quinolone (**696**) and the benzisoxazole acetic acid, **697**.

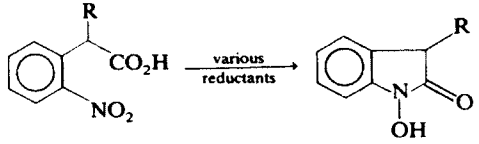


696



697

1-Hydroxyoxindole (**700**) results on a zinc–sulfuric acid reduction[602] or as a hydrogenation (Pt/HOAc) by-product[603] of *o*-nitrophenylacetic acid (**698**). Recently, 4-methyl-, 4-chloro-, and 6-chloro-1-hydroxyoxindole and 5-bromo-1-methoxyoxindole have been synthesized by zinc reduction.[604] Heller has reduced[605] the hydroxyacetic acid derivative, **699**, to 1-hydroxydioxindole (**701**) using a zinc–ammonia reduction. 1-Hydroxyoxindole has been methylated with dimethyl sulfate to the 1-methoxy analogue.[604]

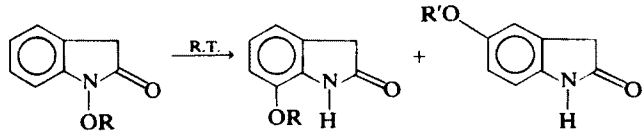


698 R = H
699 R = OH

700; R = H
701; R = OH

When 1-tosyloxy- or 1-*p*-nitrobenzenesulfonoxyoxindole (**702**), prepared at −78°, in THF–triethylamine was allowed to warm to room temperature with methanol or aqueous dioxane added to promote solvolysis, rearrangement to the 7-substituted oxindole (**703**) occurred (29–34%) and the solvolytic products, 5-methoxy- or 5-hydroxyoxindole (**704**), resulted (22-52%).[608]

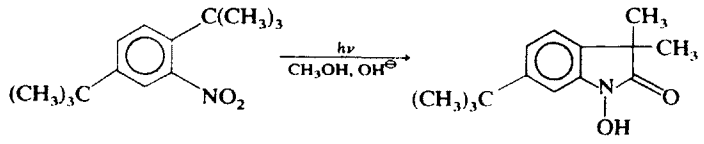
A novel 1-hydroxyoxindole synthesis employing the photochemical



702; R = *p*-$CH_3C_6H_4SO_2$-
R = *p*-$NO_2C_6H_4SO_2$-

703

704: R′ = H, CH_3



705 706

cyclization of **705** followed by triphenyl phosphine treatment to give the oxindole **706** in 34% yield has been reported by Döpp.[606] Interestingly, 2,4,6-tri-*t*-butylnitrobenzene, when photolyzed in benzene, gave a 36% yield of oxindole with *no* hydroxyoxindole being reported.[607]

IX. The Indole Alcohols

A. Pyrrole-Ring Substituted

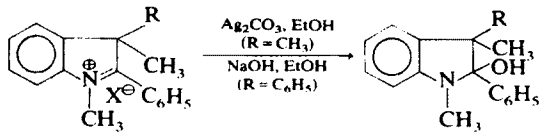
1. *2-Indolinols*

a. INTRODUCTION. Because of limitations imposed by the synthetic routes usually employed, the known 2-indolinols are generally 3,3-disubstituted derivatives with an acyl or alkyl substituent on the indoline nitrogen.

b. SYNTHESIS

(1). *Sodium–Alcohol Reduction of Oxindoles.* Ciamician and Piccinini prepared[610] 1,3,3-trimethyl-2-indolinol by reduction of the corresponding trimethyloxindole, a procedure which has been more recently used by Robinson.[611a,b] Kolosov and Preobrazhenskaya obtained the 5-methoxy derivative of the above indolinol in 33% yield as a by-product during the preparation of 1,3,3-trimethyl-5-methoxyindoline. 1,3-Dimethyl-3-ethyl-5-methoxy-2-indolinol resulted in 24% yield in an analogous reduction.[357]

(2). *Action of Hydroxide Ion on Indolenine Salts.* 2-Indolinols are formed on treatment of indolenine methiodide salts (e.g., **707**) with hydroxide ion. This method was apparently first used[612] by Brunner in 1896 for the preparation of 1,3,3-trimethyl-2-indolinol. The same procedure has also been used by Garry[613] to obtain 1,3-dimethyl-2,3-diphenyl-2-indolinol (**708a**), by Leuchs and co-workers[614] in their synthesis of 1,3,3-trimethyl-2-phenyl-2-indolinol (**708b**) and by Robinson[611a,b] for the preparation of the latter compound and of 2-*t*-butyl-1,3,3-trimethyl-2-indolinol. In all reported cases the yields were generally good.



707

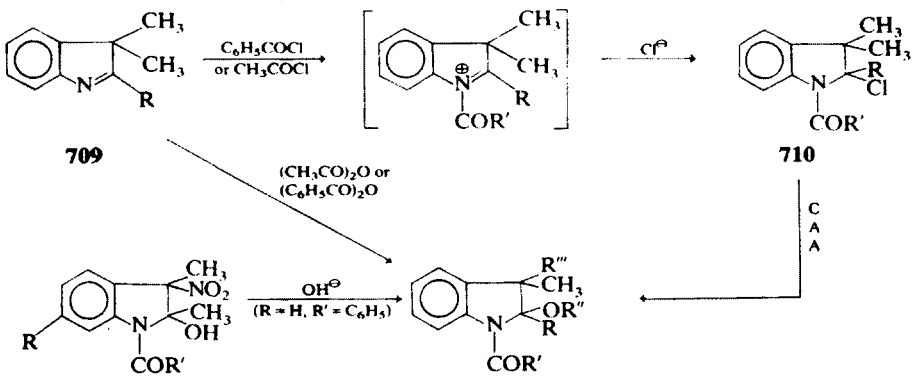
708a; $R = C_6H_5$
708b; $R = CH_3$

Neber and co-workers obtained[615] 1,2-diphenyl-3,3-dimethyl-2-indolinol directly on Fischer cyclization of phenyl isopropyl ketone *N,N*-diphenylhydrazone with aqueous HCl in ethanol.

(3). *Reaction of Acid Chlorides with Indolenines.* A second procedure for the conversion of indolenines to indolinols has been described. In 1929, Leuchs and co-workers discovered that the indolenines **709** can be converted via **710** conveniently and in high yield to the 1-acyl-2-indolinols **711** by treatment with acid chlorides under the usual Schotten–Baumann conditions[614] (Scheme 65). With the acid chloride in benzene, the intermediate 1-acyl-2-chloroindoline **710** could be isolated.[617,618] On treatment with methoxide[617] or phenoxide[618] ion, the methyl or phenyl ethers of the 1-acyl-2-indolinol **712** resulted. When the silver salt of benzoic or acetic acid was used, the appropriate 1-acyl-2-indolinol ester **713** was formed.[617,618] These esters could also be produced directly by the action of acetic or benzoic anhydride on the indolenines.[614] The ethers or esters could be hydrolyzed to the 1-acyl-2-indolinol with 90% acetic acid.[614,618]

(4). *Miscellaneous.* In the course of a study of the nitration of 1-benzoyl-2,3-dimethylindole, Plant and Tomlinson isolated a nitroalcohol to which they assigned[619] the structure **714** ($R' = C_6H_5$). Another stable nitroalcohol was later isolated by Plant and co-workers during the nitration of 1,6-diacetyl-2,3-dimethylindole[620] and was likewise assigned a 3-nitro-2-indolinol structure **715**. Confirmatory evidence for these structures has been produced by Kershaw and Taylor.[621] On alkaline hydrolysis **714** gave *trans*-1-benzoyl-2,3-dimethyl-2,3-indolinediol (**716**), N_2O_4, and products of pyrrole ring cleavage (see Section IX.A.3.a).

Buchardt and co-workers have reported[622] the synthesis of 1-acetyl-2-indolinol (**724**) in 66% yield by photochemical ring contraction of 2-methylquinoline *N*-oxide (**717**) (Scheme 66). Quinoline *N*-oxides lacking the 2-methyl substituent (e.g., **718**) yielded 1-formyl-2-indolinols[623] **725**. The presence of electron-releasing substituents in the 6-position of these quinolines favored a competing reaction, formation of carbostyrils, and reduced the yield of indolinols. The authors proposed[623] the following mechanism: oxaziridine intermediates **719** undergo either a photochemical or thermal ring opening to the dipolar ion **720** which can form a

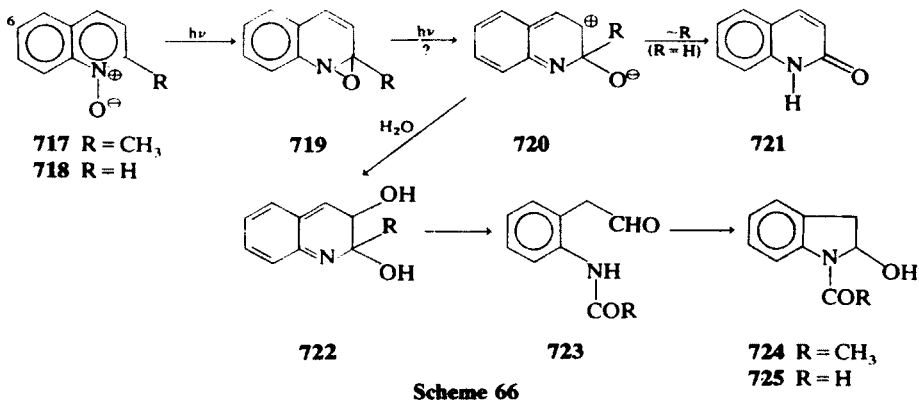


714; R = H, R′ = CH_3 or C_6H_5
715; R = $COCH_3$, R′ = CH_3

R = H or R, R′ = CH_3 or C_6H_5
711; R″ = H, R‴ = CH_3
712; R″ = CH_3 or C_6H_5, R‴ = CH_3
713; R″ = $COCH_3$ or COC_6H_5, R‴ = CH_3
716; R = CH_3, R′ = C_6H_5, R″ = H, R‴ = OH(trans)

Scheme 65

carbostyril **721** by a hydride shift or a 2-indolinol, **724** or **725**, by hydration to **722** and ring opening to the *o*-*N*-acylphenylacetaldehyde **723**, an open-chain tautomer of the indolinols.

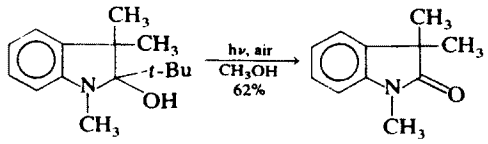


717 R = CH_3
718 R = H

Scheme 66

Galanov and Pavlova have prepared[616] 1-ethyl- or 1-phenyl-2-phenyl-3,3-dimethylindolin-2-ol by addition of phenyllithium to 1-ethyl- or 1-phenyl-3,3-dimethyloxindole. These on treatment with acid ($HClO_4$, HCl, or CCl_3CO_2H) produced indolinium salts.

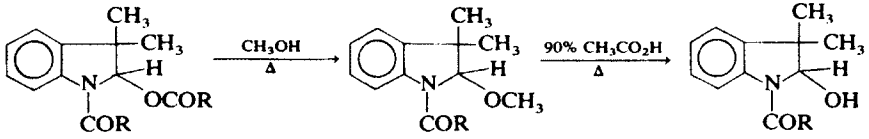
c. Reactions. Secondary 2-indolinols, which are in equilibrium with their tautomers, the aminoaldehydes, might be expected to undergo ready



726 **727**

oxidation to oxindoles. Brunner has demonstrated[612] that Tollens' reagent effects the oxidation of 1,3,3-trimethyl-2-indolinol to the oxindole. More recently Robinson has reported an interesting air-oxidation of the tertiary 2-indolinol **726** to the oxindole **727** with loss of the *t*-butyl substituent.[611a,b] 2-Indolinols with 2-phenyl or 2-hydrogen substituents are stable.[611a,b]

The ease of replacement by other functional groups is another characteristic of the hydroxyl group in 2-indolinols. Leuchs and co-workers have reported that the *N,O*-diacetyl or *N,O*-dibenzoyl derivatives **728** undergo methanolysis to the 2-methoxyindolines **729** in approximately 70% yield. The latter could be hydrolyzed to the 2-indolinols **730**.[614,618] Both these reactions very likely proceed by an elimination–addition mechanism.



728 R = CH_3 or C_6H_5 **729** **730**

Neber and co-workers have converted 1,2-diphenyl-3,3-dimethyl-2-indolinol into the 2-chloro derivative and thence to a 2-methoxyindoline with methoxide ion.[615]

Surprisingly little has been reported on the dehydration of 2-indolinols. Buchardt and co-workers have, however, described the dehydration of 1-acetyl-2-indolinol to *N*-acetylindole with acid.[622]

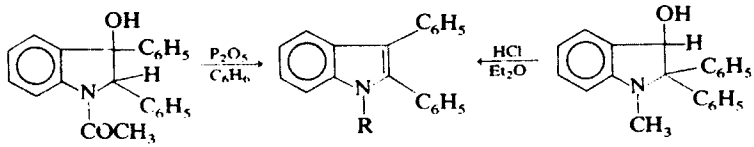
2. *3-Indolinols, Synthesis and Reactions*

Giovaninni and Lorenz have reported the synthesis of 3-hydroxyindoline in 5 and 10% yield, respectively, using lithium aluminum hydride reduction[624,625] and catalytic hydrogenation[624] of indoxyl. Reduction of isatin or dioxindole with lithium aluminum hydride gave 3-hydroxyindoline in 21[624] and 15%[625] yields, respectively, but also produced

indole, indigo, and indirubin.[624] *N*-Methylisatin, *N*-methyldioxindole, or *N*-formylindoxyl gave none of the expected *N*-methyl-3-hydroxyindoline, although this compound could be obtained in nearly quantitative yield by methylation of 3-hydroxyindoline.[626] The reduction of *N*-formyl-2,2-dimethylindoxyl with lithium aluminum hydride did, however, give the expected 3-indolinol in 43% yield.[626]

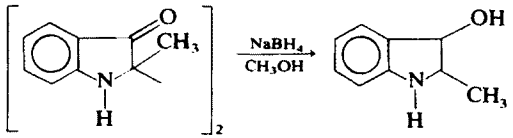
Hinman and Lang obtained 3-hydroxyindoline in only 12–14% yield using Giovaninni and Lorenz's hydride procedure for the reduction of isatin.[627] They were unable to reduce indoxyl-*O*-acetate to this compound with lithium aluminum hydride, sodium borohydride or by catalytic reduction. Interestingly, they reported that the methiodide of 3-hydroxyindoline could not be dehydrated even under the most strenuous acidic conditions.

Witkop and Ek prepared 1-methyl-2,2-diphenyl-3-indolinol (**733**) in excellent yield by the lithium aluminum hydride reduction of the corresponding indoxyl.[628] The diphenyl-3-indolinol **731** was prepared by Pretka and Lindwall from the reaction of phenylmagnesium bromide with 1-acetyl-2-phenylindoxyl.[629] Both these 3-indolinols yield the corresponding 2,3-diphenylindole **732** on dehydration, the former by rearrangement.[628,629] 3-Indolinol itself was reported to be stable to acid and base when pure, though it is converted to indole on melting.[624]



731 **732** R = CH_3 or $COCH_3$ **733**

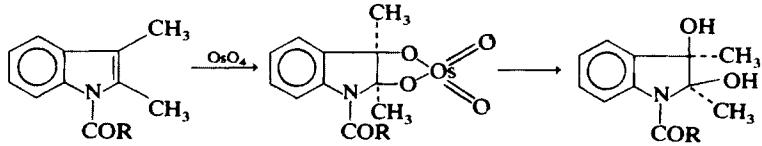
Hassner and Haddadin have reported[630] a novel synthesis of 2-methyl-3-indolinol (**735**) in practically quantitative yield on cleavage of 2,2′-dimethyl-2,2′-diindoxyl (**734**) produced by oxidation of 2-methylindoxyl) with sodium borohydride. The product, consisting of one part *cis* to four parts *trans*, was considered to arise from a hydride-induced cleavage as shown. With acid, the product mixture yielded 2-methylindole.[630]



734 **735**

3. *2,3-Indolinediols*

a. SYNTHESIS. On treatment of *N*-acetyl- or *N*-benzoyl-2,3-dimethylindole (**736**) with osmium tetroxide in pyridine–benzene, Ockenden and Schofield obtained[631a,b] quantitive yields of the corresponding osmic esters **737**. These on hydrolysis gave the *N*-acyl *cis*-2,3-diols, **738**, in fair yield. The reaction was also successful with the *N*-acetyl derivatives of 2,3-diphenylindole and of 2,3,5-trimethylindole, although it failed with *N*-unsubstituted indoles.



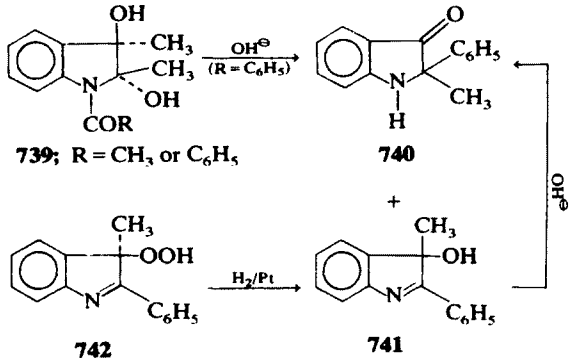
736; R = CH_3 or C_6H_5 **737** **738**

Much earlier, a 2,3-diol of 2,3-dimethylindole had been obtained[632] by Plant and Whitaker as a by-product in the nitration of 1-acetyl-2,3-dimethylindole in acetic acid. On the basis of its melting point, Ockenden and Schofield assumed it to be the same glycol which was obtained in their osmium tetroxide hydroxylation.[631a,b] Atkinson and co-workers showed,[633] however, that the glycol from the nitration reaction, which they were able to obtain in 23% yield, was only slowly cleaved with periodate, depressed the melting point of the *cis*-glycol, and exhibited a different ir spectrum. Therefore they assigned the *trans* configuration **739** (R′ = CH_3) to the diol produced by nitration, considering it to arise on hydrolysis of a nitroalcohol intermediate **714** (R′ = CH_3). Although such an intermediate could not be isolated in the nitration of *N*-acetyl-2,3-dimethylindole, one could be obtained from the corresponding *N*-benzoyl derivative **714** (R = C_6H_5).[632,633]* On hydrolysis it afforded, in addition to products of pyrrole ring cleavage, the *trans*-glycol **739** (R = C_6H_5) in 57% yield.[633] This same glycol was also produced on peracetic acid oxidation of 1-benzoyl-2,3-dimethylindole.[633] Atkinson and co-workers considered it likely that some *cis*-glycol is also produced on hydrolysis of **714** (R′ = C_6H_5), but because of its greater sensitivity to oxidation, it undergoes ring opening to an *o*-acylaminoacetophenone.

It has been claimed that the 2-methyl derivative of *N,N*-dimethyltryptamine on treatment with 10% hydrogen peroxide gives the 2,3-indolinediol *N*-oxide.[634]

* A stable nitro alcohol from 1,6-diacetyl-2,3-dimethylindole has also been isolated.[620]

b. REACTIONS. Both *cis*-[621] and *trans*-*N*-acetyl-2,3-dimethylindoline-2,3-diols[633] afforded 2,2-dimethylindoxyl on alkaline hydrolysis, as did *cis*-*N*-benzoyl-2,3-dimethylindoline-2,3-diol. Very unexpectedly, however, the corresponding *trans*-diol **739** ($R = C_6H_5$) gave 2-methyl-2-phenylindoxyl (**740**) and 3-hydroxy-3-methyl-2-phenyl-3*H*-indole (**741**).[621] Compound **741** was synthesized[621] by catalytic oxygenation of 2-phenyl-3-methylindole, followed by catalytic reduction of the resulting indolenine hydroperoxide **742**. On treatment with alkali **741** was converted into the indoxyl, suggesting its intermediacy in the transformation of the glycol to the indoxyl. The mechanism for this interesting rearrangement is still unknown.



B. Side-Chain Substituted

1. *Hydroxymethylindoles (Indole Methanols)*

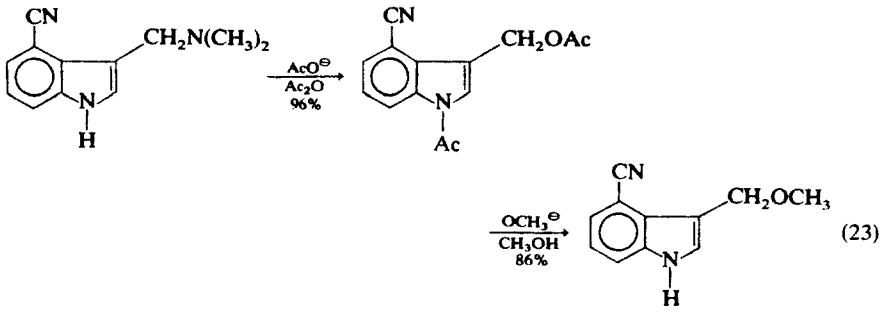
a. 3-HYDROXYMETHYLINDOLE AND DERIVATIVES

(1). *Synthesis*

(a). FROM GRAMINE. In 1937, Madinaveitia claimed[635a,b] that on attempted preparation of gramine methiodide with methyl iodide in alkaline methanol, tetramethylammonium iodide (quantitative yield) and 3-methoxymethylindole were obtained. When the quarternization was effected with ethyl iodide in alkaline ethanol, the corresponding ethoxy derivative resulted. The proposed mechanism involved rapid hydrolysis of initially formed gramine quaternary salts to 3-hydroxymethylindole followed by alkylation. Although he prepared 3-hydroxymethylindole in 90% yield using hydrogenation of indole-3-aldehyde with Adams' catalyst, he failed to demonstrate that it could be alkylated under the reaction conditions used. On the basis of later work[636,637] it now appears that

Madinaveitia most probably isolated 3-hydroxymethylindole—not the ethers—from the gramine salts.

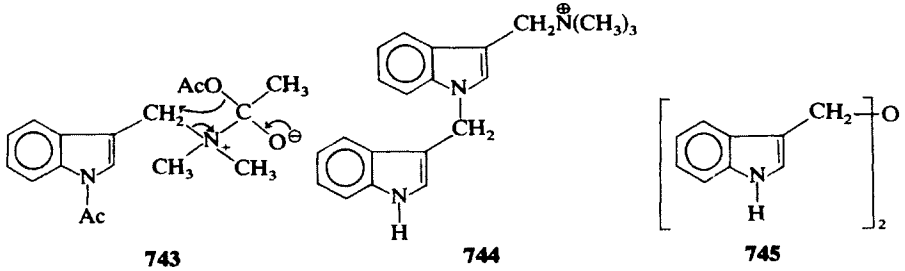
Using an inverse addition procedure, Geissman and Armen prepare the first homogeneous sample of gramine methiodide.[636] Treatment of this with methoxide or ethoxide ion provided the first pure samples of the methyl and ethyl ethers of 3-hydroxymethylindole. Treatment of gramine methiodide with acetic anhydride afforded 1-acetyl-3-acetoxymethylindole. The same compound could be obtained[636] by the action of acetic anhydride and sodium acetate on gramine itself. Although these authors considered **743** a likely intermediate, a methylene–indolenine intermediate is more probable [see Section IX.B.1.a.(2)]. Leete and Marion raised the yield in this reaction to 88% and showed that this material on treatment with sodium hydroxide in methanol or ethanol gave the methyl and ethyl ethers of 3-hydroxymethylindole in good yield.[637] These reactions are illustrated (eq. 23) by Uhle and Harris's preparation[639] of 4-cyano-3-methoxymethylindole from 4-cyanogramine.



(23)

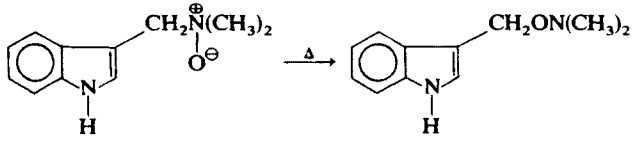
Leete and Marion also found that a reliable and convenient preparation of 3-hydroxymethylindole was achieved by subjecting gramine methiodide to alkaline hydrolysis in a two-phase ether–water system. Yields of 66% were reported. This reaction failed in the case of 1-methylgramine, where only 1,1′-dimethyl-3,3′-diindolylmethane was obtained. Thesing showed[638] that gramine methiodide or methosulfate with one-half equivalent alkali in aqueous solution gave 3-hydroxymethylindole together with the *N*-alkyl gramine salt **744** and minor amounts of the ether **745**.

Gramine *N*-oxide **746**, first prepared by Henry and Leete,[640] who treated gramine with ethanolic hydrogen peroxide, can be converted to ethers of 3-hydroxymethylindole simply by refluxing in alcohols, preferably with added alkoxide ion. Using the latter procedure, the methyl, ethyl, and isobutyl ethers of 3-hydroxymethylindole were obtained in yields of 63, 59, and 44%, respectively. Treatment of gramine oxide with



743 744 745

aqueous sodium hydroxide in the presence of ether afforded 3-hydroxymethylindole, although in poor yield, and the hydroxylamine derivative **747** on heating.



746 747

(b). FROM INDOLE-3-ALDEHYDES. Although Leete and Marion discovered that 3-hydroxymethylindole cannot be prepared by lithium aluminum hydride reduction of indole-3-carboxaldehyde, indole-3-carboxylic acid, or ethyl indole-3-carboxylate because of its ready hydrogenolysis to skatole, the use of a milder reagent, sodium borohydride in refluxing ethanol, permitted Thesing to obtain a 95% yield of 3-hydroxymethylindole from the aldehyde.[638] Silverstein and co-workers reported, independently, that an 86% yield resulted when the reduction was effected in methanol.[641] Uhle and Harris obtained 4-cyano-3-hydroxymethylindole (82%) when 4-cyanoindole-3-carboxaldehyde was reduced with sodium borohydride in pyridine.[639] They were also able to obtain this alcohol in 64% yield using lithium aluminum hydride in tetrahydrofuran; success in this case was ascribed to the formation of an insoluble product–metal ion complex. Apparently hydrogen bonds may also stabilize a hydroxyl group in indole-3-carbinols against hydrogenolysis with lithium aluminum hydride, for there exist numerous reports on the successful reduction of such indole carbonyl compounds as 3-glyceroylindole (reduction gives indole-3-glycerol) and 3-hydroxyacetylindole (reduction gives indole-3-ethylene glycol).[642] Unless an insoluble product–complex or internal hydrogen bonding can stabilize an indole-3-carbinol system, Leete showed, hydrogenolysis invariably occurs with lithium aluminum hydride unless the indole nitrogen is alkylated.[642] Presumably an elimination–addition mechanism [eq. 25 in Section IX.B.1.a.(2)] is operative.

Using borohydride reduction of the appropriate indole-3-carboxaldehyde, Leete prepared 1-methyl-, 2-methyl- and 1,2-dimethylindole-3-methanol in yields of 86, 88, and 55%, respectively.[642] 2-Phenyl- and 1-methyl-2-phenyl-indole-3-methanol could be obtained analogously. Lithium aluminum hydride reduction was successful with 1-methyl-, 1,2-dimethyl-, and 1-methyl-2-phenyl-indole-3-carboxaldehyde, although reduction to skatoles occurred in the absence of an *N*-methyl group. Noland and Reich, however, found that the reduction of 1-methyl-5-bromoindole-3-aldehyde with lithium aluminum hydride gave the corresponding indole-3-methanol in only 6% yield.[643]

Lithium borohydride, which possesses the ether solubility of lithium aluminum hydride but is generally less reactive, was used by Ames and co-workers to reduce a number of acyl indoles.[644] They successfully reduced indole-3-aldehyde and its 1-acetyl and 1-methyl derivatives at room temperature in tetrahydrofuran, the yields for the first two reactions being 90 and 50%. 1-Acetyl-3-hydroxymethylindole could be deacetylated with ethanolic triethylamine at room temperature.

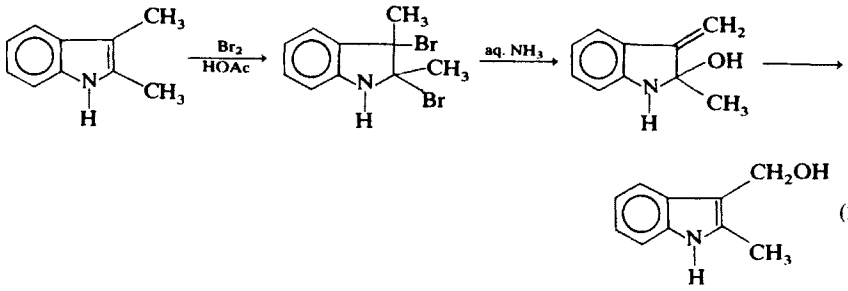
Although Madinaveitia reported[635a,b] that indole-3-carboxaldehyde could be reduced catalytically using Adams's catalyst, Leete could not obtain 3-hydroxymethylindole using this or similar hydrogenation procedures.[642] Leete did establish,[642] however, that 3-hydroxymethylindole is stable to the reduction conditions employed by Madinaveitia.

(c). OTHER METHODS. In 1932 Mingoia reported[645] that the reaction of indolemagnesium bromide with trioxymethylene in ether gave an alcohol, of melting point 158°, to which he assigned the 3-hydroxymethylindole structure. The Grignard derivative of 2-methylindole likewise gave 2-methyl-3-hydroxymethylindole. In view of the high melting points reported by Mingoia for these materials and the known lability of indole-3-methanols to the acidic conditions employed in the work-up procedures, Leete[642] and Thesing[638] have suggested that the products were 3,3'-diindolylmethanes. Indeed, Thesing was able to isolate 3,3'-diindolylmethane (mp 156–159) in 20% yield on repeating Mingoia's procedure. Although Mingoia later reported[646] a revised melting point (88°) for his 3-hydroxymethylindole, his work must be accepted with reservation.

Runti has obtained[647] 3-hydroxymethylindole in 82% yield on reaction of indole with paraformaldehyde. With piperidine in alkaline methanol, it is converted in good yield into 3-piperidinylmethylindole, supporting the intermediacy of 3-hydroxymethylindoles in the Mannich reaction.[647,648]

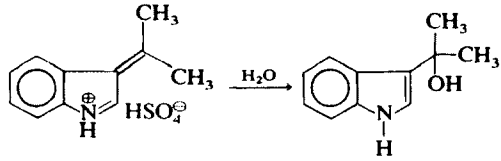
Plant and Tomlinson have described[619] an interesting transformation of 2,3-dimethylindole into 2-methyl-3-hydroxymethylindole using bromine in acetic acid followed by aqueous ammonia. Although a rational

mechanism (eq. 24) was proposed for this oxidation, it seems likely—in view of the high melting point (225°) reported by the authors—that their assignment is in error and that 2,2'-dimethyl-3,3'-diindolylmethane was isolated instead.



(24)

The hydration of the isopropylidine indolenine salt (**748**) to produce α,α-dimethyl-3-hydroxymethylindole (**749**) has been reported[649] by Joule and Smith.



748 **749**

(2). *Reactions*

(a). HYDROLYSIS AND SOLVOLYSIS. The instability of 3-hydroxymethylindole and its derivatives to acid and alkali has been well documented. Madinaveitia,[635a,b] Leete,[637,642] and Thesing[638] all describe the sensitivity of the parent compound to dilute acid. Leete and Marion isolated and characterized an oxygen-free polymer formed when 3-hydroxymethylindole was exposed to dilute acid.[637] Refluxing either a neutral or an alkaline aqueous solution of 3-hydroxymethylindole afforded the condensation product, 3,3'-diindolylmethane, in approximately 50% yield.[637] When an aqueous solution of 3-hydroxymethylindole was allowed to stand at room temperature[638,650] for 20 hours, the condensation product formed in 24% yield.[638]

The ease with which formaldehyde is lost from 3-hydroxymethylindoles varies greatly with structure.[642] 1,2-Dimethyl-3-hydroxylindole readily loses formaldehyde in the solid state or on dissolution in methanol at room temperature and yields a diindolylmethane analogous to that above.

2-Methyl-3-hydroxymethylindole required brief refluxing for a similar conversion and 1-methyl- and 2-phenyl-3-hydroxymethylindole were recovered unchanged after refluxing in dilute alkali for two hours. Interestingly, 2-phenyl-3-hydroxymethylindole was quantitatively converted into 2-phenylindole in refluxing in water for 24 hours. In this case, the bulky 2-phenyl group in the product probably prevents the bimolecular reaction with the starting material, the mechanism recently shown[651] to pertain in the formation of diindolylmethanes from indole-3-methanols. Uhle and Harris report that prolonged refluxing of 4-cyano-3-hydroxymethylindole in water afforded 4,4′-dicyano-3,3′-diindolylmethane.[639]

Because of the instability of 3-hydroxymethylindole to acid and base, attempts to acetylate it or prepare its picrate have been unsuccessful.[637] An attempted deacetylation of 1-acetyl-3-acetoxymethylindole in aqueous alkali led to the diindolylmethane; the use of alcoholic alkali led to ethers of indole-3-methanol.[637] When either 3-hydroxymethylindole or its 2-phenyl derivative were refluxed in ethanol containing traces of alkali the 3-ethoxymethyl derivatives resulted. No reaction occurred in the absence of alkali.[642]

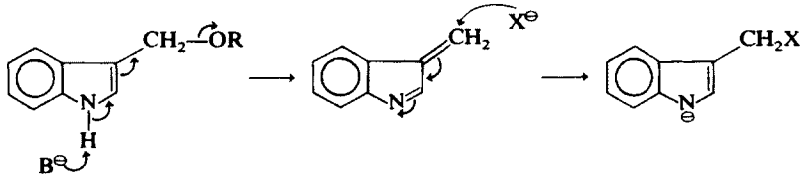
Runti has shown that 3-piperidylmethylindole was formed when 3-hydroxymethylindole was treated with piperidine in alkaline methanol.[647] Albright and Snyder have converted 3-methoxymethylindole to the same Mannich base in 65% yield with piperidine containing methoxide ion. No reaction occurred in the absence of methoxide ion.[652] Treatment of 3-hydroxymethylindole with ethanolic potassium cyanide gave indole-3-acetonitrile in 38% yield.[653] This compound is presumably an intermediate in Runti and Orlando's preparation of indole-3-acetic acid (75% overall yield) by the action of alkaline potassium cyanide on 3-hydroxymethylindole.[648]

(b). HYDROGENOLYSIS. Leete and Marion first reported[637] the surprisingly ready hydrogenolysis of 3-hydroxymethylindole (as well as indole-3-carboxaldehyde, indole-3-carboxylic acid, and ethyl indole-3-carboxylate) to skatole (87%) with lithium aluminum hydride in refluxing ether. The extreme ease with which this reduction occurs can be judged from the fact that when less than an equivalent of hydride was employed to reduce ethyl indole-3-carboxylate, only skatole and unreacted ester could be detected. Ethers of 3-hydroxymethylindole are likewise reduced to skatole in excellent yields.

2,3-Dimethylindole resulted in 80–94% yield when 2-methyl-3-hydroxymethylindole was similarly reduced.[642]

The important observation that *N*-methyl-indole-3-methanols were stable to lithium aluminum hydride led Leete and Marion to propose the

following mechanism (eq. 25) for the hydrogenolysis reaction.[637] Base-catalyzed solvolysis and the reaction with cyanide[648,653] presumably proceed by the same route.

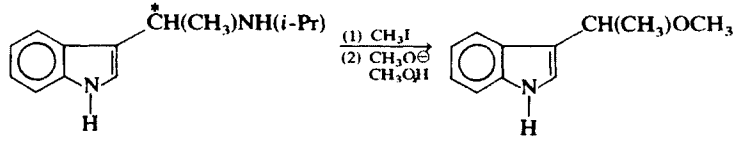


(25)

R = H, alkyl
B = AlH_4, H, CN, OH or OR

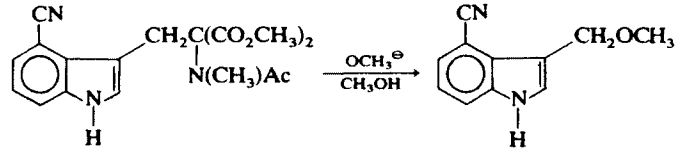
X = H, OR, CN or piperidyl

The methylene–indolenine intermediate may also be implicated in the reaction of gramines or gramine methiodides with hydroxide ion,[635a,b,637,638] alkoxide ion in alcohols,[636,637] or acetate ion in acetic anhydride[636,637,639] and in the reaction of gramine *N*-oxide with hydroxide or alkoxide ion.[640] Support for the formation of this intermediate in at least some reactions of gramine can be found in the experiment of Albright and Snyder, in which the optically active amine methiodide **750** was shown[652] to yield the racemic methyl ether **751**.



750 **751**

The unexpected, quantitative conversion of the N^{α}-methyl-4-cyanotryptophan precursor **752** into 3-methoxymethyl-4-cyanoindole **753** on exposure to sodium methoxide in methanol may also proceed via an elimination–addition mechanism rather than a direct displacement.[639]



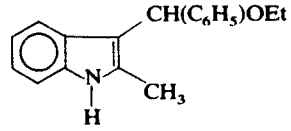
752 **753**

(3). *Synthesis and Reactions of Other Indole-3-methanols.* Ames and co-workers have reported[644] the room temperature reduction of 3-acetylindole with lithium borohydride in tetrahydrofuran which gives 3-(1-hydroxyethyl)indole in 45% yield. At reflux temperature, only the

product of hydrogenolysis, 3-ethylindole, could be isolated. Leete and Marion had earlier reported that when this reduction was performed with lithium aluminum hydride, 3-ethylindole resulted exclusively.[637] Ames and co-workers have also described the preparation of 1-acetyl-3-(1-hydroxyethyl)indole in 60% yield when 1,3-diacetylindole was reduced.

Albright and Snyder prepared[652] the methyl, ethyl, and isopropyl ethers of 3-(1-hydroxyethyl)indole in 93, 95, and 64% yield, respectively, on reaction of 3-(1-dimethylaminoethyl)indole with the appropriate alkoxide ion–alcohol mixtures. They also reported the conversion in 59% yield of the ethyl ether to 3-(1-piperidylethyl)indole on reaction with piperidine containing methoxide ion.

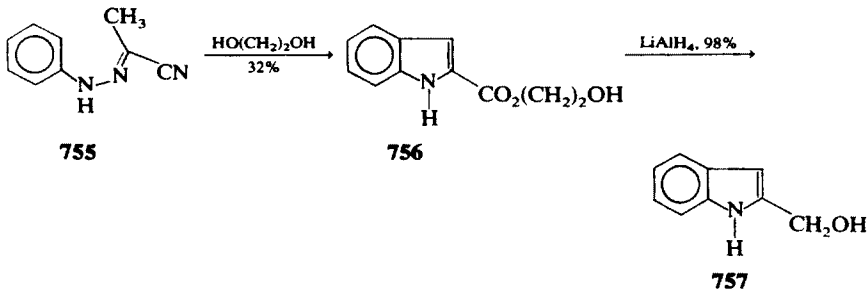
In 1913, Scholtz, using 2-methylindole, benzaldehyde, and ethanolic sodium hydroxide, obtained the ether **754** in unspecified yield,[654] and Albright and Snyder obtained[652] an 80% yield under similar conditions.



754

b. 2-Hydroxymethylindole and its Derivatives

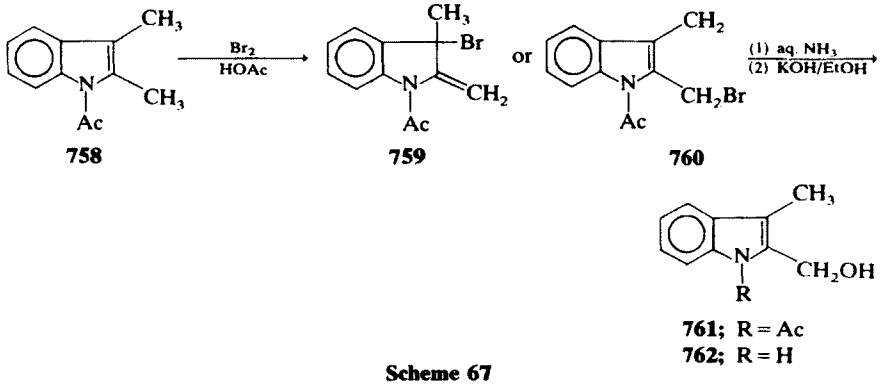
(1). *Synthesis.* The parent compound was first synthesized by Brehm in 68% yield by reduction of 2-carbethoxyindole with lithium aluminum hydride in ether.[655] Taylor[656] and Leete[642] used the same procedure in later preparations. Robinson reported[657] an interesting two-step synthesis of this compound (**757**) by the Fischer rearrangement of the phenylhydrazone of pyruvonitrile (**755**) in ethylene glycol followed by a lithium aluminum hydride reduction of the resulting glycol ester **756**. Overall yields of 32% were reported.



755 **756** **757**

Eiter and Svierak reduced[658] 1-methylindole-2-carboxylic acid with lithium aluminum hydride and obtained 1-methyl-2-hydroxymethylindole in 86% yield.

In 1933, Plant and Tomlinson reported[619] the synthesis of 2-hydroxymethyl-3-methylindole (**762**) from 1-acetyl-2,3-dimethylindole (**758**) using bromination followed by hydrolysis (see also Ref. 659) (Scheme 67). A monobromo intermediate **759** or **760** was isolated on treatment of **758** with bromine in acetic acid. Compound **759** was presumed to hydrolyze initially to a tertiary alcohol, thence to **761** by an allylic rearrangement. In 1950, Taylor confirmed[656] the structure assigned to **762** by showing it to be identical with the lithium aluminum hydride reduction product of ethyl 3-methylindole-2-carboxylate.



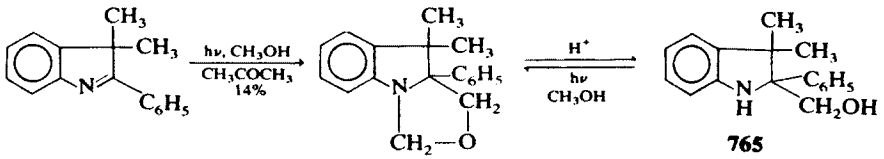
758 **759** **760**

761; R = Ac
762; R = H

Scheme 67

2-Hydroxymethyl-3-methyl-5-nitroindole has been prepared by sodium borohydride reduction of 2-formyl-3-methyl-5-nitroindole produced, in turn, by photooxidation of 2,3-dimethyl-5-nitroindole in acetic acid.[752]

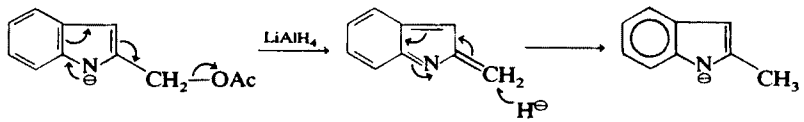
Cerutti and Schmidt have described[660] an interesting acetone-sensitized photoaddition of two moles of methanol to the indolenine **763** to give the ether **764**. Hydrolysis of the ether afforded the product of a formal addition of methanol to the indolenine **765**. Photolysis of this 2-hydroxymethylindole regenerated the ether.



763 **764** **765**

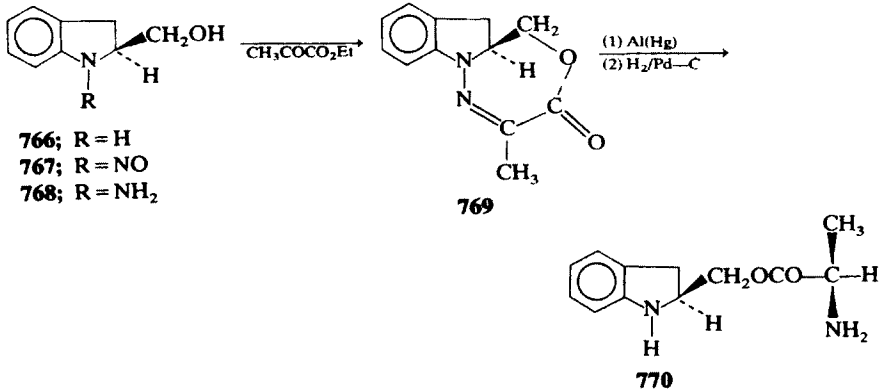
(2). *Reactions.* Unlike its 3-hydroxymethyl isomer, 2-hydroxymethylindole is stable to base.[642,655,656,661] Brehm, examining[655] the possibility that the hydroxymethyl group could be used to block the indole 2-position in the same fashion as a carboxyl group, found that no formaldehyde was eliminated on refluxing 2-hydroxymethylindole for 3 hours in aqueous barium hydroxide. Leete recovered this material unchanged after 15 hours reflux with 10% sodium hydroxide.[642] Both Taylor[656] and Leete[642] have commented, however, on the instability to acid of 2-hydroxymethylindoles. Polymeric material apparently results.[642]

Dolby and Booth also noted[661] the stability of indole-2-methanol toward lithium aluminum hydride. However, they were able to show that some hydrogenolysis of 2-acetoxymethylindole took place with the formation of 2-methylindole (3%) in addition to 2-hydroxymethylindole (80%). This hydrogenolysis, which is prevented by *N*-methylation, is considered to proceed by the mechanism shown (eq. 26).[661]



(26)

Corey and co-workers employed *S*(+)-2-hydroxymethylindoline (**766**) in an ingenious asymmetric synthesis of α-amino acids from α-keto esters.[662a] The hydrazine alcohol **768** is prepared by nitrosation and reduction (Scheme 68), and a two-step reaction of **768** with the keto ester forms the imine lactone **769**. Aluminum amalgam effects a stereoselective reduction of the imine group of **769**, and hydrogenolysis of the resulting hydrazine produces the amino acid ester (**770**). Hydrolysis regenerates the chiral reagent and provides the *D*-amino acid, with 89–90% optical purity. The reagent, **766**, was synthesized in 42% overall yield from ethyl



766; R = H
767; R = NO
768; R = NH_2

769

770

Scheme 68

indole-2-carboxylate by tin hydrochloric acid reduction, followed by lithium aluminum hydride reduction and resolution with mandelic acid. Using 2-(1-hydroxyethyl)indoline in place of **766** in the above scheme afforded even greater stereoselectivity in the imine reduction step.[662b]

2-Hydroxymethylindole has been reported to induce hypoglycemia.[663]

c. OTHER HYDROXYMETHYLINDOLES. Hofmann and Troxler have reported[664a,b] the synthesis of 4-, 5-, 6-, and 7-hydroxymethylindoles by means of lithium aluminum hydride reduction of the appropriate indolecarboxylic acid or methyl ester. Hardegger and Corrodi have reported[665] the synthesis of 4-hydroxymethylindole in 96% yield by the same route.

2. *Indole Ethanols*

a. INDOLE-3-ETHANOL (TRYPTOPHOL) AND DERIVATIVES

(1). *Importance*

(a). TRYPTOPHOL. Tryptophol was isolated[666] in 1912 by Ehrlich in nearly quantitative yield from yeast fermentation of tryptophan. It has also been isolated from beer[667a–c] and plant seedlings including cucumber[668] and *Helianthus*.[669] It is reported to function as a growth regulator in these plants[668–670] and probably arises from indole-3-acetaldehyde.[669,671] Tryptophol has been reported as one of the many products formed on uv irradiation of an aqueous solution of tryptophan.[672]

(b). OTHER TRYPTOPHOLS. 5-Hydroxytryptophol, as the glucuronide, has been shown to be one of the major metabolites of serotonin in the rat[673] and has been detected in carcinoid humans.[674] The addition of NADH to serotonin-treated rat liver homogenate increases the proportion of 5-hydroxytryptophol relative to combined 5-hydroxyindole-3-acetaldehyde and 5-hydroxyindole-3-acetic acid.[675a,b] 5-Hydroxytryptophol is formed by blood platelets after the release of serotonin mediated by reserpine and thrombin[676a,b] and is found along with 5-methoxytryptophol in the bovine pineal gland[435] and the toad *Bufo alvarius*.[414] The latter compound, as well as its *O*-acetate, has an inhibitory effect on estrus in immature rats similar to melatonin.[687] Although it is metabolized in the rat, the expected 5-methoxy-6-hydroxyindole-3-acetic acid has not been found.[677]

Octahydrotryptophol and its 1-alkyl and 1,2-dialkyl derivatives have been patented as corrosion inhibitors.[678] Another patent[679] covers the synthesis of a series of esters of *N*-alkyl octahydrotryptophols.

(2). *Synthesis*

(a). SODIUM–ALCOHOL REDUCTION. In 1930, Jackson reported the first chemical synthesis of tryptophol,[680] hitherto available only from tryptophan fermentation,[666] by means of Bouveault–Blanc reduction (Na/EtOH) of the methyl or ethyl esters of indole-3-acetic acid. Yields of 81% were reported.

In the hands of Hoshino and Shimodaira,[244a,b] this procedure gave tryptophol in 46% yield and 5-ethoxy-, 5-methoxy-, and 2-methyltryptophol in 33, 29, and 32% yield, respectively.

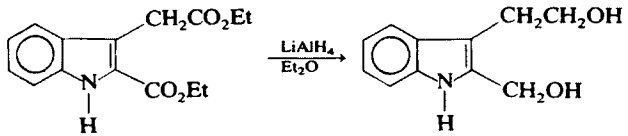
Tacconi has described[681] the preparation of α-methyltryptophol and its 5-methoxy derivative in 59% yield by reduction of the corresponding oxindole derivatives with sodium in refluxing *n*-propanol. The oxindoles were conveniently obtained by reduction of the isatylideneacetones with sodium borohydride in aqueous ethanol. A one-step lithium aluminum hydride reduction of isatylideneacetone to α-methyltryptophol (32%) has recently been reported.[739]

(b). LITHIUM ALUMINUM HYDRIDE REDUCTION

1. Acids, Esters, Acid Chlorides

The Bouveault–Blanc reduction has been replaced in modern practice by the lithium aluminum hydride reduction of indole-3-acetic acids or their esters as a high-yield, convenient route to tryptophols. Snyder and Pilgrim, who in 1948 first employed this procedure, reported[682] obtaining tryptophol in 65% yield from indole-3-acetic acid. The methyl[683] and ethyl[684] esters of this acid have been reduced to tryptophol in yields exceeding 90%. 1-Methyl-,[658] 2-methyl,[685] and 2-phenyltryptophol[686] have been prepared from the corresponding ethyl indole-3-acetates in yields of 73 and 79% for the methyltryptophols. Taylor has reported[656] the preparation of the dialcohol, **772**, required for the structural elucidation of chinchonamine, by reduction of the diester, **771**.

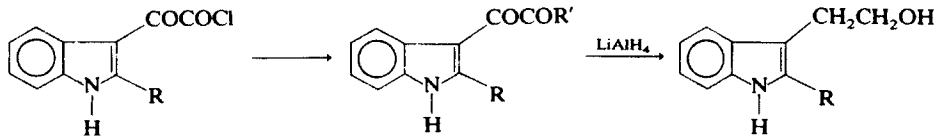
Tryptophols which have been obtained by lithium aluminum hydride reduction of indole-3-acetic acids are 5-benzyloxy- (71%),[231,687] 5-methoxy- (87%),[687,688] and 5-methoxy-6-benzyloxytryptophol (67%)[688]; 1-benzyl-,[689] 1-benzyl-5-methoxy,[329,689] 1-benzyl-β-methyl-,[690] 1-benzyl-5-methoxy-β-methyl,[690] and 1-benzyl-β-ethyltryptophol[689] in yields averaging 80–90%.[329,689]



771 **772**

Reduction of ethyl indole-3-acetates provided Julia and co-workers with the following tryptophols: 1-benzyl and 1-*p*-methoxybenzyl derivatives of 5-methoxy- and 5,6-dimethoxytryptophol (79–91%),[329] β-methyl- and β,β-dimethyltryptophol,[689] 1,β-dimethyltryptophol,[689] and 1-benzyl-2,β-dimethyltryptophol.[329]

One of the most convenient procedures for the preparation of tryptophols is that introduced by Elderfield and Fischer, who described[691a,b] the synthesis of 6-methoxytryptophol in 79% yield by the reduction of 6-methoxyindole-3-glyoxyl chloride with lithium aluminum hydride. This procedure has also been used to obtain 5-benzyloxytryptophol (66%)[673] but was reported to be unsatisfactory in the synthesis of 5-methoxytryptophol[688] and tryptophol[692a] itself, although Najer and co-workers[72] were successful in obtaining a 78% yield of the latter compound using a slow inverse addition procedure. Nogrady and Dole report[692a,b] that tryptophol **777** can be obtained in good yield in a procedure claimed to be especially satisfactory for large-scale operations by the simple expedient of converting the glyoxyl chloride **773** to the glyoxylic acid ester **775** before reduction. This procedure was first employed by Speeter and Anthony.[248] An 85% overall yield is claimed.[692a,b] Earlier, Ames and co-workers employed[268] a similar sequence in reducing the tertiary amide **776** to 2-phenyltryptophol **778**.



773; R = H
774; R = C_6H_5

775; R = H, R' = OEt
776; R = C_6H_5, R' = $N(C_6H_5)_2$

777; R = H
778; R = C_6H_5

Three different groups have reported the synthesis of 5-hydroxytryptophol by the catalytic debenzylation of 5-benzyloxytryptophol, a compound made in turn either by the reduction of 5-benzyloxyindole-3-acetic acid[231,687] or by the glyoxylic chloride route above.[673] Likewise 5-methoxy-6-hydroxytryptophol was prepared by hydrogenolysis of 5-methoxy-6-benzyloxytryptophol.[688]

2. Ketones

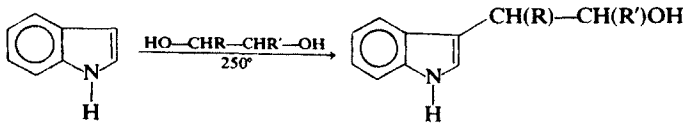
Indole-3-acetone[689,693] and its 1-methyl derivative[689] have been reduced to α-methyltryptophol and its 1-methyl homologue with lithium aluminum hydride.

(c). SYNTHESIS USING ETHYLENE OXIDE AND ITS DERIVATIVES. In 1939, Oddo and Cambieri reported[694] the synthesis of tryptophol and of its

2-methyl derivative in 52 and 68% yield, respectively, from the appropriate indole Grignard compound and ethylene oxide. This procedure had been tried earlier by Hoshino and Shimodaira[244a,b] and somewhat more recently by Snyder and Pilgrim[695]; however, both groups reported poor yields. A recent patent describes[696] the synthesis of α-methyltryptophol using propylene oxide and indolemagnesium bromide.

Julia and co-workers have described two routes to tryptophols using ethylene oxides and indole.[689,690] Tryptophol results in 45% yield from the reaction of indole with ethylene oxide in acetic acid–acetic anhydride followed by saponification of the resulting tryptophol acetate or by the reaction of indole with ethylene oxide in carbon tetrachloride containing stannic chloride. The former procedure has been used to synthesize 5-bromotryptophol.[697] When the latter procedure was extended to the reaction between indole and either propylene oxide or but-1-ene oxide, mixtures of α- and β-methyltryptophol and α- and β-ethyltryptophol resulted in 58 and 50% yield, respectively.

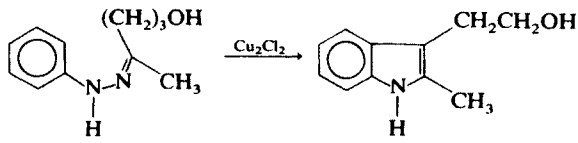
(d). MISCELLANEOUS SYNTHESES. Johnson has described[698] the synthesis of tryptophol (13% yield), α-methyltryptophol, and α,β-dimethyltryptophol from indole and the appropriate glycol by heating in an autoclave (eq. 27). When glycol monoethyl ethers were employed, tryptophol ethyl ethers resulted.



(27)

Grandberg and co-workers achieved the direct synthesis of 2-methyltryptophol **780** in a Fischer synthesis with phenylhydrazine and 4-ketopentanol. The intermediate phenylhydrazone **779** was rearranged with cuprous chloride to the tryptophol in 70% yield or with acetyl chloride in dioxane–carbon tetrachloride to its *O*-acetate in 33% yield.[699] An analogous synthesis of the *N*-*p*-chlorobenzoyl derivative of 2-methyl-5-methoxytryptophol has been reported in a Japanese patent.[700]

5-Nitrotryptophol results in 5% yield as a by-product of hydrolysis in

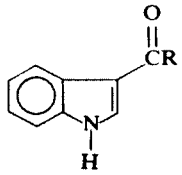


779 **780**

the Fischer cyclization of γ-chlorobutyraldehyde *p*-nitrophenylhydrazone[403]

Tryptophol resulted in quantitative yield on reduction of **781** with hydrogen and Raney nickel in ethanol. *O*-Benzyl tryptophol was produced in 85% yield when sodium borohydride in aqueous pyridine was used in this reduction.[701]

Szmuszkovicz synthesized α,α-dimethyltryptophol in 87% yield from ethyl indole-3-acetate and methylmagnesium iodide. The same product resulted in 48% yield when the acyloin **782** was reduced with lithium aluminum hydride in tetrahydrofuran.[702]



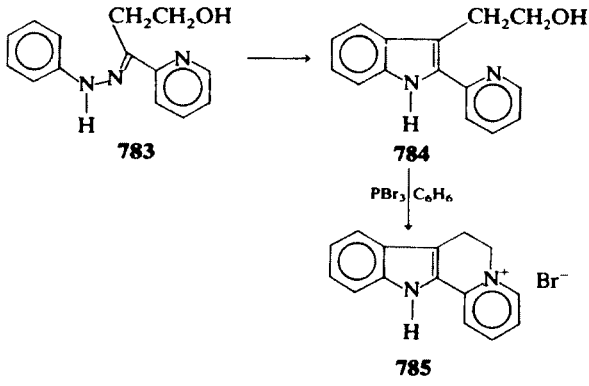
781; R = $CH_2OCH_2C_6H_5$

782; R = $C(CH_3)_2OH$

(3). *Reactions.* Most tryptophols have been synthesized as intermediates for one of the earliest yet most convenient tryptamine syntheses: phosphorus tribromide in ether or benzene converts tryptophols into 3-(2-bromoethyl)indoles in good yield and subsequent reaction with ammonia or amines makes available a wide array of tryptamines[329,683,689] (see also Part Two, Chapter VI of this monograph).

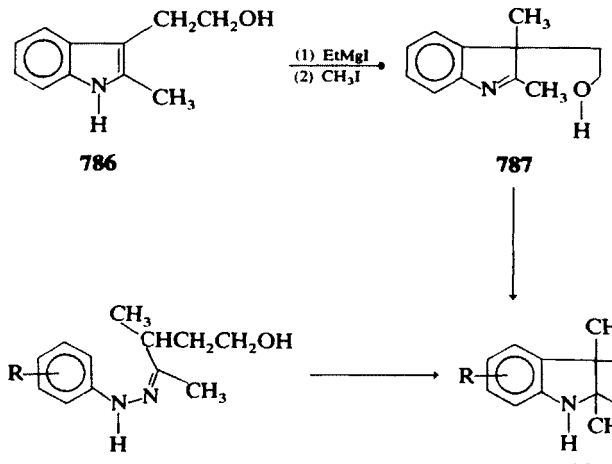
Suvorov and co-workers have described the synthesis of two tryptophol glycerol ethers (see Section IX.B.8) from tryptophyl bromide[703,704] or tosylate.[704]

The reaction of 3-(2-bromoethyl)indoles with pyridine or substituted isoquinolines has been used by Elderfield and co-workers in their synthesis of tetra- and pentacyclic β-carbolines.[684,691a,b] Sugasawa and



co-workers have described[705] the first synthesis of the 9*H*-pyrido(3,4-*b*)-indole **785**; on treatment of the 2-(2-pyridyl)tryptophol **784** with phosphorus tribromide in benzene, cyclization to **785** occurs spontaneously. Compound **784** was also made from 2-(2-pyridyl)indole by a number of steps[705] or directly by Fischer cyclization of the phenylhydrazone **783**.[706]

Tryptophols can also be cyclized to the important furo(2,3-*b*)indole system found in the alkaloid physovenine (**793**). Nagazaki effected[685] the cyclization of 2-methyltryptophol (**786**) to **788** using ethylmagnesium iodide followed by methyl iodide, a reaction proceeding via the indolenine **787**.



786 **787**

789; R = 2- or 4-CH_3, 2- or 4-OCH_3, 4-Br

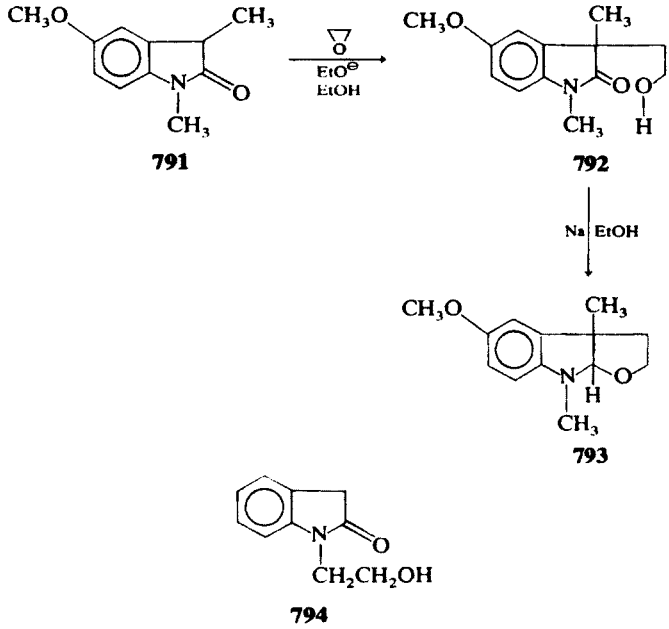
788; R = H

790; 5- or 7-CH_3, OCH_3; 5-Br

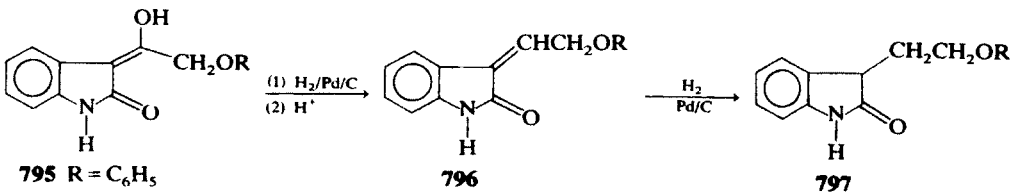
Grandberg and Dashkevich have recently reported[707] the synthesis of related tricyclic ethers **790** by cyclization of the phenylhydrazone **789**, a reaction generating similar indolenine intermediates.

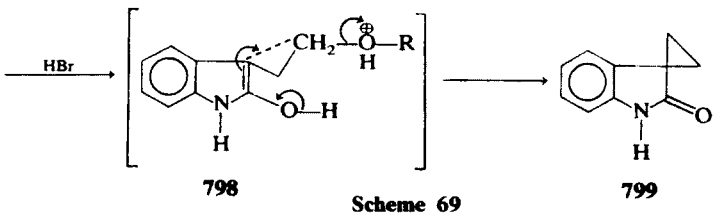
Physovenine has been synthesized[708] by Longmore and Robinson, who used reductive ring closure of the oxytryptophol **792** made in turn from the oxindole **791** and ethylene oxide. Interestingly, oxindole itself with ethylene oxide and ethoxide ion did not give the expected oxytryptophol but rather compound **794**, the product of *N*-alkylation.[709]

In an unsuccessful attempt to prepare oxytryptophol, Wenkert and Blossey employed[709] a two-step hydrogenation procedure using the Claisen-condensation product **795** from oxindole and ethyl phenoxyacetate (Scheme 69). Conversion of **797** to 3-(2-bromoethyl)oxindole with hydrogen bromide failed and gave instead the spiro oxindole **799**, presumably via **798**.

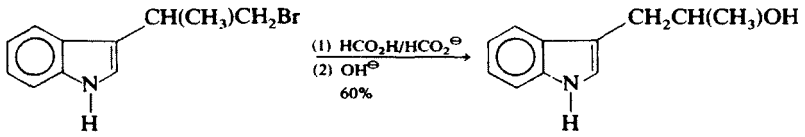


Julia and co-workers have reported[689] the occurrence of an interesting rearrangement also involving participation of the indole nucleus. When β-alkyl-substituted tryptophyl bromides were solvolyzed in formate buffer, the products, after saponification, were found to be α-alkyl-substituted tryptophols. Such rearrangements were described for β-methyltryptophyl bromide (eq. 28), 1,β-dimethyltryptophyl bromide, and β,β-dimethyltryptophyl bromide.





Scheme 69

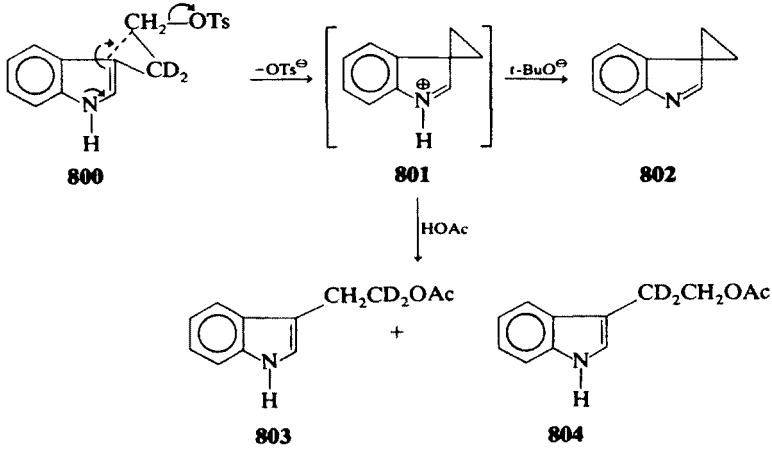


(28)

Even though a mixture of two isomeric alcohols results on reaction of indole with propylene oxide or but-1-ene oxide, conversion to bromides and solvolysis afforded nearly pure α-alkyl alcohols.[689] Likewise, α-substituted tryptamines can be prepared from mixtures of α- and β-alkyltryptophol by converting the latter to a bromide mixture and solvolyzing in ammonia or amines.

The groups of Julia[690] and Closson[710] have reported kinetic data which corroborate a very sizable anchimeric assistance by the indole nucleus in the solvolysis of tryptophyl tosylates. Depending on the substitution pattern of the benzene ring, indole nitrogen or the side chain, rate enhancements of 10^3–10^4 were observed relative to such models as *p*-anisylethyl tosylate[690] or α-naphthylethyl tosylate.[710]

Closson and co-workers have reported[710] that α,α-D_2-tryptophyl tosylate **800** on acetolysis yields an equimolar mixture of the α,α- and β,β-dideuterotryptophyl acetates (**803** and **804**), a rearrangement implying the intermediacy of **801** (Scheme 70). When unlabeled **800** was treated in tetrahydrofuran with one equivalent of *t*-butoxide ion, the spiroindolenine **802** could be isolated. This extremely reactive compound gave only tryptophol or its ethyl ether when exposed to water or ethyl alcohol, respectively.

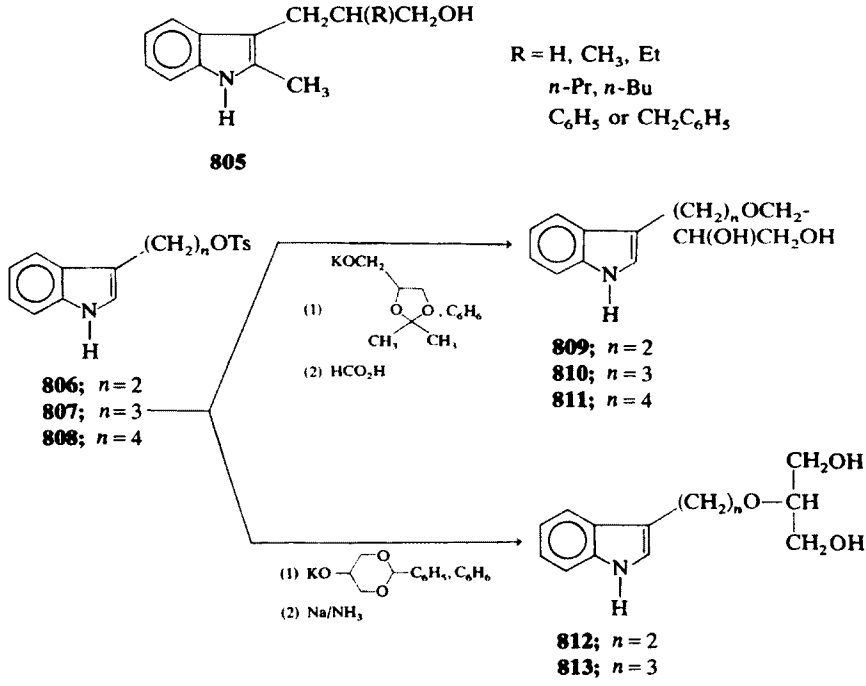


800 **801** **802** **803** **804**

Scheme 70

3. *Indole Propanols*

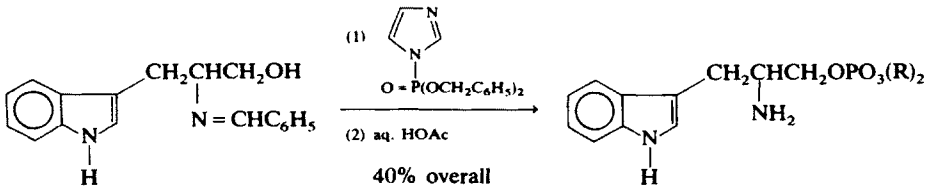
Jackson and Manske, employing a sodium-in-ethanol reduction of methyl indole-3-propionate, achieved[711] the first synthesis of homotryptophol in 67% yield. Lingens and Weiler prepared it in 88% yield as the starting material for a synthesis of homotryptophan by reduction of ethyl indole-3-propionate with lithium aluminum hydride.[712] The synthesis of the *N*-*p*-chlorobenzoyl derivative of 5-methoxyindole-3-propanol has been described in a Japanese patent[700] as resulting on Fischer rearrangement of the *N*-acylated *p*-methoxyphenylhydrazone of 5-hydroxypentanal in ethanol. Mndzhoyan and co-workers have reported[713] the synthesis of a number of indole propanols **805** substituted in the side chain in yields of 90–95% by hydride reduction of the substituted indole propionic acid esters. They also prepared[714] 2-methyltryptophol using a sodium–alcohol reduction. Homotryptophyl tosylate (**807**) has been employed by Suvorov's group in a synthesis of the two possible glyceryl ether derivatives, **810** and **813**, of this alcohol.[703,704] A Japanese patent[715] utilizes the reaction between **807** and a series of secondary amines to produce homotryptamines.



4. *Tryptophanol and its Derivatives*

Tryptophanol, the alcohol derived by reduction of tryptophan, was first synthesized by Karrer and Portmann who employed a lithium aluminum hydride reduction of L-tryptophan methyl ester. A yield of 90% was reported. Two other groups have reported yields of 63[717] and 67%[718] for this reaction. Vogl and Pöhm reduced DL-tryptophan with lithium aluminum hydride and obtained DL-tryptophanol in 70% yield.[719] Enz has reduced tryptophan methyl ester with sodium in a mixture of ethanol and quinoline at 150–180° and reports a 32% yield.[720] L-Tryptophanol has also been prepared in good yield by the reduction of L-tryptophan ethyl ester with sodium borohydride in 75% ethanol.[721a,b]

Lingens and co-workers have shown that tryptophanol phosphate (**816**), prepared from *N*-benzylidene-D,L-tryptophanol (**814**) as shown in Scheme 71,[717] is not a tryptophan precursor in a number of microorganisms which utilize indole glycerol phosphate.[722] Dehydration and transamination steps might have converted the glycerol derivative to the β-aminopropanol derivative.[723]



Scheme 71

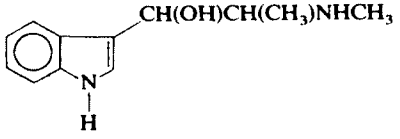
Koo and co-workers obtained 5-benzyloxy-D,L-tryptophanol in 61% yield by reduction of 5-benzyloxytryptophan with lithium aluminum hydride in ether.[231] Shaw prepared 5-methoxy-D,L-tryptophanol in 30% yield by means of an analogous reduction in THF.[65a]

5. *β-Hydroxytryptamines and Miscellaneous Amino Alcohols*

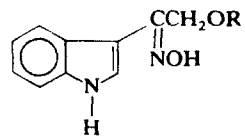
β-Hydroxytryptamines—another important amino alcohol system—result on lithium aluminum hydride reduction of 1-alkylindole 3-glyoxamides (see Section V.B.2)[227,266–268,724] or sodium borohydride or Raney nickel reduction of *N*-unsubstituted 3-β-aminoacylindoles.[725a,b] A recent synthesis employs 3-chloroacetylindole, reacting this with amines, then lithium aluminum hydride, sodium borohydride, or Raney nickel.[726]

The review by Heinzelman and Szmuszkovicz contains (Ref. 286, p. 93) a table on the hypotensive and diuretic activity of a large number of β-hydroxytryptamines. Suvorov's group has synthesized a number of indole analogues of epinephrine, one (**817**) of which is claimed[725a,b,726] to resemble ephedrine quite closely in stimulating the nervous system.

Suvorov's group has also prepared β-aminotryptophol and its ethyl and benzyl ethers by reduction, respectively, of the oximes of 3-hydroxyacetyl-, 3-ethoxyacetyl, or 3-benzyloxyacetylindole with aluminum amalgam[727] (**818**). A series of tertiary γ-hydroxyindole *N,N*-dimethylbutylamines have been synthesized by the addition of γ-dimethylaminopropylmagnesium chloride to 3-benzoylindole or aroyl analogues.[728]



817



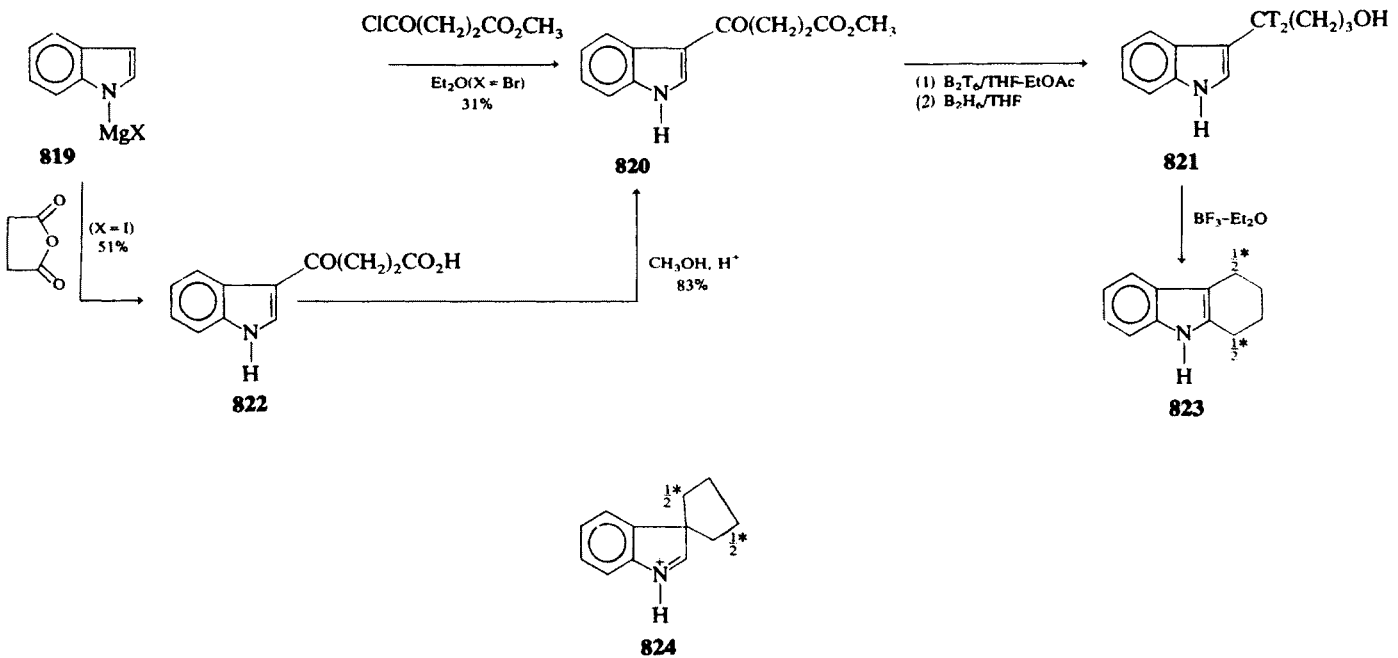
818; R = H, Et or $CH_2C_6H_5$

6. *Indole Butanols*

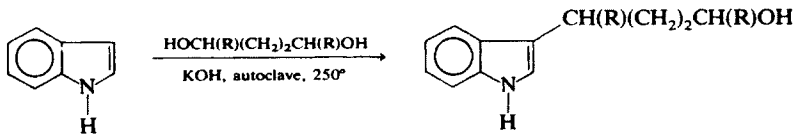
Indole-3-butanol was first prepared[711] by Jackson and Manske, who employed a sodium–alcohol reduction of methyl indole-3-butyrate and obtained the alcohol in 77% yield. A. H. Jackson and co-workers have synthesized[729] both labeled and unlabeled indole-3-butanol using a diborane reduction[730] of the keto ester **820**, which was obtained from **819** and **822** as shown in Scheme 72. A two-step reduction of **820**, first with B_2T_6 in ethyl acetate–THF (the ethyl acetate protects the indole ester function), then with B_2H_6 in THF alone, produced the tritiated indole-3-butanol (**821**). Cyclization with boron trifluoride gave tetrahydrocarbazole (**823**) in 72% yield with the label equally distributed between the 1- and 4-positions, indicating the intermediacy of the spiroindolenine **824** in this cyclization and providing additional evidence for the generalization[731] that electrophilic substitution in the indole nucleus proceeds by way of initial attack at the 3-position.

Indole-3-butanol *O*-tosylate (**808**) has been converted to the glycerol ether **811**, as shown above.[703]

Johnson has reported[698] the synthesis of indole-3-butanol (**825**) and its α,δ-dimethyl derivative **826** from indole and butane-1,4-diol or hexane-2,5-diol, respectively (eq. 29). Indole-3-pentanol and indole-3-hexanol were made in the same way.[698]


ClCO(CH2)2CO2CH3
Et2O(X = Br)
31%
CO(CH2)2CO2CH3
(1) B2T6/THF-EtOAc
(2) B2H6/THF
CT2(CH2)3OH
MgX
819
820
821
(X = I)
51%
CO(CH2)2CO2H
CH3OH, H+
83%
BF3-Et2O
822
823
824

Scheme 72



(29)

825; R = H
826; R = CH_3

7. *Indole Ethylene Glycols and Indole Propanediols*

Indole-3-ethylene glycol (**830**) was synthesized[701] by Suvorov and co-workers according to Scheme 73. On treatment with sodium periodate, the expected indole-3-carboxaldehyde resulted. When **827** was reduced with lithium aluminum hydride, the indole-3-ethylene glycol benzyl ether **832** resulted in 80% yield. Methylation of **827** followed by a Raney nickel hydrogenation and a lithium aluminum hydride reduction afforded the 1-methyl derivative of indole-3-ethylene glycol **831**.[732] A second route via **833** also provided **831**.

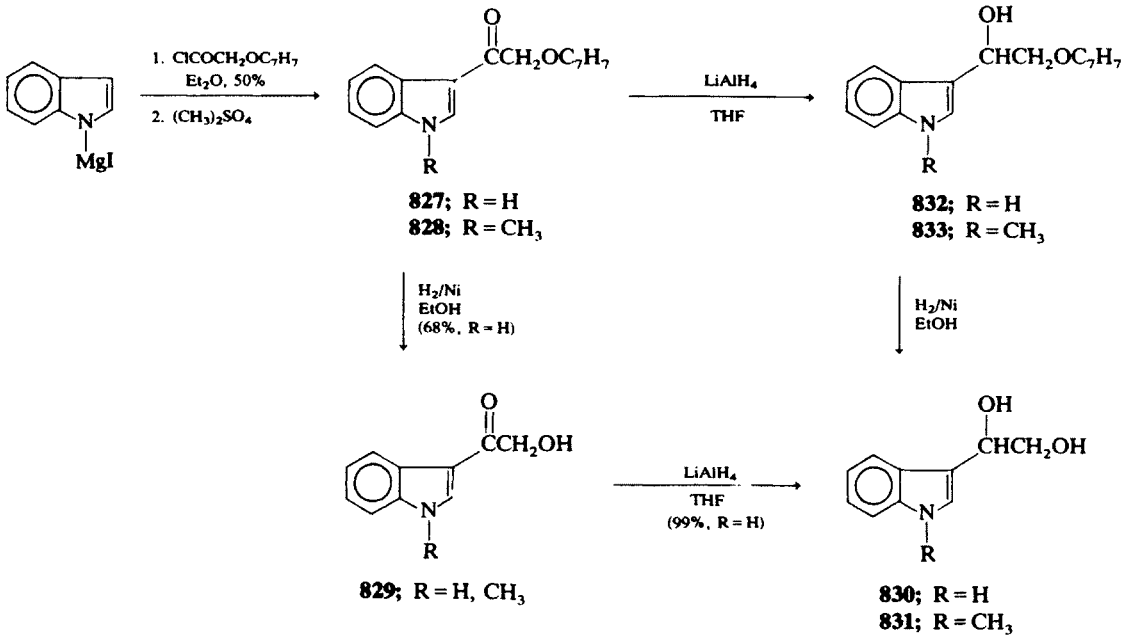
Szmuszkovicz has reported[702] the synthesis of the α- and β-methyl derivatives of indole-3-ethylene glycol **838–840** by the routes shown in Scheme 74. The reduction of acyloin **835** with lithium aluminum hydride led to appreciable (45%) C–O cleavage and the formation of α,α-dimethyltryptophol (**837**), whereas sodium borohydride gave the expected diol **840** in 59% yield and a dimethyltryptophol isomer, possibly **841**.

Elderfield and Fischer have reported, without details, that the reduction of 6-methoxyindole-3-oxalyl chloride with sodium borohydride gave 6-methoxyindole-3-ethylene glycol.[691b]

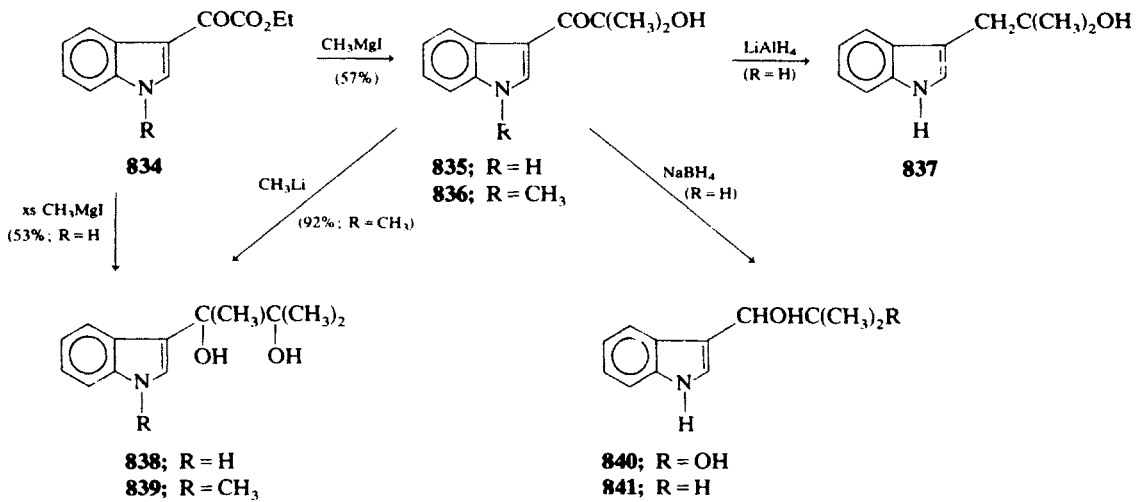
Suvorov and co-workers have described[733] the synthesis of indole-3-propane-1,2-diol **864** in 43% yield by reduction of indole-3-lactic acid with lithium aluminum hydride in THF. The same propylene glycol derivative was also obtained as a hydrogenolysis by-product in the Raney nickel reduction of **857** as shown in Scheme 76.[733]

8. *Indole Glycerol*

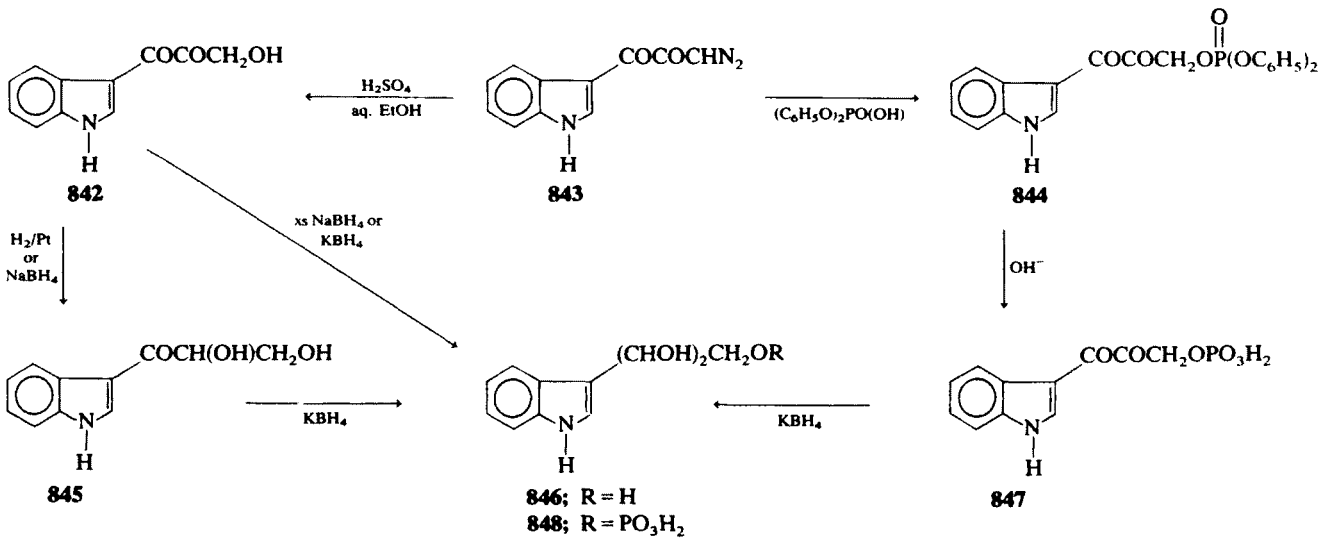
Yanofsky first showed[723,734] that the primary phosphate ester of indole-3-glycerol (**848**) is a tryptophan precursor in the microorganisms *E. coli* and *Neurospora crassa* (Scheme 75). Lingens and Hellman reported[735] the first synthesis of indole-3-glycerol by hydrolysis of the diazoketone **843**, followed by lithium aluminum hydride reduction of the hydroxypyruvoyl derivative **842**, although no experimental details were given. Erdmann has recently repeated[736] Lingens and Hellman's procedure and finds that


1. ClCOCH2OC7H7
Et2O, 50%
2. (CH3)2SO4
MgI
827; R = H
828; R = CH3
LiAlH4
THF
832; R = H
833; R = CH3
H2/Ni
EtOH
(68%, R = H)
H2/Ni
EtOH
829; R = H, CH3
LiAlH4
THF
(99%, R = H)
830; R = H
831; R = CH3

Scheme 73

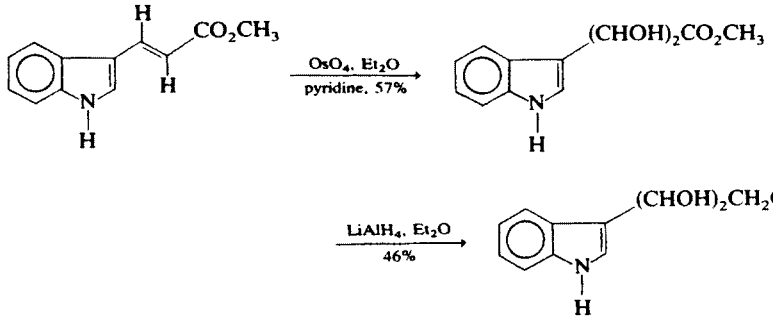

COCO2Et
CH3MgI
(57%)
COC(CH3)2OH
LiAlH4
(R = H)
CH2C(CH3)2OH
834
835; R = H
836; R = CH3
837
xs CH3MgI
(53%; R = H
CH3Li
(92%; R = CH3)
NaBH4
(R = H)
C(CH3)C(CH3)2
OH OH
CHOHC(CH3)2R
838; R = H
839; R = CH3
840; R = OH
841; R = H

Scheme 74


COCOCH2OH
H2SO4
aq. EtOH
COCOCHN2
(C6H5O)2PO(OH)
O
COCOCH2OP(OC6H5)2
842
843
844
H2/Pt
or
NaBH4
xs NaBH4 or
KBH4
OH−
COCH(OH)CH2OH
KBH4
(CHOH)2CH2OR
KBH4
COCOCH2OPO3H2
845
846; R = H
848; R = PO3H2
847

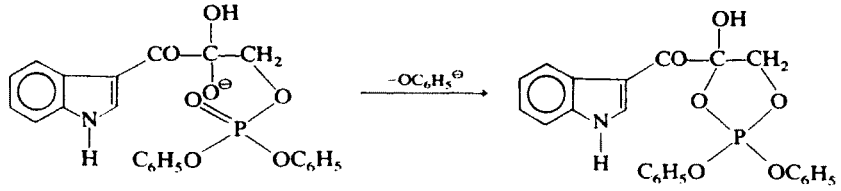
Scheme 75

the hydrolysis proceeds in a yield of 48%, whereas the reduction with sodium borohydride—in place of the original lithium aluminum hydride—gives indole-3-glycerol in 67% yield. An inverse addition in the reduction permitted him to isolate 3-glyceroylindole in 52% yield. He also devised a two-step route to one of the stereoisomers of **846** (eq. 30). Both preparations were converted to indole-3-glycerol phosphate by phosphatase. Archer and Harley-Mason decomposed diazoketone **843** in the presence of diphenylhydrogen phosphate and used successive steps of hydrolysis and reduction to achieve the first synthesis of indole-3-glycerol phosphate[737] (**844** → **847** → **848**).



(30)

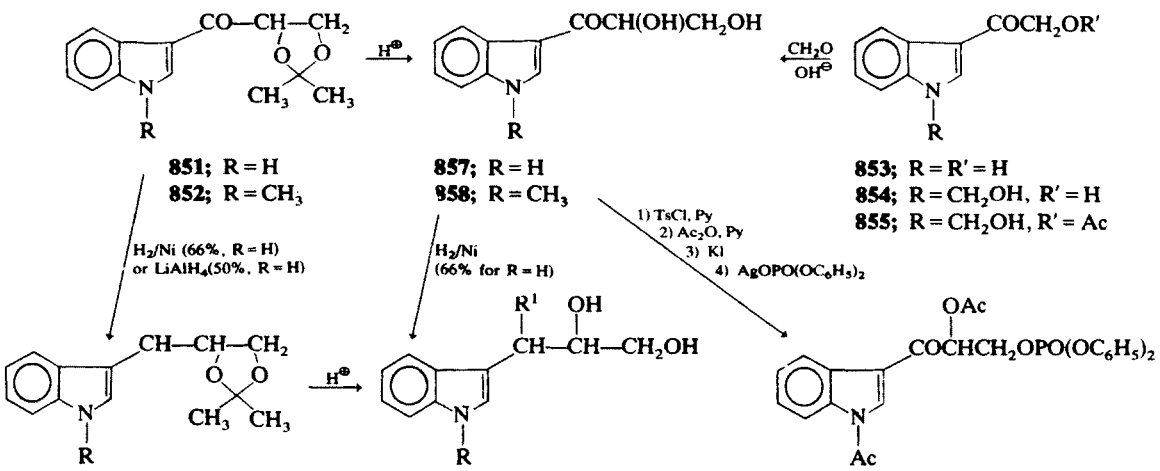
The unusually facile alkaline hydrolysis of the tri- to the monoester (**844** → **847**) is ascribed to the formation and participation of ketol **849** in the hydrolysis, producing the cyclic phosphate **850**. Ring opening and repetition of the process would yield the monoalkylphosphate ester **847**.[737] Interestingly, Yanofsky showed[723,734] that indole is produced by the action of dilute alkali on indole-3-glycerol phosphate.



849 **850**

Archer and Harley-Mason also reported a synthesis of **846** using either a one-step reduction of 3-hydroxypyruvoylindole **842** with potassium borohydride or a two-step reduction of **842**, first to 3-glyceroylindole **845** by catalytic reduction, then to **846** with potassium borohydride.[737]

Suvorov and co-workers have described another practical synthesis of indole-3-glycerol[733] as well as its *N*-methyl derivative[732] according to


CO—CH—CH2
O O
CH3 CH3
N
R
H⊕
COCH(OH)CH2OH
CH2O
OH⊖
COCH2OR'
851; R = H
852; R = CH3
857; R = H
858; R = CH3
853; R = R' = H
854; R = CH2OH, R' = H
855; R = CH2OH, R' = Ac
H2/Ni (66%, R = H)
or LiAlH4(50%, R = H)
H2/Ni
(66% for R = H)
1) TsCl, Py
2) Ac2O, Py
3) KI
4) AgOPO(OC6H5)2
CH—CH—CH2
R1
OH
CH—CH—CH2OH
OAc
COCHCH2OPO(OC6H5)2
Ac
861; R = H
862; R = CH3
863; R = Ac
859; R = H, R' = OH
860; R = CH3, R' = OH
864; R = H, R' = H
856

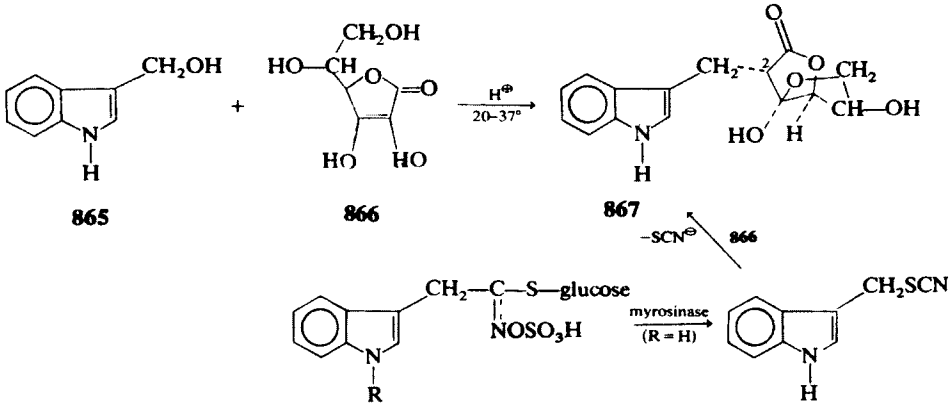
Scheme 76

Scheme 76. Compounds **851** or **852** arise from the reaction of indolemagnesium iodide and the acetonyl derivative of 2,3-dihydroxypropionyl chloride. In addition to the Grignard route to 3-gylceroylindole **857**, they found this key intermediate could be obtained in 28% yield by the reaction of 3-hydroxyacetylindole **853** with formalin in dilute alkali or in 40% yield from 1-hydroxymethyl-3-acetoxyacetylindole (**855**) with dilute alkali.[738] Compound **854** is presumably an intermediate in this conversion, for it gives **857** in 25% yield when treated with dilute alkali. They also report the preparation, in several steps, of the phosphate ester derivative **856**, which would appear useful in a synthesis of **848**.[732]

9. *Ascorbigen*

The enzymatic hydrolysis of the indole-3-acetic acid derivative, glucobrassicin **868**, which proceeds via the reactive skatyl isocyanate **870**, produces, in the presence of ascorbic acid **866**, a "bound" form of ascorbic acid called ascorbigen[742a,b,c] (Scheme 77). Ascorbigen is stable only from pH 4 to 7; at pH 2 or below, ascorbic acid is released,[743] while above pH 7, another mode of decomposition produces indole-3-acetic acid.[744] Virtanen and co-workers showed that ascorbigen resulted when L-ascorbic acid was reacted with 3-hydroxymethylindole (**865**) in warm water at pH 7[742b] or preferably at pH 4–5, where 70–80% yields were obtained after one hour.[742c] This product was shown to be identical with the ascorbic acid-releasing plant growth factor isolated from Savoy cabbage[743–745] and partially characterized[744] by Procházka and co-workers as a derivative of indole-3-propylene glycol. Recently, Procházka has reported[746] another synthesis of ascorbigen. He employed the reaction of L-ascorbic acid with gramine or gramine methiodide and obtained yields of 41 and 45%, respectively. He also reported a revised elemental analysis, later confirmed in the structure **867** proposed[747] by Kiss and Naukom. They showed that Pirronen and Virtanen's reaction[724c] produced two isomeric materials in 55–60 and 2% yield, the former being indentical with the natural product, found, incidentally, in a number of other cabbages and several varieties of radishes.[748] The two materials were shown to be epimeric products of skatylation at the 2-position of ascorbic acid. Steric arguments could explain the preponderance of the natural isomer in this reaction.

Neoglucobrassicin, **869**, the 1-methoxy analogue of glucobrassicin, likewise yields, in the presence of ascorbic acid and myrosinase, a neoascorbigen.[749]



Scheme 77

X. The Indolethiols

A. 2-Substituted

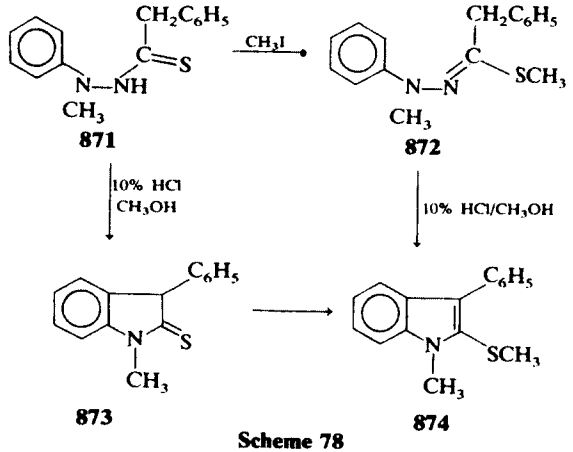
1. *Synthesis*

a. INTRODUCTION. Early work in this area focused mainly on the reaction of indoles or indole Grignard derivatives with sulfur. More recent work stems largely from the impetus provided by the researches[754] of Theodore Wieland's group into the toxic principles of the mushroom, *Amanita phalloides*. They showed these extremely potent toxins to be a closely related series of cyclic polypeptides having in common a thioether cross-link formed from a cysteine sulfhydryl group and the 2-position of a tryptophan residue. This led to the development[755–757] by this group of new reactions of sulfenyl and sulfinyl chlorides with indoles as a means of preparing 2-thio-substituted indoles for uv models[756,757,760] and as intermediates in peptide[759,760] or 2-hydroxy- and 2-thiotryptophan[758] syntheses. More recently, Fontana and Scoffone have extended[761,763,781,782] the sulfenyl chloride reaction using the more stable mono- and dinitrophenylsulfenyl chlorides as tryptophan–modifying reagents for probing structure–activity relations or introducing cross-links into proteins.

Recent work[764] by Hino and his co-workers has clarified the reaction of P_2S_5 on oxindoles, the nature of the thione–thiol tautomerism in the

resulting products as well as the oxidation chemistry of indole-2-thioethers.

b. From Non-indole Precusors. Wuyts and Lacourt in 1935 reported[765] the synthesis of the methylthioindole **874** by Fischer cyclization of the *S*-methyl thiohydrazide **872** (Scheme 78). Interestingly, even the *un*methylated hydrazide **871**, in a reaction with the solvent, gave minor amounts of **874** accompanying **873**.



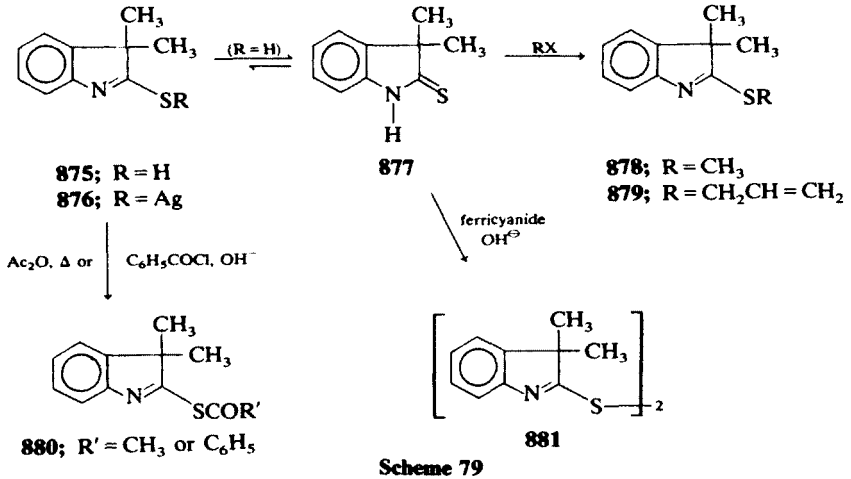
Scheme 78

c. From Indoles

1. *Alkylation of Thiones.* A review on the chemistry of indoline-2-thiones has recently appeared.[764]

Brunner in 1933 applied[766] Sugasawa's oxindole reaction with P_2S_5[767] to 3,3-dimethyloxindole—as well as methylated benzene ring derivatives—and methylated the resulting thione, **877**, or its silver salt, **876**, with methyl iodide in a sealed tube to give the 2-methylthioindoline, **878** (Scheme 79). On the basis of alkylation and acylation reactions to **880**, as well as its easy oxidation to the disulfide, **881**, Brunner felt the Sugasawa product from 3,3-dimethyloxindole was best represented as an indolenine thiol, **875**, rather than the indolinethione. Recent work[768] by Bourdais, however, indicates that the thione tautomer, **877**, predominates in solution. This is true also of 3-monosubstituted indoles, even when conjugating–extending 3-aryl substituents are present.[769]

More recently Ficken and Kendall have reported[770] improvements in Brunner's procedure whereby the thione, **877**, produced in 88% yield, is converted in 80% yield to **878** with dimethyl sulfate. 2-*S*-Allyl-3,3-dimethylindolenine (**879**) results on alkylation of **877** with allyl bromide.[775]



875; R = H
876; R = Ag

877

878; R = CH_3
879; R = $CH_2CH=CH_2$

880; R′ = CH_3 or C_6H_5

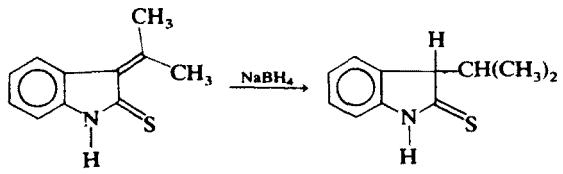
881

Scheme 79

Hino has prepared[771,772] a series of 2-methylthioindoles in excellent yield by the room-temperature alkylation of indoline-2-thiones with methyl iodide in carbonate-buffered acetone. 1-Methyl-, 1,3-dimethyl-, and 1,3,3-trimethyl-2-methylthioindole were prepared in this way, as well as the parent 2-methylthioindole. 2-Ethylthioindole and -skatole were prepared in quantitative yield using ethyl iodide.[773,774] Pmr studies on these two compounds showed them to be in the indole—not the indolenine—form.[774]

Bourdais has reported[789] 85% yields of 2-methylthioindole and its 1-methyl derivative using Hino's procedure as well as a 75% yield of 2-benzylthioindole when benzyl bromide was employed. The Hino procedure has also been used by Bycroft and Landon in obtaining[775] high yields of 1-methyl- and 1,3-dimethyl-2-allylthioindole from the thiones and allyl bromide. 1,3-Dimethyl-2-propargylthioindole and 1-methyl-2-(γ,γ-dimethylallyl)thioindole were prepared in analogous fashion.[775]

Bourdais has developed[777,779] a synthesis of 3-monoalkylthiones by exploiting the increased acidity of the 3-position of indolinethiones *vis-à-vis* oxindoles. Facile condensations with ketones in the presence of triethylamine afford 3-alkylidinethiones, for example, **882**, which can be

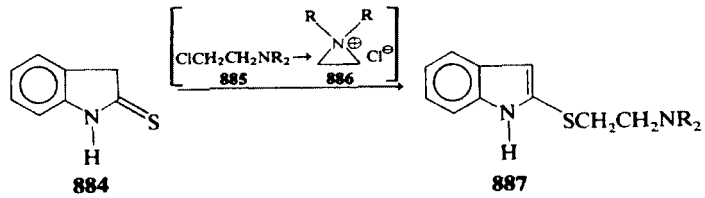


882

883

easily reduced to the 3-alkylthione **883**. 3-Cyclopentylindoline-2-thione was also made in this way.

Hino's group[776] and Bourdais[777,778] have independently developed procedures to prepare **887** by alkylating thiones **884**, with dialkylaminoethyl or aminoethyl halides, **885**, through the probable aziridinium salts **886**.[777,778]



884 **887**

Another consequence of the lability of the 3-proton in indoline-2-thiones appears to be facile radical formation at that position. Hino and co-workers in reexamining[771,772] the Sugasawa reaction have noted the formation of a number of by-products of subsequent reaction of the indoline-2-thiones. When oxindole was treated with P_2S_5 in refluxing benzene, indoline-2-thione was the major product accompanied by 3,3′-biindolyl and 3,3′-biindolyl 2,2′-tetrasulfide [**908**, see Section X.A.1.C.(3).(b)]; in the higher-boiling xylene, the latter two products predominate. *N*-Methyloxindole gave analogous results with, however, an additional by-product, **888**, being observed.

These workers consider either the thiones or thione dimers, for example, **888**, as likely intermediates in the production of the biindolyls and the biindolyl tetrasulfides, since both the latter are stable to the reaction conditions and either of the former gives a mixture of the observed products. The thione dimers probably arise from the thiones. With oxindoles substituted in the 3-position, the thiones produced, for example, 3-methyl- or 1,3-dimethylindoline-2-thione, are relatively stable and give only the product of desulfurization, namely, skatole or 1,3-dimethylindole, on further reaction with P_2S_5 in toulene. 1,3,3-Trimethylindoline-2-thione is stable toward P_2S_5 even in refluxing xylene.

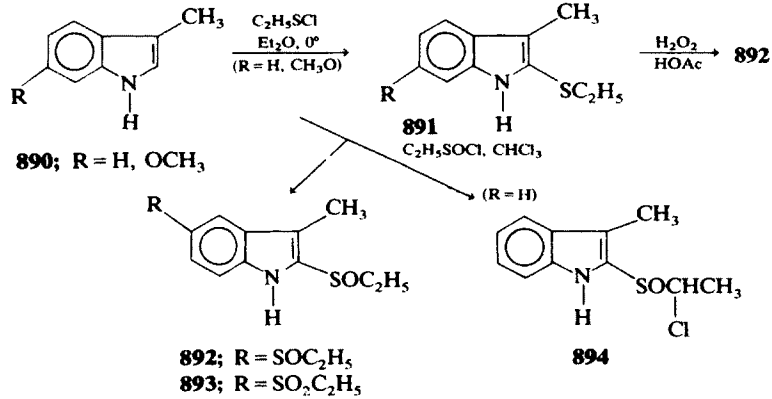
Wieland and co-workers have reported[755] difficulties in obtaining the thione from 3-methyloxindole with P_2S_5 in refluxing toluene, obtaining

888 **889**

instead mainly a trisulfide, identical with the diskatyl trisulfide **889**, first prepared[785] by Oddo and Raffa [see Section X.A.1.c.(3).(a)]. This apparent discrepancy with Hino's work does not appear to have been resolved. To circumvent the apparently capricious P_2S_5 reaction, Wieland and co-workers introduced a new synthesis of thiones. They reduced the 2,2′ symmetrical disulfides which result from reaction of disulfur dichloride with 2-unsubstituted indoles (see next section).

(2). *Disulfur Dichloride, Sulfenyl or Sulfinyl Chlorides.* In the context of their investigations on the *A. phalloides* toxins, Wieland and his co-workers developed what has become the most popular method for the introduction of 2-thio substituents into 3-alkyl-substituted indoles, namely, the reaction with S_2Cl_2 or alkylsulfenyl chlorides.[755,756] These reactions made accessible model compounds for spectral studies as well as "tryptathione" intermediates for peptide synthesis.[759,760]

The reaction of skatole and its 6-methoxy derivative, **890**, with ethanesulfenyl chloride in ether at 0° results in 50 and 54% yields, respectively, of the 2-ethylthio derivatives, **891**[756] (Scheme 80). Nakagawa and Hino report[774] a quantitative yield in the former reaction. Ethanesulfinyl chloride, on the other hand, gave with skatole only a poor yield of the sulfoxide **892**, accompanied by the sulfone **893** and the α-chlorosulfoxide **894**.[757] The sulfoxide **892** could, however, be prepared in good yield by hydrogen peroxide oxidation of the thioether **891**.[757,791]

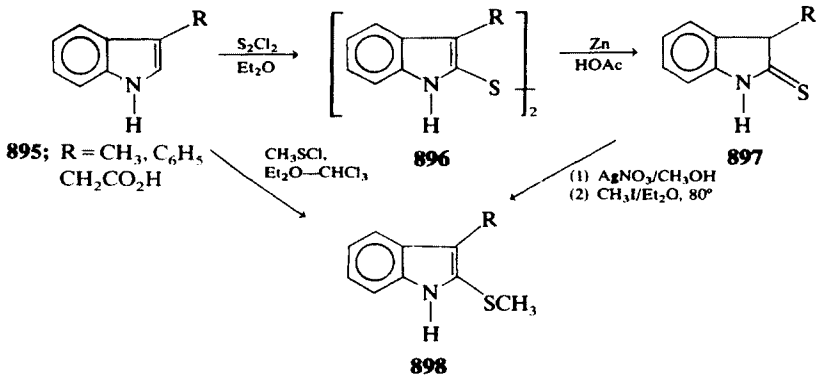


Scheme 80

Indole with 3-methyl, 3-phenyl, or 3-acetic acid substituents **895**, on reaction with S_2Cl_2, gives excellent yields of the disulfides **896**, reducible in high yield to the thiones **897** (Scheme 81). These, by a two-step methylation, afford the 2-methylthio derivatives **898** ($R = C_6H_5$, 43%),

obtained more satisfactorily (R = C_6H_5, 84%) by reaction of **895** with methanesulfenyl chloride.[755]

Indole-3-acetic acid and its 1-methyl derivative provided 45 and 40% yields, respectively, in this latter reaction. Interestingly, in the reaction of skatole with S_2Cl_2, diskatyl 2,2′-sulfide is isolated in low yield. This may be a result of traces of SCl_2 present in the reagent.



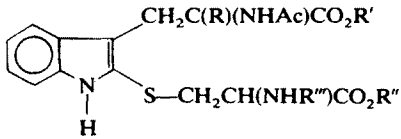
898

Scheme 81

The disulfur dichloride reaction has also been applied to tryptamine and tryptophan derivatives, producing 2,2′ symmetrical disulfides in high yield.[758,792] These have been used in turn to prepare 2-hydroxy or 2-thio derivatives (see Sections X.A.2.b–d).

The reaction between *t*-butylsulfenyl chloride and skatole in THF proceeds normally with 2-substitution.[780]

Appropriate cysteine derivatives with *N*-chlorosuccinimide in chloroform containing benzene or THF form, *in situ*, sulfenyl chlorides capable of reacting at low temperatures with various tryptophan derivatives to provide "tryptathione" derivatives, for example, **899** and **900**, having a 2-thioether link between the indole ring and the cysteine sulfur—the same grouping as is found in the phalloidin toxins.[757,760] A similar product also arises from 6-methoxygramine and *N*-trifluoroacetylcysteine sulfenyl chloride.[759]

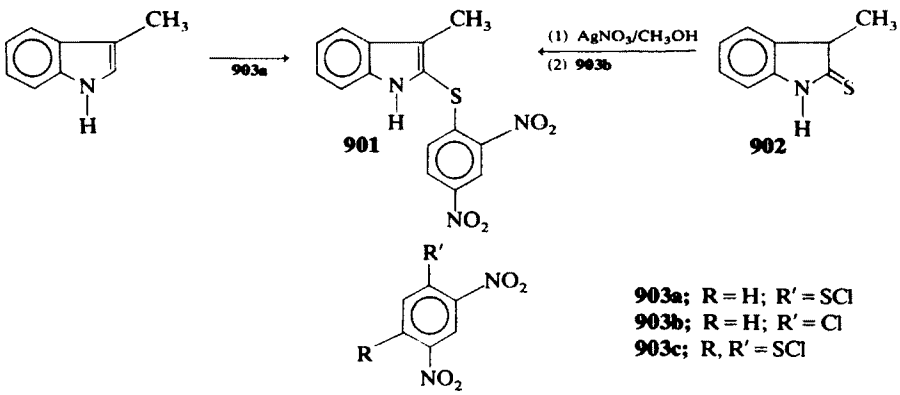


899; R = $CO_2C_2H_5$, R′ = C_2H_5, R″ = H, R‴ = H[757]
900; R = R′ = H, R″ = CH_3, R‴ = $C_6H_5CH_2OCO$[760]

A number of tryptophan-containing peptides react in the above fashion with *N*-carbobenzyloxycysteine sulfenyl chloride; however, the reaction unfortunately fails, probably for steric reasons, with *peptides* containing the cysteine sulfenyl chloride moiety.[759] Hydrolysis of tryptathione peptides produces 2-hydroxytryptophan and cystine.[760]

In 1966, Fontana and co-workers discovered[761,782] that a commonly used amino-protecting group, the *o*-nitrophenylsulfenyl (NPS) group, when treated with HCl under the usual conditions for its removal, led instead to the formation of a stable 2-arylthioether linkage with the indole ring in tryptophan-containing peptides. At 0°, tryptophan substituted on the side-chain nitrogen with the NPS group or the 2,4-dinitrophenylsulfenyl (DNPS) group, rearranges within 5 minutes to 86 and 91% yields, respectively, of the 2-substituted isomers. The reaction probably proceeds through the *in situ* formation of NPS–Cl or DNPS–Cl since the same products arise when tryptophan under the same conditions is treated with those reagents. These reagents, particularly the former, are now widely used in protein chemistry[762,763,781,782,859] for the selective modification or quantitation of tryptophan. The introduction of one NPS group per tryptophan in a peptide or protein leads to a molar extinction increment of 4000 at 365 nm, thus permitting an accurate determination of the number of residues per mole of protein.[762,859]

The structure proposed for the reaction product **901** from skatole and DNPS–Cl (**903a**) was confirmed by a two-step alkylation (24% yield, overall) of thione **902**, with **903b** following Wieland's procedure.[761,782] Barton and co-workers prepared[810] the same compound (58%) by reaction of 2,4-dinitrophenylsulfenyl acetate with skatole in refluxing benzene. This reagent with indole gives 3-DNPS-indole in 80% yield. In this case the structure was proved by synthesis from 3-thiocyanoindole (see Section X.B.1.b).

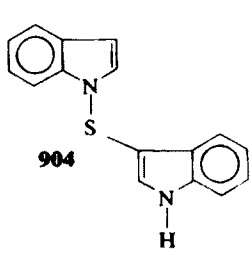


Raj and Hutzinger have proposed[783] the use of DNPS—Cl for the determination and isolation of naturally occurring indoles and indoleethylamines.

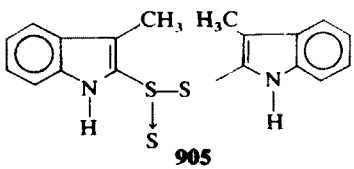
Veronese and co-workers have introduced[763] the bifunctional reagent **903c** for use in cross-linking tryptophan residues in proteins. Reactions have also been reported with skatole, *N*-acetyl-L-tryptophan, L-tryptophan methyl ester, glucagon, and other peptides containing tryptophan.

(3). *Reactions with Sulfur*

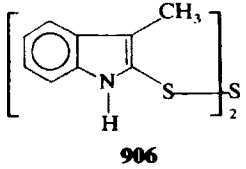
(a). INDOLE- AND SKATOLEMAGNESIUM BROMIDE. Oddo and Mingoia have reported[784] that benzoyl chloride upon the reaction product of indolemagnesium bromide and sulfur in ether gives 2-benzoylthioindole accompanied by the 3-isomer and 3,3′-diindolylsulfide. Acetyl chloride followed by acetic anhydride treatment in the same reaction produced 2-acetylthioindole accompanied by 1-acetyl-3-acetylthioindole and the unusual sulfide **904**. 2-Acetylthioindole on treatment with alkali yielded the so-called indole-2-thiol (actually indoline-2-thione). Oddo and Raffa extended[785] the reaction to skatolemagnesium bromide and obtained 2-benzoylthioskatole. In the absence of benzoyl chloride, a trisulfide resulted for which structure **905** or **906** was proposed. Wieland and co-workers obtained[755] the same trisulfide by reaction of 3-methyloxindole with P_2S_5 in toluene (see Section X.A.1.c.(1)) and revised the structure to that shown in formula **889**. Curiously, it is even a minor by-product in the reaction of skatole with S_2Cl_2.[755]



904



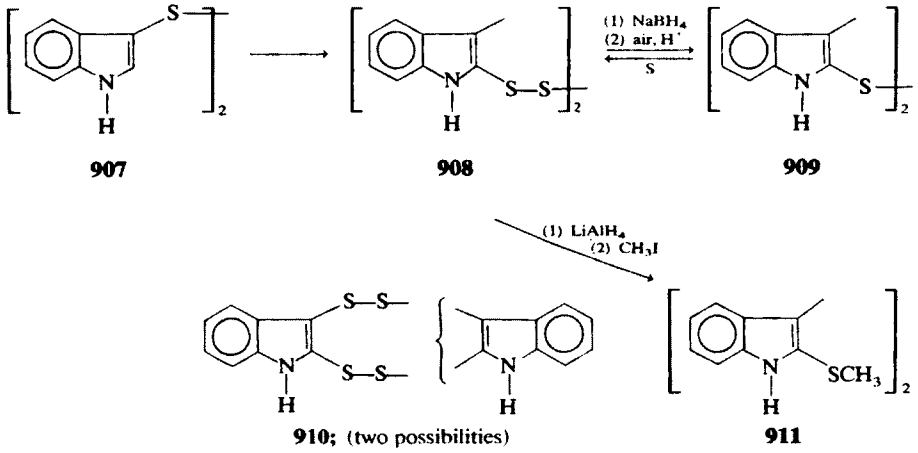
905



906

(b). INDOLE. The reaction of indole with sulfur at elevated temperatures without solvent has been the subject of a number of early investigations. These have been succinctly summarized[786] by Carpenter and coworkers, who discovered in 1960 that one of the early reaction products, formulated as either of the isomers **910** (Scheme 82), could be obtained in much better yield (55–60%) simply by heating indole with excess sulfur in DMF. They revised the structure to that of the unusual biindolyl

tetrasulfide, **908**, on the basis of the following observations: Raney nickel desulfurization gave 3,3'-biindolyl, borohydride reduction of **908** followed by air oxidation gave the 3,3'-biindolyl disulfide **909** which could be reconverted to **908** by reaction with sulfur, and finally, lithium aluminum hydride reduction of **908** followed by methylation gave 2,2'-dimethylthio-3,3'-biindolyl (**911**). Quite surprisingly, when limited amounts of sulfur are employed in the DMF reaction, indole 3,3'-disulfide (**907**) results. Even more surprisong is the observation that 3,3'-biindolyl with sulfur does *not* give the tetrasulfide **908**, although the treatment of **907** with sulfur does? The mechanism for these transformations is still a mystery.

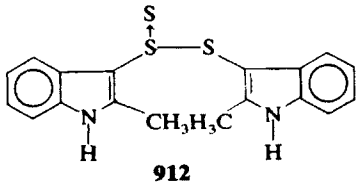


Scheme 82

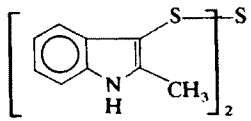
The tetrasulfide **908** and its 1,1'-dimethyl derivative also arise as minor by-products in the reaction of oxindole and 1-methyloxindole with P_2S_5 in refluxing benzene[771,772] along with the 3,3'-biindolyls, becoming the major products when the reaction is conducted in refluxing xylene. 1,1'-dimethyl-3,3'-diindolyl 2,2'-tetrasulfide has been synthesized by Hino's group using the sulfur–DMF reaction on 1-methylindole.

The structures proposed for the reaction products of sulfur on 2-methylindole (**912** or **913**) and indole (**914**) should be confirmed.[819,821]

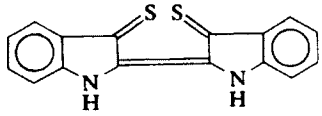
(4). *Miscellaneous.* Wieland and Grimm have utilized[756] the Leuchs addition product **915** from 3,3-dimethylindolenine and benzoyl chloride as a means of introducing the 2-ethylthio substituent in the preparation of **916**. This route has seen more recent application[787] in the synthesis of anhydrogliotoxin analogues where 2-carbethoxy-3,3-dimethylindolenine was employed with a number of acyl chlorides.



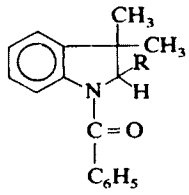
912



913

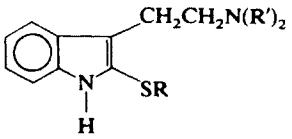


914

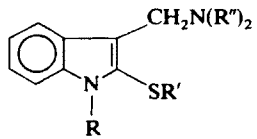


915: R = Cl
916; R = SC_2H_5

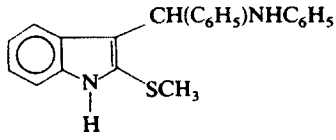
(d). 2-ALKYLTHIOTRYPTAMINES AND -INDOLEMETHYLAMINES. Bourdais and co-workers have prepared[788,790] a series of 2-methylthio- and 2-benzylthiotryptamines **917** using the following tryptamine syntheses from 2-alkylthioindoles: the gramine route to the 3-acetonitriles followed by reduction to the tryptamines, conversion of indole-3-acetic acids to *N,N*-dialkylamides, and reduction or reaction of indoleglyoxalyl chlorides with *N,N*-dialkylamines and reduction. The same indole starting materials were also used[789] to prepare a series of Mannich bases of the general formula **918**. More complex indolemethylamines resulted on alkylation with Schiff's bases or amidomethylation. Typical of these reactions are the preparation of **919** and **920**, respectively.



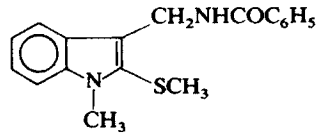
917: R = CH_3 or C_7H_7;
R' = CH_3, C_2H_5;
$(R')_2 = (CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2N-(alkyl)-(CH_2)_2$



918; R = H or CH_3,
R' = CH_3 or C_7H_7;
R'' = CH_3;
$(R'')_2 = (CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2N$-(alkyl)-$(CH_2)_2$



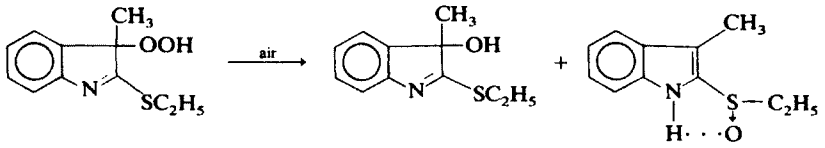
919



920

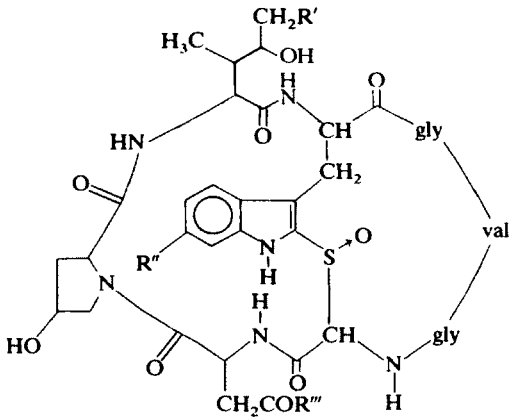
2. *Reactions*

a. OXIDATION. Hino and co-workers have reported[773,774] the facile air oxidation of 2-ethylthioskatole to an approximately equimolar mixture of **922** and **923**. The indolenine hydroperoxide **921** or the derived hydroperoxy radical is the presumed intermediate. Both **922** and **923** are stable to further oxidation, the latter supposedly by virtue of a strong intramolecular hydrogen bond which is thought to prevent the abstraction of the N–H proton required for the formation of an indolenine hydroperoxide. In this context, it should be noted that 1,3-dimethyl-2-ethylthioindole is stable to autoxidation.[791] In general, no correlation was found between the ease of oxidation and the proportion of thiol present in indoline-2-thiones. Indoline-2-thione and its 1-methyl derivative are both stable toward autoxidation.



921 **922** **923**

The sulfoxide **923** also results on hydrogen peroxide oxidation of 2-ethylthioskatole.[757,791] Hino's group reported a 77% yield and 6% yield of the related sulfone with one mole of H_2O_2, and Wieland's group reported an 85% yield of the sulfoxide with a threefold excess of oxidant. Wieland's group also effected the oxidation of 1-methyl-2-ethylthioskatole to a sulfoxide in 60% yield. Using a large excess of hydrogen peroxide, Wieland obtained a sulfone product (66%) from 2-ethylthioskatole, although Hino asserts this to be the major product formed even with three moles of reagent. When 2-ethylthio-6-methoxyskatole was treated with a large excess of hydrogen peroxide, 60% of the related sulfoxide and 50% sulfone resulted. The former compound was useful as a uv model for the slow-acting but potent toxin, methyl α-amanatin **925**, the diazomethane product of α-amanatin (**924**). The latter toxin is the

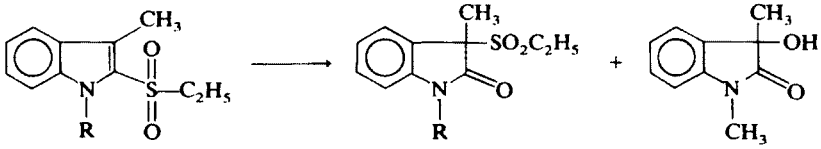


Representative amatoxins and derivatives (see also Ref. 754)

	R′	R″	R‴
924 (α-amanitin)	OH	OH	NH_2
925 (methyl α-amanitin)	OH	OCH_3	NH_2
926 (β-amanitin)	OH	OH	OH
927 (γ-amanitin)	H	OH	NH_2
928 (amanin)	OH	H	OH

major poisonous constituent of the *A. phalloides* mushroom.[754] The amantin group of toxins [α-, β-, and γ-amanatin (**924**, **926**, **927**) and amanin (**928**)] are less stable to acid than the phalloidin group by virtue of the 2-thioether sulfoxide grouping. Hydrolysis gives mainly cysteic acid and an unsubstituted indole moiety.[754]

Hino has reported[791] that, in addition to the sulfone **929**, the interesting by-product **931** arises (6%) when 2-ethylthioskatole is exposed to excess hydrogen peroxide. The sulfone was shown to be an intermediate in this unusual oxidative rearrangement of the ethylsulfonyl group. 1,3-dimethyl-2-ethylthioindole provides a sulfoxide in high yield with one mole of H_2O_2. With three moles, the sulfone **930** arises accompanied by rearranged sulfone **932** and the dioxindole **933**.



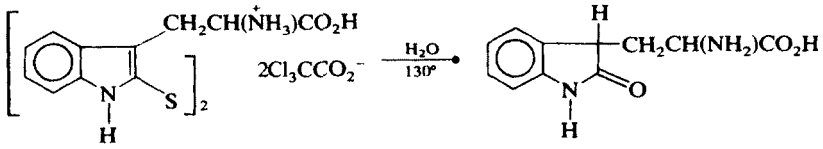
929; R = H
930; R = CH_3

931; R = H
932; R = CH_3

933

2-*t*-Butylthioskatole is reported[780] to give a poor yield of sulfoxide on hydrogen peroxide oxidation.

b. HYDROLYSIS. The action of disulfur dichloride on the trichloroacetic acid salt of L-tryptophan in chloroform results in an 87% yield of the 2,2′-disulfide **934**. Hydrolysis of this material affords β-oxindolyl-L-alanine (**935**) in 63% yield and provided until recently the best synthesis of that naturally occurring biochemical.[758]

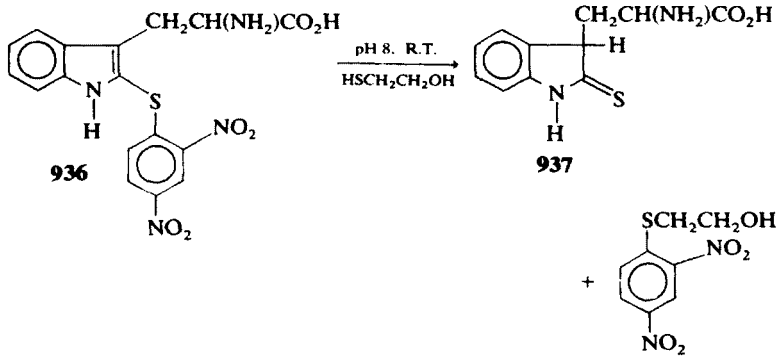


934 **935**

In the same way, tryptamine, *N*-carbobenzyloxytryptamine, 5-benzyloxytryptamine, and 5-benzyloxytryptophan were converted to symmetrical disulfides and by a modified reductive hydrolysis (Zn–HCl–HOAc), transformed to 2-hydroxytryptamines or -tryptophans. 2-Hydroxy-5-benzyloxytryptophan, on hydrogenolysis, yields 2,5-dihydroxytryptophan.[792]

Veronese and co-workers have improved on Wieland's synthesis of **935** by employing[793] sealed-tube hydrolyses with 15% HOAc of 2-(2-nitrophenylthio) (2-NPS-), 2-(4-nitrophenylthio)-, or 2-(2,4-dinitrophenylthio)tryptophan. Peptides containing 2-NPS-tryptophan are converted to peptides containing 2-hydroxytryptophan residues, although the conditions are more severe. 2-NPS-tryptamine is likewise converted to 2-hydroxytryptamine.

c REDUCTION. Zinc dust reduction of **934** in aqueous pyridine–acetic acid gives 2-thio-L-tryptophan (**937**) in 42% yield which can be purified



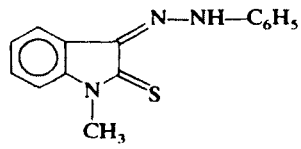
936 **937**

via its lead salt.[758] Pmr and ir studies by Bourdais[768] and by Hino and co-workers[769] indicate the thione structure predominates in solution for simple indole-2-thiols. Hino has used the S_2Cl_2 reaction coupled with sodium borohydride reduction to prepare a series of 3-arylindoline-thiones.[769]

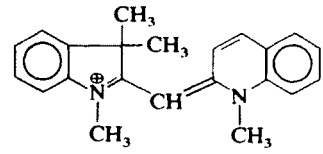
In work on the structure of methyl α-amantin (**925**), it was observed that Raney nickel reduction halts at the thioether stage, desulfurization apparently being prevented by steric effects. Pfaender and de Urries have examined[780] the rates of desulfurization in boiling methanol of 2-ethylthio- and 2-*t*-butylthioskatole as well as their sulfoxides. Surprisingly, the *t*-butyl derivatives were desulfurized the most rapidly, not incorporating hydrogen from the solvent, and the ethyl derivatives incorporated deuterium from CD_3OD.

d. THIOLYSIS. Another route to 2-thiotryptophan (**937**) has been developed[794] by Wilchek and Miron, who employ a large excess of mercaptoethanol at pH 8 to quantitatively remove the 2,4-dinitrophenyl group from 2-DNPS-tryptophan (**936**) by nucleophilic displacement. The reaction proceeds at room temperature and has been applied to tryptophan-containing peptides and proteins, where it should prove useful in probing tryptophan involvement in structure and function. In addition, the creation of binding sites for heavy atoms and new disulfide cross-links in proteins should be feasible.

e. AMINOLYSIS. Hino and co-workers have described[860] the reaction of indoline-2-thione and its 1-methyl and 3-methyl derivatives with primary or secondary aliphatic amines. The reactions are carried out at reflux with an excess of the amine alone or in *n*-butanol and provide 2-aminoindoles in 30–80% yield. The reaction is not general however; 1-methylindoline-2-thione and aniline or *N*-methylaniline gave instead, traces of 1,1′-dimethyl-3,3′-biindolyl and its 2,2′-tetrasulfide with no aminoindoles. With excess ethyleneimine, the same thione gave 1-methyl-2-(2-aminoethyl)thioindole [see Section X.A.1.c.(1)]. With phenylhydrazine, the deep red compound **938** resulted in low yield accompanied by 1,1′-dimethyl-3,3′-biindolyl. With 1,3,3-trimethylindoline-2-thione and butylamine, a 2-butyliminoindoline results in low yield.



938

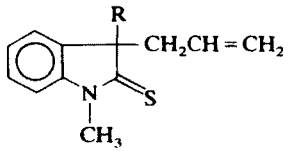


939

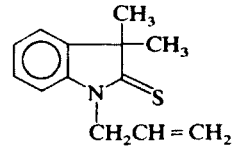
f. MISCELLANEOUS. Faulstich and co-workers have reported[757] the *N*-methylation of 2-ethylthioskatole with methyl iodide and sodamide in ammonia, the thioether group withstanding these rather severe conditions. Carpenter and co-workers have methylated 3,3′-biindolyl 2,2′-tetrasulfide **908** with methyl iodide and sodium in THF.[786]

The reaction of indolenine thiol ethers with heterocyclic quaternary ammonium salts and methyl tosylate has been used[770] to produce cyanine dyes. An example is provided by the reaction of quinaldine and **878** to give **939**.

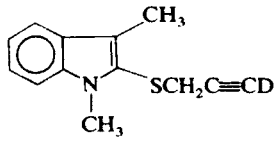
2-(*S*-allylthio)-substituted 1-methyl- and 1,3-dimethylindole as well as 2-(*S*-allylthio)-3,3-dimethylindolenine have been studied[775] as substrates in the thio-Claisen rearrangement. The products **940** and **941**, respectively, arise quantitatively from the first two materials in refluxing toluene, and **942** results from the indolenine thioether in refluxing tetralin. A concerted 3,3-sigmatropic rearrangement is supported by the rearrangement of **943** to **944** with no label scrambling. Interestingly, the dimethyl-



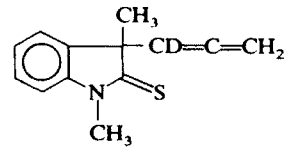
940; R = H
941; R = CH_3



942



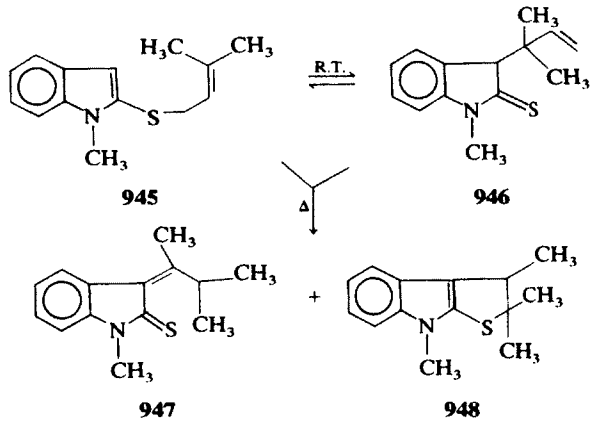
943



944

allyl thioether **945**, even at room temperature, rearranges to an equilibrium mixture of **945** and **946** (Scheme 83). When that mixture is heated, the abnormal Claisen product **947** results accompanied by its ring-closed isomer, the thienyl(2,3-*b*)indole derivative **948**.

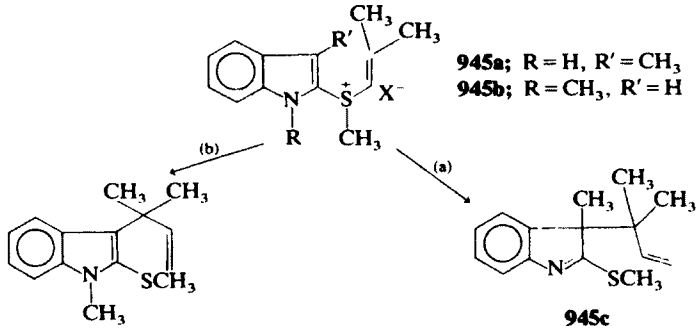
In contrast to the easy rearrangement of **945**, its 3-methyl isomer does not rearrange, even in refluxing toluene.[861] In refluxing tetralin, 3-methylindoline-2-thione and skatole result, probably by a radical process. This compound could, however, be induced to undergo a facile thio-Claisen rearrangement to **945c** (Scheme 84) via the sulfonium ion intermediate **945a** produced by the action of dimethylallyl bromide on 2-methylthioskatole in acetone or DMF buffered with potassium carbonate. The



945 946 947 948

Scheme 83

methylsulfonium salt, **945b**, of **945** was produced from 1-methyl-2-methylthioindole under the same conditions or with methyl fluorosulfonate on **945** and was likewise observed to undergo immediate rearrangement, in this case producing **945d**. These rearrangements may represent a possible biochemical pathway for the introduction of dimethylallyl units into alkaloids of the ergot or echinulin types.[861]



945d 945c

Scheme 84

Electron impact mass spectra of indoline-2-thiones and their 3,3'-dimers have been reported.[862]

Plieninger and Werst prepared 3-benzylindole in 70% yield by the Raney nickel reduction of a crude 3-benzylindoline-2-thione preparation.[863] This method may have some utility in converting oxindoles to indoles.

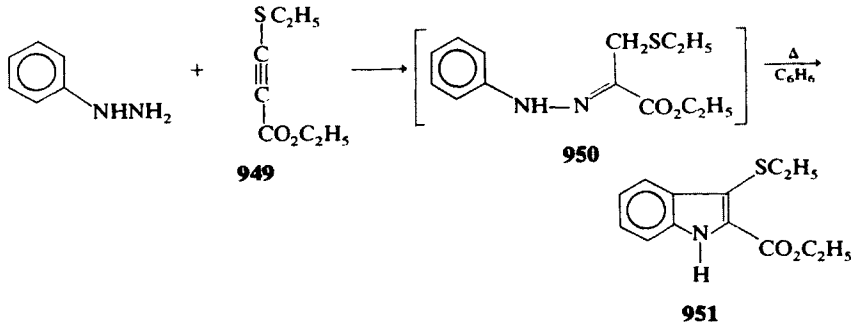
The disulfide of 3-phenylindole-2-thione has been proposed[864] for use in light-sensitive photographic preparations.

B. 3-Substituted

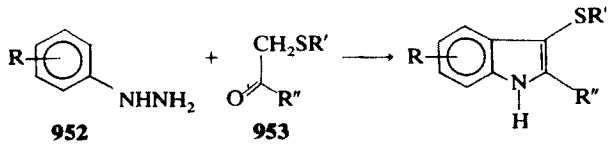
1. *Synthesis*

a. From Non-indole Precursors

(1). *Fischer Cyclization.* Bonnema and Arens have reported[795] that 2-carbethoxy-3-ethylthioindole (**951**) results in low yield from the reaction of phenylhydrazine and ethylthiopropynoate (**949**). This reaction may proceed via the phenylhydrazone **950**.



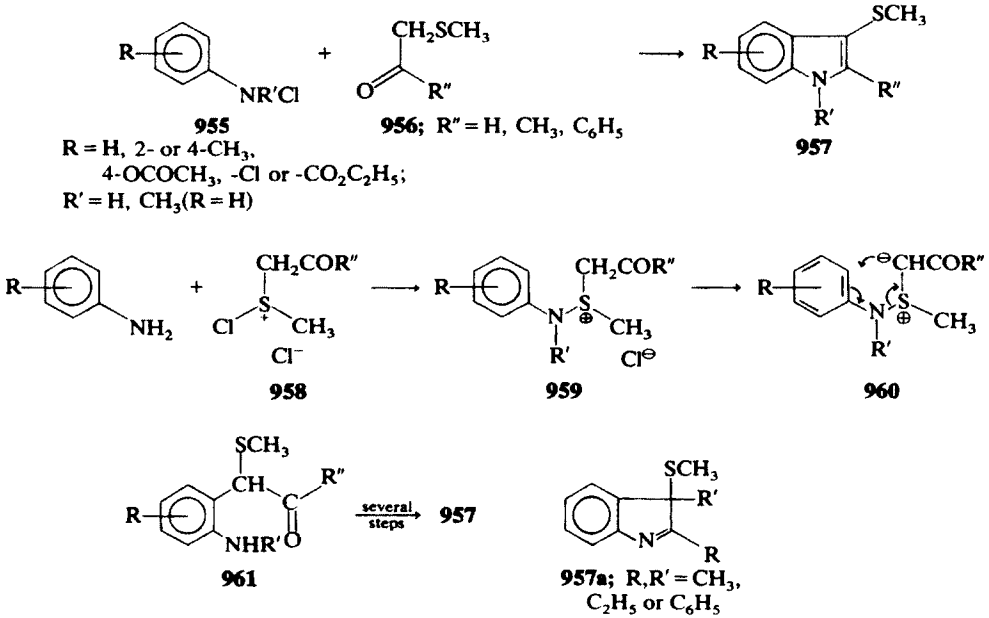
Wieland and Ruehl have described[796] the synthesis of a large number of indoles, **954**, substituted with either 3-phenylthio or 3-carboxymethylthio groups by reaction of various chloro-, methyl-, or methoxyphenylhydrazines, **952**, with α-thiopropan-2-one or α-thioacetaldehyde derivatives, **953**. The hydrazones were prepared in acetic acid and rearranged with HCl in ethanol to 80–90% yields of the indoles. Interestingly, *m*-substituted phenylhydrazones gave only the 6-substituted indole. Also of interest is the finding that the Fischer rearrangement of methyl ketones gave none of the 2-alkylthiomethyl isomer.



R = H, 2,3,4-CH_3, 3-Cl, 3-CH_3O R′ = $CH_2CO_2C_2H_5$ or C_6H_5 R″ = H or CH_3

Jardine and Brown employed[797] the reaction of phenylhydrazine and ethylthioacetaldehyde diethyl acetal with BF_3 etherate catalysis to obtain 3-ethylthioindole in 60% yield.

(2). *Via N-Chloroanilines.* Gassman and van Bergen have recently reported a novel route to 3-methylthioindoles, **957**, utilizing the reaction between *N*-chloroanilines, **955**, and α-methylthioketones[798] or aldehydes, **956**[799] (Scheme 85). The *N*-chloroaniline is formed *in situ* using *t*-butyl hypochlorite or some other source of positive chlorine, then permitted to react with the methylthiocarbonyl compound and finally one equivalent of triethylamine, all at −65°. This indolization is thought[799] to proceed via the sulfonium ylid, **960**, which undergoes a Sommelet–Hauser type rearrangement to the *o*-substituted aniline, **961**, and finally yields the indole by condensation. This reaction has several advantages over the Fischer indole synthesis in utilizing the more convenient aniline starting materials, requiring only mildly basic catalysis, and proceeding at low temperatures. Yields of 60–80% result with the ketones, and 30–50% has been reported with the aldehydes. Gassman and co-workers have devised[800] a modification in the above procedure which permits its extension to 5-methoxyindole derivatives. *p*-Methoxyaniline, whose *N*-chloro derivative is too unstable at −78° for use in the original procedure,

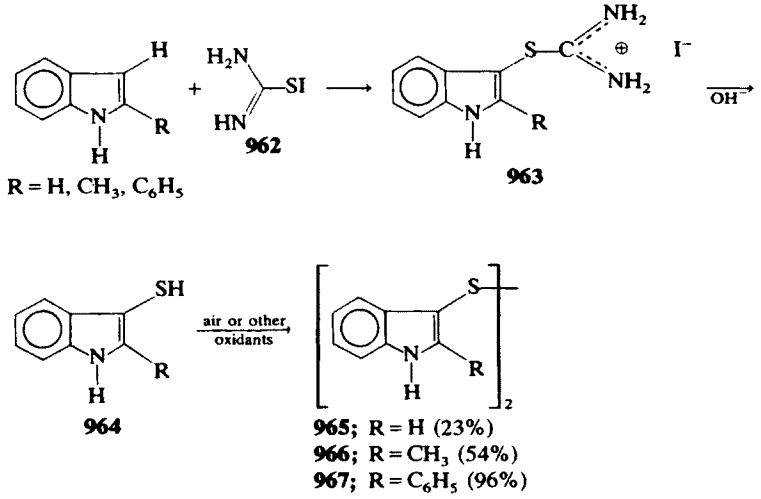


Scheme 85

does, however, form the anilinosulfonium salt **959** on reaction with the *chlorine complex* (**958**) of methylthioacetone. This affords the 5-methoxyindole (**957**; R = 5-OCH_3, R′ = H, R″ = CH_3) in 38% yield. The desulfurization of these materials is discussed in Section X.B.2.a. When α-alkyl- or α-aryl-β-keto sulfides were employed in the above sythesis, 2,3-disubstituted indolenine 3-thiol ethers, **957a**, resulted which were desulfurized (Raney nickel, $LiAlH_4$ or $NaBH_4$) without isolation to 2,3-disubstituted indoles (34–85% yields, overall). Several of the intermediate indolenine thiol ethers were characterized by nmr and ir.[866]

b. From Indoles

(1). *Thiourea–Triiodide.* Woodbridge and Dougherty discovered[801] that 3-unsubstituted indoles with excess thiourea and one equivalent of iodine in aqueous ethanol produced fair to excellent yields of diindoyl 3,3′-disulfides **965–967** following an alkaline, oxidative work-up (Scheme 86). Recently Harris has modified[802] this procedure by employing triiodide at room temperature and has isolated the intermediate isothiouronium salt **963** (R = H) in 80–90% yield from indole. Alkaline hydrolysis of this salt under nitrogen gave indole-3-thiol (**964**, R = H) which could be oxidized (I_2, air, $FeCl_3$, H_2O_2, or alkaline ferricyanide) to the disulfide **965**. This disulfide also formed on storage of **964**. Harris feels this reaction probably involves the *in situ* generation of the reactive electrophile, isothiourea sulfenyl iodide (**962**).[803]



Scheme 86

(2). *Thiocyanation.* Another reaction whereby a sulfur nucleophile and halogen leads to the introduction of a thiol function at the indole 3-position is the thiocyanation reaction. This reaction was first applied[804] to indoles by Grant and Snyder. Thiocyanogen, $(SCN)_2$, is presumably the thiolating agent in these reactions.

Yields of 3-thiocyanoindoles, **968**, were 89 and 92% from indole and indole-2-carboxylic acid, respectively (Scheme 87). Initial attempts to prepare indole-3-thiol by alkaline hydrolysis of 3-thiocyanoindole gave instead indolyl 3,3′-disulfide, **970**, a product which results (37%) even on basic alumina chromatography.[804] Indole-3-thiol could be demonstrated as an intermediate in the alkaline hydrolysis of 3-thiocyanoindole or the lithium aluminum hydride reduction of **970** (R = R′ = H) by trapping with chloro-2,4-dinitrobenzene (ClDNB) to give **971**. The same product results from the reaction of 2,4-dinitrophenylsulfenyl acetate with indole (see Section X.A.1.c.(2)).[810] The disulfide from indole-2-carboxylic acid undergoes decarboxylation (85%) on refluxing in 10% NaOH to the same disulfide as results from indole, thus proving 3-substitution.[804]

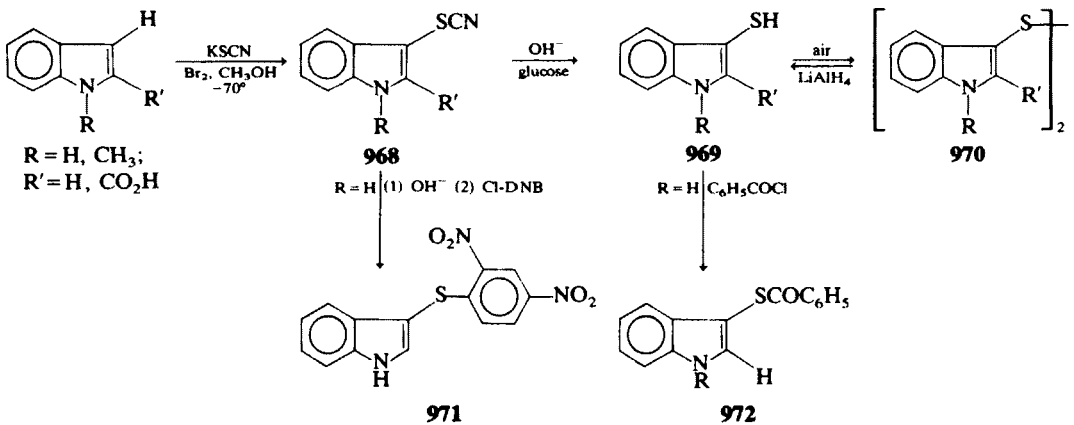
Marchese and Panzeri have recently repeated[805] Grant and Snyder's synthesis of 3-thiocyanoindole and its 1-methyl derivative as well as the disulfide of each. The thiocyanates could be hydrolyzed in the presence of glucose or sodium sulfide to produce indole-3-thiol and its 1-methyl derivative in 66 and 40% yields, respectively. These were converted to *S*-benzoyl derivatives, **972**, for characterization.

A number of *N*-methyl- or *N*-acetylindole-3-thiocyanates have been proposed[806] for protection of wood against fungi and bacteria. *N*-Alkyl- and *N*-acylindole-3-thiocyanates, particularly 1-ethylindole-3-thiocyanate, are energy transfer inhibitors of photophosphorylation in spinach.[807]

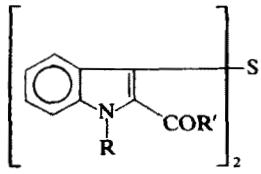
(3). *Disulfur Dichloride.* Kunori has reported[808] that ethyl indole-2-carboxylate and S_2Cl_2 in ether, followed by an alkaline work-up, produces a good yield of the sulfide **973**. This also results in quantitative yield in a photolysis reaction in CCl_4 with benzoyl peroxide present. Szmuszkovicz has reported[286,809] a similar product with methyl 1-methylindole-2-carboxylate and S_2Cl_2, although his product, **974**, was accompanied by the related di- and trisulfides.

(4). *Thionyl Chloride.* Kunori has also reported[811] that product **973** also arises on reaction with thionyl chloride in refluxing benzene, accompanied by a small amount of the 3,3′-biindolyl derivative. Ethyl 3- or 5-bromoindole-2-carboxylates did not react. Comparable results were obtained in the indole-2-carboxamide system.[812]

Szmuszkovicz, on finding that an attempt to make the acid chloride

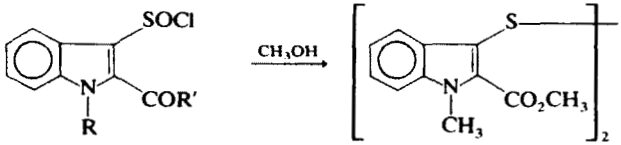

R = H, CH3;
R' = H, CO2H
KSCN
Br2, CH3OH
-70°
968
OH⁻
glucose
969
air
LiAlH4
970
R = H (1) OH⁻ (2) Cl-DNB
R = H C6H5COCl
971
972

Scheme 87



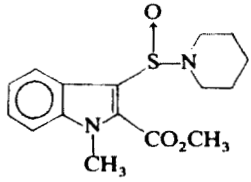
973; R = H; R′ = OC_2H_5
974; R = CH_3; R′ = OCH_3
975; R = CH_3; R′ = $NHCH_3$

from 1-methylindole-2-carboxylic acid gave instead a sulfur-containing product, **976**, undertook a study[809,813] of the reaction of $SOCl_2$ with a number of indole-2-carboxylic acid derivatives. The methyl ester of the above material and ethyl indole-2-carboxylate gave the sulfinyl chlorides **977** and **978** in excellent yield. The former on heating in vacuo yielded the sulfide **974**, and reaction with hydrazine in the cold gave the disulfide **979**, also obtained in a disproportionation of the acid chloride, **976**, in methanol. The reaction of **977** with amines gives a series of sulfinamides whose interesting oxidation and hydrolysis chemistry is discussed in a review.[286] One such reaction is the oxidation of the piperidine reaction product, **980**, to give the sulfoxide of **974**. When *N*,1-dimethylindole-2-carboxamide is treated with $SOCl_2$, the sulfide **975** results directly, accompanied by the cyclized product **981**.

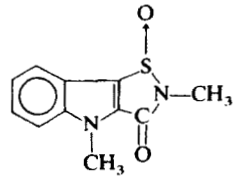


976; R = CH_3, R′ = Cl
977; R = CH_3, R′ = OCH_3
978; R = H, R′ = OC_2H_5

979



980



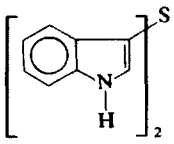
981

(5). *Reactions of Indolemagnesium Bromides*

(a). WITH SULFUR. Oddo and Mingoia in 1932 reported[784] a synthesis of 3-benzoylthioindole **972** (R = H) by action of sulfur on indolemagnesium bromide, followed by treatment with benzoyl chloride. Alkaline hydrolysis was reported to generate indole-3-thiol ("thioindoxyl"), although disulfide **970** (R = R′ = H) is the more probable product. The sulfur reaction also produced smaller amounts of diindolyl 3,3′-sulfide (**982**) and 2-benzoylthioindole [see Section X.A.1.c.(3).(a)]. When acetyl chloride was employed in place of benzoyl chloride and followed by a second acetylation step with acetic anhydride, 1-acetyl-3-acetylthioindole and 2-acetylthioindole resulted. The former on limited hydrolysis gave 3-acetylthioindole.

Oddo and Raffa have studied[785] the sulfur–acyl chloride reaction with 2-methylindole and obtained 2-methyl-3-acetylthio- or 2-methyl-3-benzoylthioindoles. Hydrolysis of the former compound allegedly gave indole-3-thiol (or thione), though again the disulfide seems the more likely product.

Earlier Madelung and Tencer, using different conditions, reported[814] compounds analyzing for diindolyl sulfides, in reactions of indole- or 2-methylindolemagnesium bromide with sulfur. The structure **982** was proposed for the indole product and an analogous structure for the 2-methyl derivative. This has been confirmed in recent pmr and ir studies[815] by Jardine and Brown. Diindolyl 3,3′-sulfide also arises on reaction of indolemagnesium bromide with ethanesulfenyl chloride, accompanied by 3-ethylthioindole, 3-ethylindole and other products.[815,820]

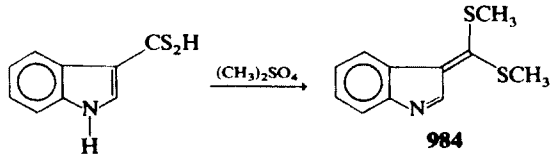


982

(b). WITH SO_2, $SOCl_2$, AND CS_2. Madelung and Tencer reported[814] that the sulfoxide of **982** arises on reaction of indolemagnesium bromide with SO_2 in ether. This was confirmed by Oddo and Mingoia who also isolated **982** in this reaction.[816] Interestingly, with 2-methylindolemagnesium bromide, the diindolyl *sulfide* is the major product.

The latter group also reported[816] that indole- and 2-methylindolemagnesium bromides with thionyl chloride produced diindolyl 3,3′-sulfones.

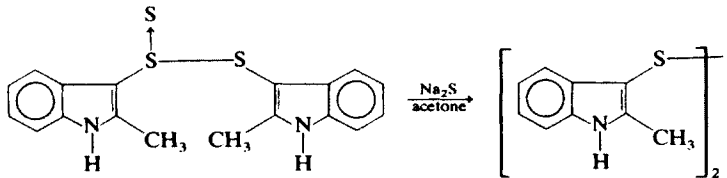
The reaction of indolemagnesium bromide[816] or iodide[858] with CS_2



983 **984**

produced the indole 3-thioacid **983**, which could be isolated as a lead salt.[816] Alkaline dimethyl sulfate converts **983** to the indolenine **984**.[858]

(6). *Sulfur and Indoles.* Depending upon conditions, the reaction of sulfur and indole at elevated temperatures leads to products (1) containing no sulfur, (2) substituted at the 2-position with thio groups, or (3) substituted at the 3-position with thio groups. Early work by Madelung[817] and by Oddo and Raffa[818] showed that the action of sulfur upon indole in any proportion led to 3,3′-biindolyl with the yield increasing as the proportion of sulfur to indole increased. Madelung observed[817] a different but unspecified reaction with 2-methylindole. Later Raffa,[819] employing ammonia-washed sulfur, isolated a diindolyl 3,3′-trisulfide. Since this could be converted to the disulfide **986** by reaction with benzoyl chloride in pyridine or as shown, Raffa proposed structure **985** for the trisulfide. A linear structure, **913**, would seem more probable.

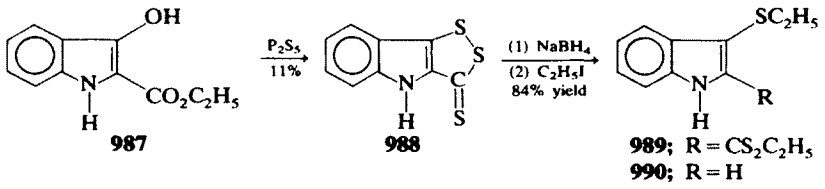


985 **986**

(7). *Miscellaneous.* Jardine and Brown obtained[820] 3-ethylthioindole (**990**) in low yield by reaction of 1-benzoyl-3-bromoindole with ethyl mercaptan in refluxing DMF containing potassium carbonate. A number of by-products including 3-ethyl- and 3-bromoindole were also isolated.

A more satisfactory synthesis was devised[797] by reaction of ethyl iodide on the sodium borohydride reduction product, **989**, of **988**, obtained in turn by the action of P_2S_5 on the indoxyl **987**. The 2-thioacid ester **989** undergoes easy alkaline hydrolysis and decarboxylation in vacuo to **990**.

Wieland and Grimm prepared 3-ethylthiooxindole by action of sodium ethyl mercaptide upon 3-bromo-3-methyloxindole. Attempted reduction to the indoline gave, instead, skatole.[756]



987 **988** **989**; R = $CS_2C_2H_5$ **990**; R = H

2. *Reactions*

a. DESULFURIZATION. Raney nickel desulfurization of 3-alkylthioindoles has been used to prepare good yields of 6-methoxyindole and its 2-methyl derivative,[796] 2-methyl-5-methoxyindole,[800] various 2,5- and 2,7-substituted indoles,[798] as well as indoles substituted only in the benzene ring.[796,799] *N*-Benzoyl-3-thiocyanoindole was converted to *N*-benzoylindole on refluxing with Raney nickel in ethanol. The *N*-acetyl analogue, however, was converted to *N*-acetylindoline.[804] Compound **988** undergoes desulfurization to 2-methylindole.[797]

b. MISCELLANEOUS. Substitution of the indole 3-position with thiocyano, benzoylthio, acetylthio, trisulfide, or ethylthio groups appears to deactivate the indole nitrogen to a greater or lesser degree toward acylation. The last of these fails to undergo acylation with acetic anyhydride or acetyl chloride in pyridine,[797] the trisulfide undergoes benzoylation only under such strenuous conditions that it first undergoes conversion to the disulfide,[819] and the others require more vigorous conditions than are usual for indoles. Benzoylthioindoles fail to undergo acylation.[784] 3-Acetylthio-[784] and 3-thiocyano-[804] indole can be acylated but the latter fails to react with ketene or isopropenyl acetate.

3-Thiocyanoindole, on reaction with phenyl- or ethylmagnesium bromide gives diindolyl 3,3′-disulfide.[804]

3-Ethylthioindole, on treatment with ethanolic mercuric chloride, gives a precipitate of ethylthiomercuric chloride and a mixture of indole and 3-ethoxyindole.[797,820]

Diindolyl 3,3′-disulfide is reported[820] to be *extremely and seriously allergenic.*

C. Synthesis of Indoles with Thiol Function in the Benzene Ring

1. *Classical Methods*

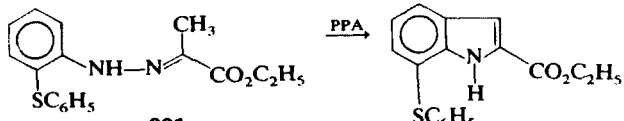
Three traditional indole syntheses have been adapted to the preparation of mercaptoindoles, these being used in turn as starting materials for

thiotryptamine analogues of the physiologically active hydroxy- and alkoxytryptamines (see Section X.C.4).

a. REISSERT REACTION. Piers and co-workers have prepared[822] 4-, 5-, 6-, and 7-benzylthioindole by ferrous ion in ammonia reduction of the appropriate benzylthio-substituted nitropyruvates. Yields of 31–62% were reported for the cyclization step. A modified decarboxylation procedure for 4- and 7-benzylthioindole-2-carboxylic acid, featuring *catalytic* amounts of their copper salts, provided the benzylthioindoles in 80 and 85% yield, respectively. The usual copper chromite in quinoline was employed with the 5- and 6-benzylthio acids and gave 52 and 67% yields, respectively, of the benzylthioindoles. Debenzylation of these four benzylthioindoles with sodium in liquid ammonia gave the mercaptoindoles in 47–87% yield.

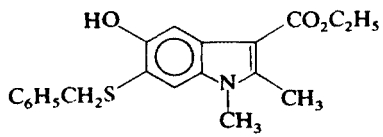
A Sandoz patent[823] reports the syntheses of 4-methylthio- and 4-benzylthioindole using an alkaline dithionite reduction of the nitropyruvate and decarboxylation by distillation under vacuum. *N*-Alkylation of 4-benzylthioindole was effected with potassium amide in ammonia, then treatment with methyl iodide or benzyl bromide.

b. FISCHER CYCLIZATION. Duncan and Andrako have cyclized[824] the phenylhydrazone **991** in 71% yield to **992** using polyphosphoric acid. Compound **991** was obtained in a Japp–Klingemann reaction from 2-phenylthiobenzenediazonium chloride and ethyl 2-methylacetoacetate in 49% yield.



991 **992**

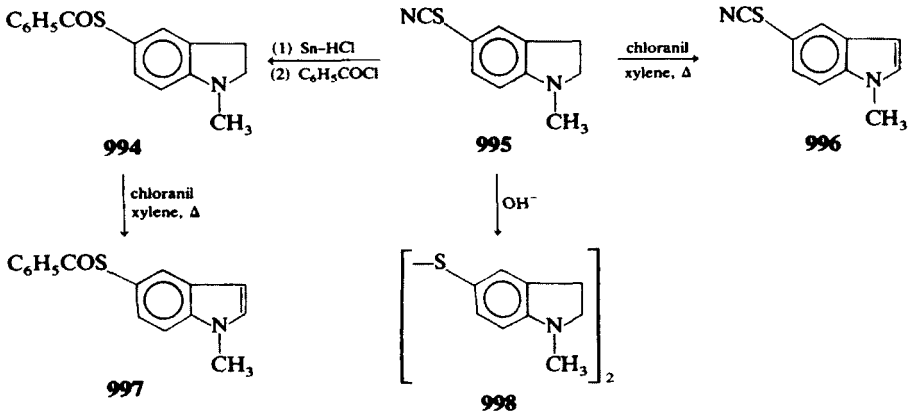
c. NENITZESCU REACTION. Steck and co-workers have synthesized[162] the 6-benzylthio-5-hydroxyindole derivative **993** in 46% yield by reaction of benzylthio-*p*-benzoquinone with ethyl β-methylaminocrotonate in acetone.



993

2. *Via Indolines*

Terentev and Preobrazhenskaya have introduced[825] an elegant procedure for the synthesis of 5-mercaptoindole derivatives using, as their first step, the reaction of thiocyanogen with indoline to give 5-thiocyanoindoline in 97% yield. Dehydrogenation with chloranil in refluxing xylene afforded 5-thiocyanoindole in 68% yield. 1-Methylindoline, in this sequence, gave 84 and 51% yields, respectively, of 1-methyl-5-thiocyanoindoline (**995**) and -indole (**996**) (Scheme 88). The former on treatment with tin in HCl, then benzoyl chloride, gave 5-benzoylthio-1-methylindoline (**994**) (33%) which was dehydrogenated to the indole, **997**, in 61% yield. Alkaline treatment of the 5-thiocyanoindolines gave the diindoline 5,5′-disulfides, for example, **998**.

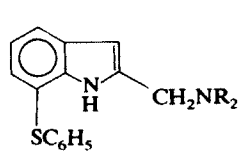


Scheme 88

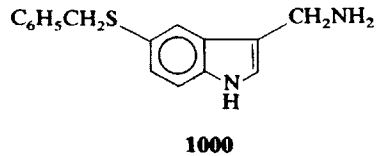
3. *Mercaptoindolemethylamines*

a. 2-Substituted. Duncan and Andrako have reported[824] the syntheses of a number of 2-aminomethyl-7-phenylthioindoles, **999**, by conversion of **992** to the acid chloride, reacting this with various dialkylamines, morpholine, or piperidine, and lithium aluminum hydride reduction of the resulting tertiary amides. Yields of 54–82% resulted in the aminolysis step and 74–93% were obtained in the reduction step.

b. 3-Substituted. Keglevic and Goles[826] prepared the benzylthioindolemethylamine **1000** by Fischer cyclization of the 4-benzylthiophenylhydrazone of 3-aminopropionaldehyde diethylacetal.



999; R = CH_3, C_2H_5,
NR_2 = morpholino,
piperazino



1000

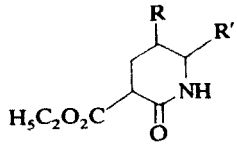
4. *Mercaptotryptamines*

a. Oxalyl Chloride Procedure. Hofmann and Troxler have synthesized 4-benzylthiotryptamine and its *N,N*-dimethyl derivative as well as 4-methylthiotryptamine using 4-benzylthio- or 4-methylthioindole and this procedure.[827] Debenzylation of 4-benzylthio-*N,N*-dimethyltryptamine with sodium in liquid ammonia[828] provided the thio analogue of psilocin.

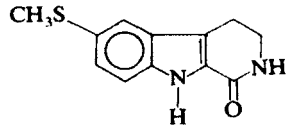
b. Indolealdehyde–Nitroalkane Route. 4-Benzylthio- and 4-methylthio-α-methyltryptamine were prepared by Hofmann and Troxler,[829] who condensed the appropriate indole thioether aldehyde with nitroethane and reduced the resulting nitrovinylindole with lithium aluminum hydride in THF.

c. Abramovitch–Shapiro Synthesis. Horner and Skinner have synthesized[830,831] 5-mercaptotryptamine, the thio analogue of serotonin, by Japp–Klingemann reaction of 4-benzylthiobenzene diazonium chloride with **1001** (35%) and subsequent steps of cyclization with HCl in HOAc (73%), hydrolysis with ethanolic KOH (100%), and decarboxylation with HCl in HOAc (70%). Debenzylation of the resulting 5-benzylthiotryptamine with sodium in liquid ammonia under nitrogen gave 5-mercaptotryptamine in 67% yield. A number of 5-benzylthio- and 5-methylthiotryptamines with α-methyl, β-methyl, or α,α-dimethyl substituents were synthesized[832] in the above manner from methyl-substituted 3-carbethoxy-2-piperidones, **1002**. 5-Methylthio-β,β-dimethyltryptamine could not be prepared owing to the failure of the β-carboline intermediate **1003** to undergo alkaline hydrolysis. A procedure for the *N*-monomethylation of these thiotryptamines by reduction of their methyl carbamates with lithium aluminium hydride has been described.[833]

Protiva and co-workers have reported the synthesis of 5- and 7-methylthiotryptamines using the Abramovitch–Shapiro adaptation of the Japp–Klingemann reaction.[73a–d] Yields of 87 and 73%, respectively, were reported[73b] for hydrolysis of the carbolines, and 38 and 55% for the decarboxylation step in 10% HCl.

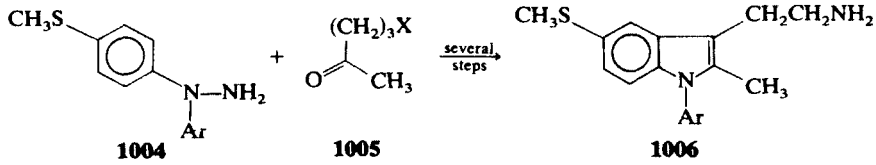


1001; R = R′ = H
1002; R,R′ = H, CH_3



1003

d. FISCHER CYCLIZATION. Archer has prepared[834] a number of 5-methylthio-2-methyltryptamines substituted on the indole nitrogen with various benzyl derivatives, **1006**, by Fischer cyclization of the phenylhydrazones stemming from **1004** and 5-phthalimidopentan-2-one (**1005**).

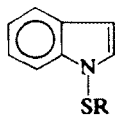


1004 **1005** **1006**

X = phthalimido

D. *N*-Substituted Indole Thioethers

Very little is known about this potentially useful system. The three nitrophenyl thioether isomers, **1007**, have allegedly been prepared[835] from *o*-, *m*-, or *p*-nitrophenylsulfenyl chloride and indole in refluxing benzene, although the 3-substituted indole seems more likely under these unbuffered conditions (see Ref. 810). A French patent[836] describes the preparation of 1-trichloromethylthioindole (**1008**) for use as a fungicide by reaction of the sodium salt of indole with trichloromethylsulfenyl chloride in benzene.



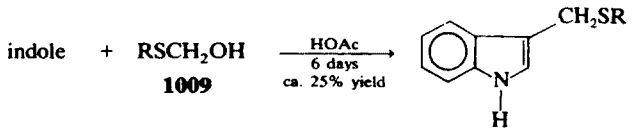
1007; R = *o*-, *m*-, or *p*-NO_2-C_6H_4
1008; R = CCl_3

E. Side-Chain-Substituted Indolethiols

1. *3-Substituted Indolemethylthiol Ethers*

a. MANNICH-LIKE REACTIONS. A reaction deserving more attention is that discovered by Poppelsdorf and Holt whereby various alkyl ethers of indole-3-thiomethanol, **1010**, result from the reaction of indole with 40%

aqueous formaldehyde and *n*-alkylthiols[837] (eq. 31). Benzylmercaptan gave only a 14% yield, and thiophenol apparently failed in this reaction. Replacing the acetic acid catalyst by triethylamine led to no reaction. Alkylthiomethanols, **1009**, arising from the acid-catalyzed addition of the thiol to formaldehyde are considered to be intermediary, producing, in turn, the alkylating species, $RSCH_2^{\oplus}$.



(31)

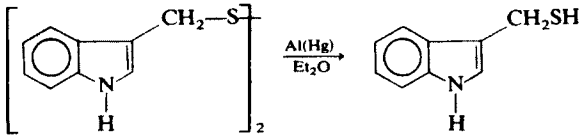
1010

$R = C_2H_5$, *n*-C_3H_7, *n*-C_4H_9

b. Via Gramine or Its Salts. Gill and co-workers first reported[838] the ready conversion (85%) of gramine to indole-3-thiomethanol ethers by heating at 136° with benzylmercaptan or *p*-thiocresol. Similar reactions were later described in a German patent[839] where a sealed-tube reaction in aqueous methanol was employed, by Poppelsdorf and Holt[837] who used slightly higher temperatures than Gill's procedure, and by Licari and Dougherty[840] who used a brief period of reflux in aqueous NaOH. By these procedures, thioethers of **1012** derived from methyl-,[840] ethyl-,[837,840] *n*-propyl-,[837,840] *n*-butyl-,[837,840] *n*-amyl-,[840] and benzylmercaptan[837,839] were prepared, as well as those derived from thiophenol,[837] mercaptoacetic acid,[839,840] and esters of the latter acid.[852]

Many of the same compounds also result from the room-temperature reaction of gramine salts and thiols in the presence of sodium methoxide.[837] Typical of this reaction are the 75 and 100% yields of thioethers from 1-methylgramine and gramine salts and *p*-thiocresol.[841]

The use of Na_2S,[840] NaSH,[840] or *S*-methylthiourea[839] with gramine afforded the disulfide **1011**.

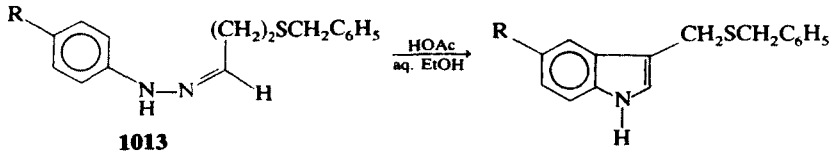


1011 **1012**

c. Indolealdehyde and Ammonium Sulfide. Disulfide **1011** also arises on reaction of 3-formylindole with ammonium sulfide in ethanol.[842,843] An aluminum amalgam reduction gives indole thiomethanol[843] **1012**. The disulfide, incidentally, is reported to exhibit reduced

fluorescence owing to internal quenching by the disulfide group.[844]

d. FISCHER SYNTHESIS. Keglevic and co-workers have cyclized[845] the phenylhydrazones, **1013**, of 3-benzylthiopropionaldehyde diethyl acetal to prepare *S*-benzyl indole-3-thiomethanol (**1014**) and its 5-methoxy and 5-benzyloxy analogues in poor yield.



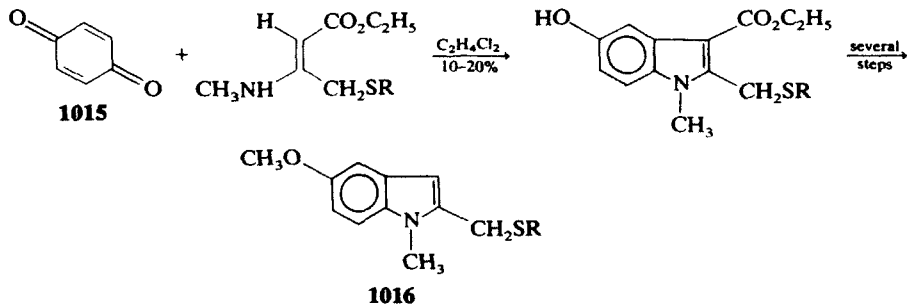
1013

1014

R = H, 4-CH_3O, 4-C_7H_7O

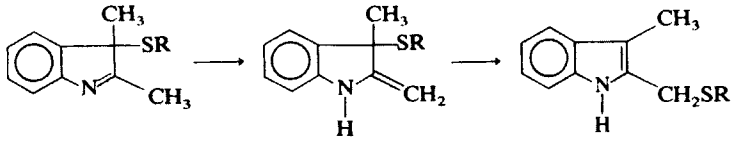
2. *2-Substituted Indolemethylthiolethers*

a. NENITZESCU REACTION. Trofimov and co-workers have synthesized[846,847] a number of ethers, **1016**, of 1-methyl-5-methoxyindole-2-thiomethanol by reaction of *p*-benzoquinone and the thioether-substituted enamine **1015**, then ensuing steps of methylation, alkaline hydrolysis, and decarboxylation.



1016

b. 2,4-DINITROPHENYLSULFENYL CHLORIDE ON 2,3-DIMETHYLINDOLE. Hutzinger and Raj have reported[848] the formation of the thioether, **1017**, in 93% yield from the reaction of 2,3-dimethylindole and 2,4-dinitrophenylsulfenyl chloride in methylene chloride containing formic acid. Although no mechanism was proposed for this reaction, a $1 \rightarrow 3$ rearrangement of the type first generalized by Taylor would appear likely (eq. 32).



(32)

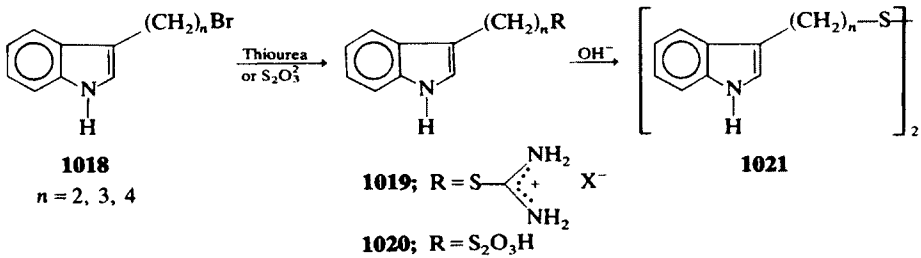
3. *Reactions*

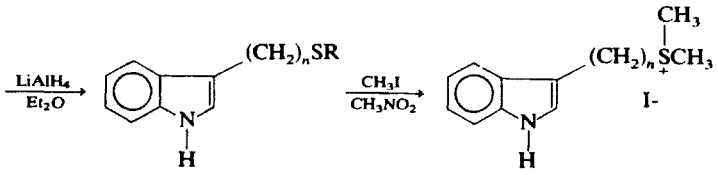
a. NUCLEOPHILIC DISPLACEMENT. Poppelsdorf and Holt, in the only published study[849] on the reactivity of ethers of indole-3-thiomethanol, observed that the thioether group could be displaced by piperidine, phthalimide ion, or cyanide ion, although with much less facility than in the case of gramine. Catalysis by hydroxide ion was required; even then, only 15–20% yields resulted. In these displacements, the *S*-ethyl ethers were found to be more reactive than the *S*-benzyl ethers. Potassium cyanide in aqueous ethanol produced a 1:2 mixture of indole-3-acetamide and indole-3-acetic acid in contrast to the 1:4 mixture obtained with gramine itself.

b. DESULFURIZATION. Ethers of indole-3-thiomethanol undergo easy Raney nickel desulfurization to skatole.[837] Desulfurization of **1017** in D_2O was used to prove that structure.[848]

4. *Thiotryptophols: Derivatives and Homologues*

a. THIOUREA OR THIOSULFATE ON INDOLEALKYL BROMIDES. Suvorov and Buyanov have prepared[850,851] thiotryptophol (**1022**, $n = 2$) (Scheme 89) and higher homologues ($n = 3,4$) in good yield by reaction of the indolealkyl bromides, **1018**, with either thiourea or sodium thiosulfate in ethanol. Alkaline hydrolysis of the isothiouronium salts, **1019**, or the indole thiosulfates, **1020**, afforded the disulfides, **1021**, which could be





$n = 2, 3, 4$

1022; R = H
1023; R = CH_3

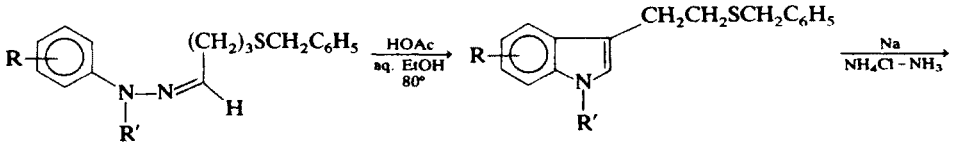
1024

Scheme 89

reduced to the thiols, **1022**. Stepwise methylation provided the methyl sulfides, **1023**, and the methylsulfonium salts, **1024**.

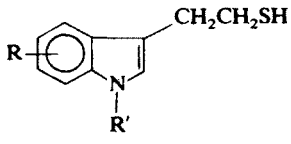
b. FISCHER SYNTHESIS. Keglevic and co-workers have cyclized[845] the phenylhydrazones, **1025**, of 4-benzylthiobutyraldehyde diethyl acetal to obtain the thiotryptophol benzyl ethers, **1026** and **1027** (Scheme 90). Debenzylation yielded the thiotryptophols, **1028**. In the case of the 5-benzyloxy-S-benzyl ether, 5-hydroxythiotryptophol resulted. During alumina chromatography, these thiols underwent oxidation to disulfides. The 3-benzyloxyphenylhydrazone **1025** (R′ = H) on Fischer cyclization produced a 1:2 mixture of 4- and 6-benzyloxythiotryptophol ethers, respectively. The 3,4-dimethyl-substituted phenylhydrazone gave a 1:2 mixture of 4,5- and 5,6-dimethyl isomers.

5-Methylthiotryptophol and its disulfide have been proposed as radioprotective drugs.[853]



1025

1026; R = 5 − H, $-CH_3O$, $-C_2H_5O$, $-C_6H_5CH_2O$; 7-CH_3O
R″ = H
1027; R = H, R′ = CH_3

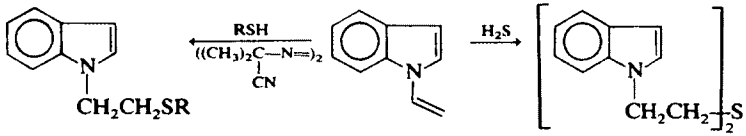


1028

Scheme 90

5. *Miscellaneous*

Reppe and co-workers have reported[854,855] the synthesis of the sulfide **1030** by the addition of hydrogen sulfide to *N*-vinylindole. Addition of mercaptan radicals to *N*-vinylindole provides 75–77% yields of the *N*-β-alkylthioethylindoles, **1029**.[856,857,865]



1029 R = C_2H_5, *i*-C_3H_7, *t*-C_4H_9 **1030**

XI. Acknowledgment

I wish to express appreciation to Dr. Ulli Eisner for reading large parts of this chapter and for many useful suggestions concerning it. I wish to apologize to the large and important community of Russian investigators for my lack of facility in their language and for having to rely on *Chemical Abstracts* alone for their accomplishments.

XII. Addenda

The numbering of the paragraphs corresponds to the numbering of the sections within the main part of this chapter.

II.A. Marchelli and co-workers have found the Fenton–Cier system superior to that of Udenfriend in producing a mixture of 4-, 5-, 6-, and 7-hydroxy derivatives of indole-3-carboxylic acid with minimal by-products.[1056]

Julia and Ricalens have studied the hydroxylation of *N,N*-dimethyltryptamine with the Fenton–Cier reagent and have observed formation of the 4-, 5-, 6-, and 7-hydroxy derivatives.[883] They were able to maximize the production of psilocin (9% yield, 85% of product) by replacing ferric sulfate with cuprous salts and ascorbic acid and by conducting the reaction at pH 9.

III.A.1. With the Fischer cyclization of the *m*-methoxyphenylhydrazone of diethyl ketone to 4- and 6-methoxy-2-methyl-3-ethylindole, the isomer ratio was found to depend on the catalyst employed.[885]

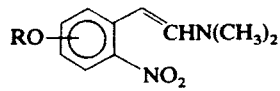
Suvorov and co-workers have prepared[886c] 4-, 5-, 6-, and 7-methoxyindole (10–15%) by Fischer cyclization with γ-Al_2O_3 as catalyst. They report a 51% yield of 2-methyl-5-methoxyindole by cyclization of acetone 4-methoxyphenylhydrazone at 325°.[886a,b]

Lee and co-workers found the Fischer cyclization unsatisfactory in preparing 5-benzyloxy-7-chloroindole.[924]

Zee and Ho prepared 4,5,6-trimethoxyindole by the Japp–Klingemann reaction and Fischer cyclization of the ethyl pyruvate hydrazone followed by saponification and decarboxylation.[1052]

III.C. The following mono- and dialkoxyindoles have been prepared by dinitrostyrene reductions: 4-ethoxy (60%)-,[901] 5-benzyloxy-7-chloro-,[924] 4-ethoxy-5-methoxy-,[1046] 5,7-dibenzyloxy-,[924] and 6,7-dibenzyloxyindole.[924]

III.D. Batcho and Leimgruber have introduced an important new indole synthesis of general utility which features the reaction of *o*-nitrotoluene derivatives and acetals of dimethylformamide to prepare β-dimethylamino-*o*-nitrostyrenes **1031**. These cyclize on reduction to indoles. Among a wide variety of indoles synthesized in this manner were the following mono- and dialkoxyindoles: 5- and 6-methoxy-, 5-benzyloxy-, 5,6-dimethoxy-, 5,6-dibenzyloxy-, and 5,6-methylenedioxyindole.[890] More recently 6-fluoro-,[927] 6-chloro-,[927] and 7-methyl-5-methoxyindole[923] (66%) were prepared this way. The starting material for the lattermost synthesis was prepared in an interesting 2-step sequence from 2,5-dimethylpyrone and nitromethane.[923]



1031

III.E.2. The Bischler reaction has been used to prepare the following di- or trimethoxyindoles: 2-methyl-4,7-dimethoxy-,[1047] 2-aryl-4,7-dimethoxy-,[950,951,1047] 2,3-dimethyl-4,7-dimethoxy-[951,952] and 2-phenyl-4,5,6-trimethoxy-indole.[887]

Roth and Lepke have prepared the following 2,3-dimethyl hydroxy- or methoxyindoles by reaction of acetoin with the appropriate hydroxy- or methoxyaniline and the aniline hydrochloride as catalyst: 5-hydroxy-(22%), 6-hydroxy-(32%), and 5-methoxyindole (50%). When 4-aminosalicylic acid was used and the product decarboxylated, a 79% yield of 2,3-dimethyl-6-hydroxyindole resulted.[888]

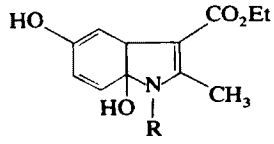
III.G.1. Allen has reviewed[892] the synthesis of 5-hydroxyindoles by the Nenitzescu reaction.

III.G.3. Allen and co-workers have prepared the following 5-methoxyindoles by the Nenitzescu reaction: 2,4-,[925b] 2,6-,[925a] and 2,7-dimethyl-,[925a] 4-chloro-2-methyl-,[925a] 4-chloro-2-ethyl-7-methyl-,[925a] 4-chloro-2-methyl-7-ethyl-,[925a] and 7-chloro-2-methyl-5-methoxyindole.[925a]

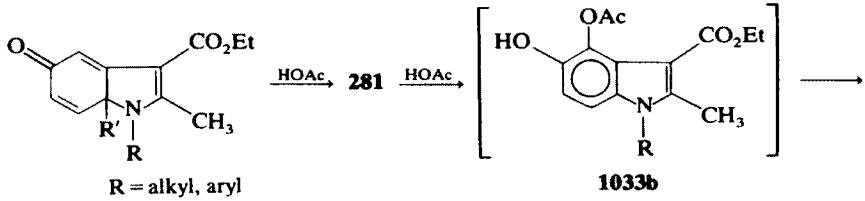
Catalytic hydrogenation of the 4-chloro-7-alkyl derivatives above produced 2-ethyl-7-methyl- and 2-methyl-7-ethyl-5-methoxyindole in 20 and 32% overall yield, respectively.[925a]

III.G.5. Kucklaender has shown the crucial importance of solvent and reactant ratios in determining the course of the Nenitzescu reaction. He was successful in isolating[261] carbinolamines of the type **1033** ($R = CH_3$) from reactions conducted in nonprotic, apolar solvents and in the absence of excess hydroquinones. Surprisingly, he showed these were *not* intermediates (cf. **268**) in the production of 5-hydroxyindoles under these conditions but were, rather, a source of by-products such as 4,4′- or 4,6′-dimers[345] or pyrroloindoles,[262] previously observed. Raileanu and co-workers have also isolated pyrroloindoles, though they ascribed these to the intermediacy of quinone imines.[894] Kucklaender argues that the dimers probably arise from the reaction of **1033** with the 5-hydroxyindole products in the 4- or 6-position and that the pyrroloindoles result from **1033** and excess crotonate. Kucklaender proposes a *nonredox* mechanism for the production of 5-hydroxyindoles in solvents such as CH_2Cl_2 with no excess hydroquinone which features intermediates of the type **263** isomerizing to enamines. These undergo cyclization to form **1032** which then dehydrate to the 5-hydroxyindoles. Carbinolamines of the type **1033** ($R = CH_3$, $CH_2C_6H_5$, aryl) produced 5-hydroxyindoles only in the presence of *both* acetic acid and excess hydroquinones. In acetic acid alone, they produced dihydroxyindole derivatives **1033c**, probably by the pathway shown in eq. 33.[261,897–900] Kucklaender proposes acetate attack in the 4-position of **281** to give **1033b**; however, a 1,3-acyl shift from **1033a** would also seem possible. The novel $4 \rightarrow 5$ acyl shift, postulated by Kucklaender to explain the production of **1033c** from **1033b**, was confirmed by the following observation. Ethyl 1-benzyl-2-methyl-4-acetoxy-5-benzyloxyindole-3-carboxylate on hydrogenolysis gave solely the rearranged 5-acetoxy-4-hydroxyindole.[898] Furthermore, when sterically hindered acids are used in the reaction with **1033**, stable 4-acyloxy analogues of **1033b** result.[899] An intramolecular hydrogen bond between the 4-hydroxyl group and the 3-carbethoxy carbonyl group has been proposed[899] as the driving force for the $4 \rightarrow 5$ acyl shift.

In another surprising development, Eiden and Kucklaender have reported[344] the isolation (20%) of 6-hydroxyindoles from *N*-aryl crotonates and *p*-benzoquinone in acetic acid at 0°. In acetone, the expected 5-hydroxyindoles result. Shvedov and co-workers have confirmed[966] the production of 6-hydroxyindoles in acetic acid with three different *N*-arylcrotonates; the *N*-methyl or unsubstituted aminocrotonates gave the normal 5-hydroxyindoles. Evidently under these conditions, direct Michael addition of the crotonate amino group to *p*-benzoquinone must occur.



1032

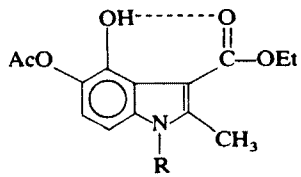


R = alkyl, aryl

1033; R′ = OH
1033a; R′ = OAc

281; R = alkyl
R′, R″ = H

1033b



(33)

1033c

III.G.6. Wehrli and co-workers, using Fremy's salt in dilute $NaHCO_3$ or acetic acid or oxygen at pH 6, have oxidized 6-hydroxydopamine (**311**, R = H) to the quinone anion, **314a**, in nearly quantitative yield. In strong alkali, cyclization occurred to give only 5,6-dihydroxyindole. Dithionite reduction of **314a** followed by acetylation gave 1-acetyl-5,6-diacetoxyindoline. No trihydroxyindolines or indolequinones could be detected (cf. Ref. 367).[891] Piattelli-Oriente and co-workers have prepared 1-acetyl-5,6-diacetoxyindoline by ferricyanide oxidation of dopamine followed by acetylation.[1060]

III.H.1. 1-Methyl-5-hydroxy- and 1-methyl-5-methoxyindole were prepared[904] in 89 and 85% yield, respectively, by reduction of the oxindoles with diborane in THF at 0°.

Various 4-oxotetrahydroindoles have been aromatized to 4-hydroxyindoles using Raney nickel in refluxing xylene[909] or 10% palladium–carbon.[935]

Julia and Pascal have developed[902] a new route to both 4- and 7-hydroxyindoles by Hoesch cyclization of the pyrrolebutyronitriles **1035** and **1036** produced in a 4:1 ratio from pyrrolemagnesium bromide and γ-chlorobutyronitrile. Aromatization (Pd/C) of **1034** and **1039** provided

the hydroxyindoles. A more satisfactory route to **1039** employed the $ZnCl_2$-catalyzed cyclization of the mixed anhydride of the acid **1037** resulting on hydrolysis of **1035**. Another route to 4-oxotetrahydroindoles featured the Stobbe condensation with 2-formylpyrrole, then hydrogenation to give **1038** which could be cyclized to **1040** and aromatized to **1041** (R = Et). El-Rayyes has determined that the initial Stobbe condensation product from 2-formylpyrrole or 1-methyl-2-formylpyrrole (80, 95%, respectively) has the *E* configuration and can be cyclized directly and quantitatively with $NaOAc/Ac_2O$ to **1041** (R = Me).[905] Although **1041** could be hydrolyzed to **1042**, neither group reported decarboxylation attempts.

III.H.4. Another new indole synthesis, also based upon the cyclization of pyrrole derivatives, has been developed by Oikawa and co-workers, who prepared 5-methoxy- or 5-ethoxy-2-phenylindole in 80 and 72% yield, respectively, on treatment of the β-ketosulfides **1043** with *p*-TsOH in alcohol. Spontaneous aromatization occurs by elimination of methylthiol from the intermediate **1044**, which is the product (63%) when the cyclization is conducted in THF.[896]

Petrova and co-workers report[914] a new synthesis of 5- and 6-methoxyindole by hydrogen peroxide oxidation of the appropriate methoxy-β-naphthols to diacids **1045** which are converted with PCl_5 and ammonia to the diamides **1046**. Hofmann rearrangement with cyclization provided the indoles.

III.H.4. Fujiwara and co-workers have prepared 2,3-dimethyl-4-hydroxyindole (60%) and its 1-ethyl derivative by rearrangement of the 4-aminobenzofurans with acid.[913]

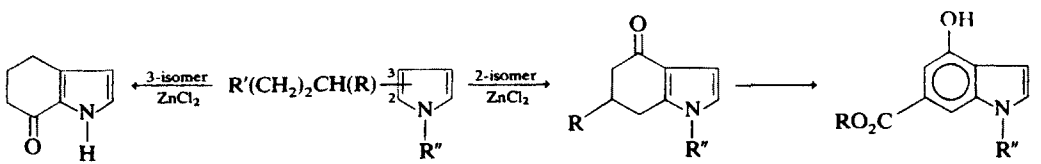
Alper and Prickett prepared[907] the 2-styryl-substituted 6-methoxyindole **1048** in 90% yield by cobalt octacarbonyl-catalyzed rearrangement of the azirine **1047**.

2-Methyl-6-methoxyindole has been prepared in 81% overall yield by Hegedus and co-workers, who treated 2-allyl-5-methoxyaniline with a palladium chloride–acetonitrile complex in THF followed by treatment with triethylamine.[906]

Lalloz and Caubere report[917] a synthesis of 2-phenyl-6-methoxyindole in 61% yield by base treatment of the acetophenone anil of 2-chloro-5-methoxyaniline in HMPT–THF at 60°. The reaction proceeds through anionic addition to an aryne intermediate.

Details on Gassman's novel syntheses of 5- and 7-methoxy-2-methylindole have appeared.[1022c]

Malesani and Rigatti have prepared 2,3-dialkylated 4,7-dimethoxyindoles by alkylation of 4,7-dimethoxyindolemagnesium bromide with methyl or ethyl iodide to 3-alkylindoles, then, on repetition of this



1034

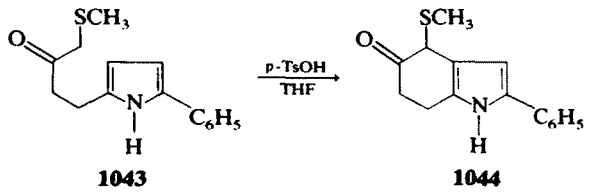
isomer $R'' = H$ or CH_3

1035; 2- $R = H$, $R' = CN$, $R'' = H$
1036; 3- $R = H$, $R' = CN$, $R'' = H$
1037; 2- $R = H$, $R' = CO_2H$, $R'' = H$
1038; 2- $R = CO_2CH_3$ or CO_2Et, $R' = CO_2H$, $R'' = H$

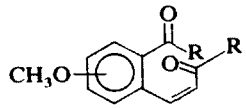
1039; $R = R'' = H$
1040; $R = CO_2Et$, $R'' = H$

$R'' = H$ or CH_3

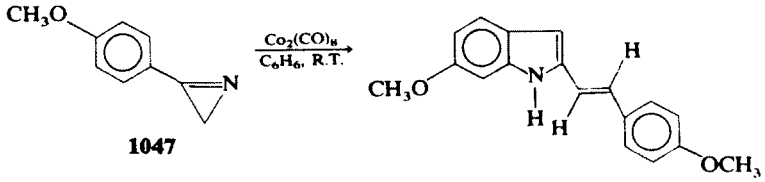
1041; $R = CH_3$ or Et
1042; $R = H$



1043 **1044**



1045; R = OH
1046; R = NH_2

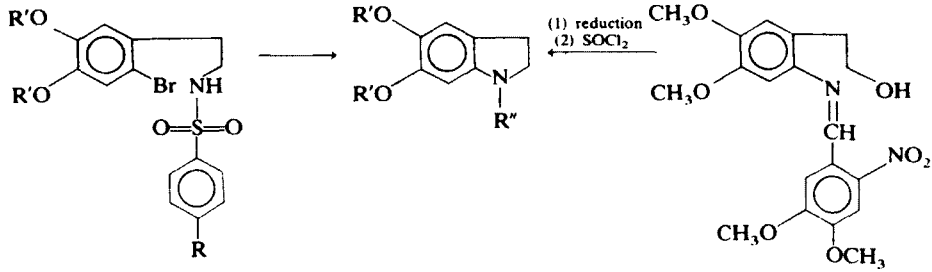


1047 **1048**

sequence, to 3,3-dialkylindolenines. On acid treatment, these rearrange to the 2,3-dialkyl isomers.[951]

Iida and co-workers have prepared 6-methoxyindoline in 47% yield by Julia's aryne cyclization.[915]

Another aryne cyclization reaction has been employed by Ito and co-workers who prepared a number of 5,6-dialkoxyindolines **1050** by reaction of the 2-bromophenethylamine sulfonamides **1049** with DMSO anion. Interestingly, cyclization of the free amines gave a mixture of the indoline and the related indole.[916] Kametani and co-workers prepared the 5,6-dimethoxyindoline **1051** by reduction of the Schiff's base **1052** and cyclization using thionyl chloride.[893]



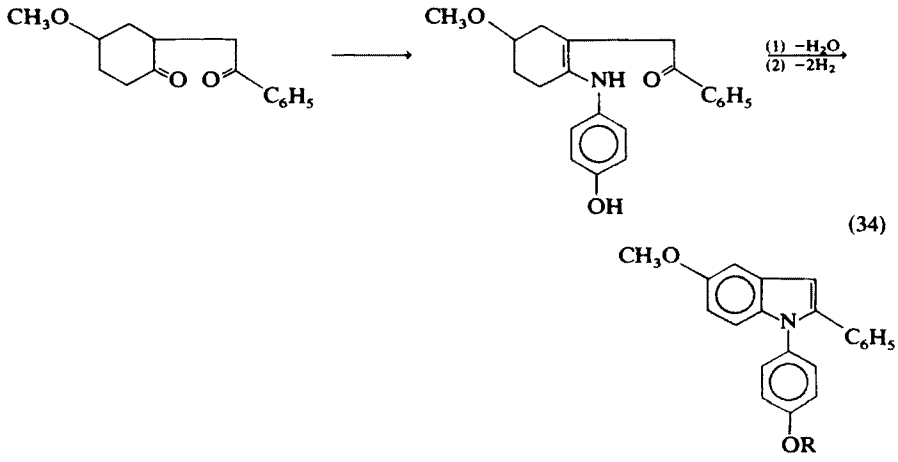
R = H, CH_3
R' = CH_3, C_7H_7
R,R' = CH_2-
1049

1050; R'' = $SO_2C_6H_4$-R(p)
1051; R'' = $CH_2C_6H_2(OCH_3)_2NO_2$

1052

A patent on Kametani's radical cyclization of **406** to 5-hydroxy-6-methoxyindoles has been issued.[910]

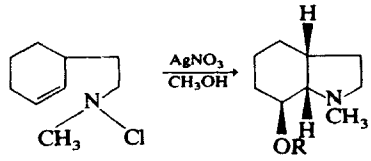
Using a synthesis related to that of Stetter and Lauterbach, Bell and Zalay have prepared an *N*-aryl-2-phenyl-5-methoxyindole **1053** by the route given in eq. 34. The derivative **1054** is reported to be an oral contraceptive in rats.[908a,b]



(34)

1053; R = H
1054; R = $CH_2CH_2N(Et)_2$

Mokotoff and Sprecher have isolated,[889] as principal products in the nitrenium ion cyclization of the *N*-chloroamine **1055**, *cis*-octahydroindoles substituted in the 7-position with methoxy (**1056**) or nitrato groups (**1057**).



1055

1056; R = CH_3 ratio 3
1057; R = NO_2 ratio 1

IV.A. Details on the preparation of 4- and 6-methoxygramine by the novel method of Germain and Bourdais have appeared.[884]

V.A.1. Bufotenidine has been isolated as its hydrogen citrate.[918]

V.B.1. Serotonin labeled in the α-position with ^{11}C[919] or ^{14}C[911,912] has been prepared from 5-benzyloxygramine methosulfate and the labeled sodium cyanides, followed by $LiAlH_4$ reduction and hydrogenolysis.

Julia and Pascal have prepared[901] 4-ethoxytryptamine (31%) by the gramine–cyanide route, and 4-ethoxy-*N*,*N*-dimethyltryptamine (31%) by conducting the reduction of the nitrile in the presence of dimethylamine. Germain and Bourdais, on the other hand, synthesized *O*-methylpsilocin by hydrolysis of 4-methoxyindole-3-acetonitrile to the 3-acetic acid derivative, then conversion to the dimethylamide and reduction to the tryptamine.[937] The 1-methyl or 1-benzyl *O*-methylpsilocin or *O*-isopropyl psilocin were similarly prepared.

Zirngibl and co-workers, using the gramine–nitroalkane route, have prepared a series of α-mono and α-dialkyl 1-substituted 5-methoxytryptamines as anoretics.[920]

Flaugh and Clemens have prepared 6-halo-5-methoxytryptamines by the gramine–cyanide route. *N*-Acetyl-6-chloro-5-methoxytryptamine inhibited ovulation in the rat on oral administration.[927]

Shvedov and co-workers prepared 1-methyl(or benzyl or phenyl)-2-benzyl-5-methoxytryptamine by the gramine–cyanide route.[1058]

V.B.2. $\alpha,\alpha,\beta,\beta$-$D_4$-Serotonin has been prepared by the oxalyl chloride route from 5-benzyloxyindole by $LiAlD_4$ reduction of the ensuing glyoxamide,[921,922] and hydrogenolytic debenzylation.

Poletto and co-workers have prepared various 2,4-, 2,6-, or 2,7-dimethyl-5-methoxy-N^{ω},N^{ω}-dialkyltryptamines employing the oxalyl chloride route.[925a–e]

Lee and co-workers report[924] the synthesis of 5,7- and 6,7-dihydroxytryptamine and their N^{ω}-methyl or N^{ω}-ethyl or N^{ω},N^{ω}-dimethyl or N^{ω},N^{ω}-diethyl derivatives by the oxalyl chloride procedure from the appropriate dibenzyloxyindoles. Lithium aluminum hydride reduction of the glyoxamides in refluxing THF for not longer than four to five hours gave best results.

Smythies reports an interesting preparation of 2-benzyl-5-methoxytryptamine as a serotonin antagonist and sedative. 5-Methoxytryptamine was obtained employing the oxalyl chloride route and the benzaldehyde Schiff's base prepared and cyclized to the β-carboline **571** ($R'' = C_6H_5$) which was hydrogenolyzed with a Pd/C catalyst.[928a–c]

Repke and co-workers have prepared psilocin analogues from 4-acetoxyindole, oxalyl chloride, and a number of acyclic and cyclic secondary amines.[935] Lithium aluminum hydride reduction of the glyoxamide intermediate also cleaved the acetoxy group.

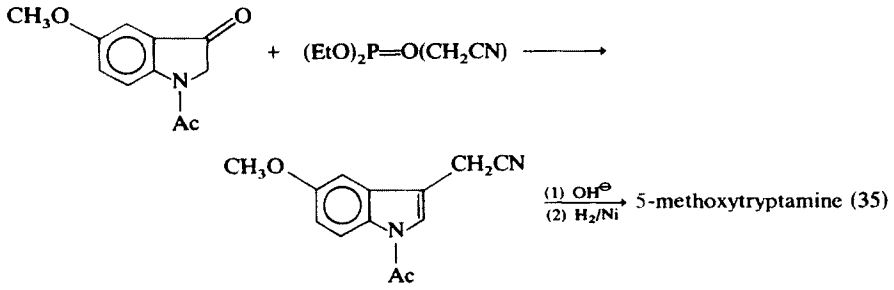
Papanastassiou and Neumeyer have prepared[1051] a number of 4-methoxytryptamines dialkylated at N^{ω} with propynyl groups using reduction of glyoxamides or aminolysis of 3-bromoethyl derivatives.

V.B.3. The indole-3-aldehyde–nitroalkane route has been employed by Lee and co-workers in the synthesis of 5-hydroxy-7-methyltryptamine,

5,7-dihydroxytryptamine, and its α-methyl derivative.[924] Misztal has prepared 1-methyl- and 1,α-dimethyl-5-methoxytryptamine by this procedure.[926]

V.B.4. Poletto and co-workers prepared[925a] various 2-methyl-5-methoxytryptamines by reaction of 5-methoxyindolemagnesium bromide with α-chloroacetyl chloride, then aminolysis and lithium aluminum hydride reduction.

V.B.5. Buzas and co-workers have applied the Wittig–Horner reaction with 1-acetylindoxyl derivatives to a general tryptamine synthesis. 5-Methoxytryptamine (60%) was synthesized in this manner[929] (eq. 35).

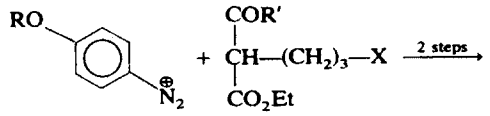


V.C.1.b. 5-Methoxytryptamine has been prepared by the Grandberg method from γ-chlorobutyraldehyde and 4-methoxyphenylhydrazine in methanol.[934a] 5-Benzyloxytryptamine and its 2-methyl derivative were prepared in an improved procedure using the bisulfite adducts of the above aldehyde or γ-chloropentan-2-one, respectively.[934b]

V.C.1.c. An interesting variation of the Grandberg tryptamine procedure was recently disclosed[931a,b] by Szantay and co-workers for their preparation of 5-methoxytryptamine (13% overall yield) by Japp–Klingemann reaction of **1058** with **1059** or **1060**. The latter compounds are much easier to prepare than the γ-chlorobutyraldehye required in the Grandberg procedure. Steps of deacetylation or decarboethoxylation, cyclization (preferably in *n*-butanol), saponification of **1062**, and decarboxylation gave 5-methoxytryptamine.

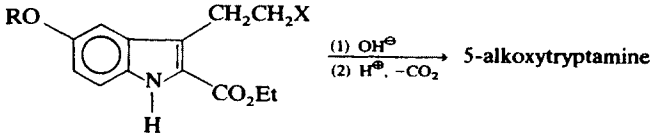
Gordeev and co-workers have employed[932] a variation of Sletzinger's route to tryptamines by using **1061** to prepare a number of 5-alkoxytryptamines including ethoxy, propoxy, and complex 5-hydroxy glycol ethers via **1063**.

V.C.2. Kirk has recently prepared[933] 6-fluoro- and 4,6-difluoroserotonin by the Abramovitch–Shapiro procedure from diazonium salts of 2-fluoro- and 2,6-difluoroanisidine, respectively. In the former case, only one carboline of the two possible is produced, evidently because



1058; R = CH_3, and others

1059; R′ = OH, X = Cl
1060; R′ = CH_3, X = Cl
1061; R′ = CH_3; X = phthalimido

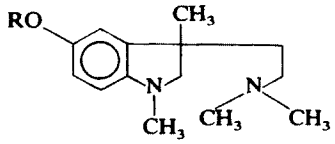


1062; X = NH_2
1063; X = phthalimido

of the directive effect of the fluoro substituent. Both the mono- and difluoro-substituted methoxycarbolines were more resistant to alkaline hydrolysis than the usual methoxycarbolines, but could be successfully hydrolyzed and decarboxylated to the mono- and difluoro-5-methoxytryptamines. These were demethylated in 50 and 30% yield, respectively, to the mono- and difluoroserotonins with boron tribromide, apparently the first published application of this reagent in the methoxyindole field. The mono- and difluoromelatonins were prepared by *N*-acetylation of the fluoromethoxytryptamines.

V.C.4. Seebach and co-workers have reported[936] details on their syntheses of intermediates **550** and **558** for Harley-Mason's bufotenine and Julia's 1,*O*-dimethylpsilocin syntheses. In their hands, 74 and 70% yields, respectively, of these tryptamines were obtained.

Mahamadi and co-workers have prepared indolines **1064** related to eserine by C-3 alkylation of 1,3-dimethyl-5-alkoxyoxindoles with β-chloroethylamines and $LiBH_4$ reduction to the indolines.[903] Indoline–propylamines were also prepared.



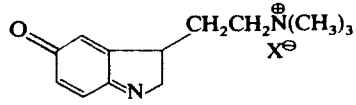
1064; R = CH_3, C_2H_5

V.D.2. Boch and Molle have prepared various 5- or 6-mono- and 5,6-dialkoxytryptamines alkylated at N^{ω} via Schiff's base intermediates.[944]

Aries has prepared an *N,N*-diethyl-7-methoxytryptamine substituted at N-1 with a γ-butyrophenone derivative.[942]

Kametani and co-workers have reported[941] that the reaction of N^{ω}-ethoxycarbonyl-5-methoxytryptamine with CH_3OSO_2F ("magic methyl") gives as the main products, N^{ω}-methyl-N^{ω}-ethoxycarbonyl-5-methoxytryptamine and a rearranged N^{ω}-ethoxycarbonyl isotryptamine with N^{ω}-ethoxycarbonyl-5-methoxytryptamine-6-methylsulfonate and other materials as minor products.

Hydrogenation of the quarternary methyl ammonium salts of serotonin with a palladium catalyst in 5% HCl leads to the 2,3-dihydro derivative which can be oxidized by dichromate to the quinone imines **1065**.[938] These rearrange slowly with acid to the starting indole or undergo borohydride reduction to the 2,3-dihydro derivative.[939] Reduction of 5-methoxytryptamine with the palladium catalyst fails to produce a 2,3-dihydro derivative.[938]

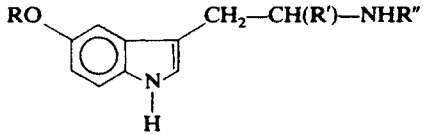


1065

X = Cl, I

Deuterium exchange of the aromatic protons of 5- and 6-hydroxytryptamine has been studied by nmr and the following relative rates assigned: for 5-OH; 4 > 6 > 2 and for 6-OH; 7 ≥ 2 ≥ 5.[940]

Neklyudov and co-workers have reported syntheses of the diamino 5-alkoxyindole derivatives **1066** and **1067** by lithium aluminum hydride reduction of *N*-glycyl-5-methoxytryptamine and 5-benzyloxytryptophanamide, respectively.[930]



1066; R = CH_3, R′ = H, R″ = $(CH)_2NH_2$

1067; R = $CH_2C_6H_5$, R′ = CH_2NH_2, R″ = H

Pullman and co-workers have published[1048] molecular orbital calculations on serotonin, 5-methoxytryptamine, psilocin, psilocybin, and bufotenine with regard to conformations and hydration sites of the protonated amines.

VI.B. 2-Methyl-5-methoxyhomotryptamine has been prepared by the

Grandberg method,[945] and 5-methoxy-, 5-ethoxy-, and 7-ethoxyhomotryptamine were synthesized by classical procedures.[946] Kawamura and Yoneda have prepared a number of 1-(alkylaminopropyl) derivatives of 2-phenyl-4,5,6-trimethoxyindole.[948] 3-Phenyl-substituted 5-methoxy-, 5-ethoxy-, and 5-benzyloxyisotryptamine were prepared by the indole-2-aldehyde–nitromethane route.[983]

VI.C. Alemany, Soto, and co-workers have prepared a series of *N*-propargyl-substituted 3-aminomethyl-5-alkoxyindoles as inhibitors of monoamine oxidase.[943a,b] These were prepared by 3-formylation of 5-methoxy- or 5-benzyloxyindole, Schiff's base formation with primary amines, reduction, and finally alkylation with propargyl bromide. Other *N*-propargyl-substituted 3-aminomethyl-4-methoxyindoles were prepared by Papanastassiou and Neumeyer.[1051]

Fauran and co-workers have prepared a series of 1-phenyl-2-methyl-5-methoxyindole 3-alkylaminomethyl derivatives with a wide range of physiological activities.[947]

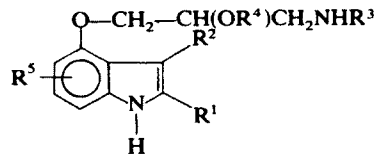
Germain and Bourdais have prepared a series of 3-(dimethylaminomethyl)indoles substituted at N-1 with various benzyl derivatives.[937]

VII.B.1. Shaikh has reported[952] the direct formation of 4,7-indoloquinone from 2,3-dimethyl-4,7-dimethoxyindole by silver oxide in nitric acid oxidation.

VII.B.2. A review by Swan on melanin preparations and structural work has appeared.[895]

VII.C. Wrotek has prepared various ethers of 2-methyl-5-hydroxyindole with alkyl sulfates.[949a,b] Julia and Pascal have prepared 4-ethoxy-, 4-benzyloxy-, and 4-allyloxyindole by alkylation of 4-hydroxyindole with alkyl halides and NaH in HMPT.[902]

An unusually large number of γ-amino-2-hydroxy (or alkoxy or acyloxy)propoxy ethers **1068** of 4-hydroxyindole or its derivatives have been synthesized by Sandoz[1009a–o] and Boehringer[1041a,b] chemists as drugs for circulatory or heart disorders. These were prepared by *O*-alkylation of 4-hydroxyindoles with epichlorohydrin followed by aminolysis of the resulting 2,3-epoxy ethers.



1068; R^1, R^2, R^3 = H, alkyl or hydroxyalkyl
R^4 = H, alkyl, acyl
R^5 = CH_3, CH_2OH

Heacock and Forrest have prepared the bis(trimethylsilyl) derivative of 1-methyl-5,6-dihydroxyindole. Adrenochrome gave this derivative as well as the tris(trimethylsilyl) derivative of 5,6-dihydroxy-1-methylindoxyl among other products.[954]

The sterically hindered nitrogen of 7-methoxyindole was methylated by use of methyl iodide and sodamide–ammonia in 95% yield.[955]

VII.D. Malesani and co-workers have demethylated various 4,7-dimethoxyindoles to the 4,7-indoloquinones with $AlCl_3$ in benzene.[950,951] They note[1047] that 2,3-dialkylation evidently favors the proportion of dihydroxy tautomer in equilibrium with the quinone. With the 2-phenyl or 3-acyl derivatives, the demethylated material is solely in the phenolic form, giving the quinone only upon sublimation. These results support Malesani's hypothesis that electron-withdrawing groups, particularly at C-2 or C-3, favor the diphenol tautomer. During the preparation[1046] of 3-benzoyl or 3(*p*-methoxybenzoyl)-4,7-dimethoxyindole by the reaction of 4,7-dimethoxyindolemagnesium halide with the benzoyl chlorides, a selective 4-*O*-demethylation occurs. In this case, as in the example provided by Kucklaender (cf. **1033c**), the driving force may be the establishment of a strong 4-hydroxy–3-C=0 hydrogen-bond. Normal 4,7-dimethoxyindole products resulted, however, from reactions with acetyl chloride or *p*-nitrobenzoyl chloride. All these 3-acyl derivatives on demethylation with $AlCl_3$ in benzene gave the diphenolic tautomers exclusively.

VII.E.2. Mokotoff has prepared *cis*-octahydro derivatives of 1-methyl-5-methoxy- and 1-methyl-7-methoxyindole by hydrogenation of the indoles with a platinum catalyst in acetic acid. The hydrogenolysis by-product, *cis*-1-methyl-octahydroindole, was also obtained in 50 and 40% yield, respectively.[955] Mokotoff showed, interestingly, that the methoxyoctahydroindoles are not intermediates in the hydrogenolysis. Toth and Gerecs have reduced 6-methoxyindole to the 2,3-dihydro derivative.[1055]

VII.E.4. Iida and co-workers reduced 6-methoxyindoline to the 4,5-dihydro derivative with $LiAlH_4$ in CH_3OH–THF–liquid NH_3 in quantitative yield.[915]

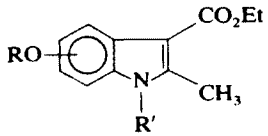
VII.E.4. Troxler and Hofmann prepared[1040] 5-methyl-4-hydroxyindole by hydrogenation (Pd/Al_2O_3) of 5-dimethylaminomethyl-4-hydroxyindole in methanol.

VII.F. In agreement with the results of Troxler,[384] Monti and Johnson have shown that piperidinomethylation of 5-hydroxyindole occurs solely in the 4-position (81% yield), probably via an H-bonded complex. If the 4-position is blocked, then substitution occurs at C-3 or N-1.[956]

A number of studies have appeared on electrophilic substitutions of

hydroxyindoles and their *O*-methyl or acyl derivatives. These deal chiefly with indoles prepared by the Nenitzescu reaction, typically 1-substituted 2-methyl-5(or 6)-hydroxyindole-3-carboxylic acid ethyl esters **1069**. The 5-hydroxy derivatives undergo the Mannich reaction[958,1058] or diazo coupling[957] in the 4-position, and the methyl ether undergoes Mannich reaction (35–55%) in the 6-position.[959,960] Nitration of the 5-methoxy or 5-acetoxy derivatives with HNO_3 in H_2SO_4 at $-10°$ gave solely the 6-nitro derivatives,[962] and the 5-hydroxy derivative gave some 4-substitution in addition. When the nitration is conducted in the weak acid, acetic acid, the 4,6-dinitro derivative is the major product from the 5-hydroxy substrate,[957,961] whereas the 5-methoxy compound gave a mixture of 4- and 6-mononitro products and the 5-acetoxy derivative gave only the 6-nitro product.[961] The 5-hydroxy and 5-acetoxy compounds undergo *o*-nitrophenylsulfenylation and bromination, respectively, in the 6-position.[957,965] When the 6-position of the 5-acetoxy compound is blocked by methylation, then bromination occurs in the 4-position.[965] Vilsmeier formylation of the 5-methoxy compound gives the 6-formyl derivative.[963] Friedel–Crafts acetylation of ethyl 5-hydroxyindole-2-carboxylate yields the 4-acetyl derivative while ethyl 2-methyl-5-hydroxyindole-3-carboxylate gave the 6-acetyl derivative.[1054]

The 6-hydroxy derivatives **1069** (R′ = phenyl, substituted phenyl) undergo Mannich reactions in the 7-position,[966] dibromination (66%),[964] and dinitration (31%)[964] in the 5,7-positions. The 6-methoxy or 6-acetoxy derivatives undergo bromination in the 5-position (71, 86% yield, respectively).[964]

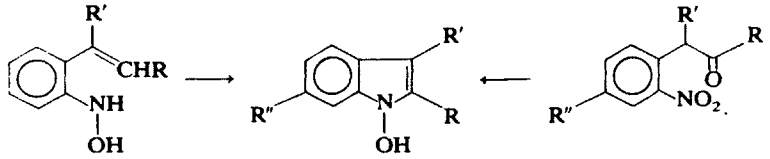


1069; RO = 5- or 6- OH, OCH_3, or OAc
R′ = CH_3 or aryl

7-Methoxy-2,3-dimethylindole undergoes nitration in H_2SO_4 in the 6-position (32%).[962]

VII.G. Sundberg and Parton have studied[953] the lithiation of 1-methyl-5-methoxyindole with *n*- and *t*-butyllithium. The more hindered reagent exchanges with hydrogen only at C-2 but the other introduced lithium also at the C-4 and C-6 positions. 1-Benzenesulfonamido-6-methoxyindole also gives 2-lithiation with *t*-butyllithium. The 2-lithioindoles, on reaction with various aryl aldehydes or ketones, provided secondary or tertiary indole-2-methanols.

VIII. Hazard and Tallec have reported electrochemical syntheses of a



1070a **1071** **1070b**

R = H, alkyl, Cl, CN, CO_2Et, C_6H_5
R′ = H, CN, CO_2Et, Ac, C_6H_5
R″ = H or CF_3

large number of 1-hydroxyindoles **1071** from aromatic hydroxylamines **1070a**[968] or nitro compounds **1070b**.[967]

Acheson and co-workers have synthesized, for the first time, 2-unsubstituted 1-alkoxyindoles, namely, 1-methoxy- and 1,5-dimethoxyindole, by Zn–NH_4Cl reduction of 2-nitrophenylacetaldehydes, followed by *O*-acetylation, hydrolysis, and methylation.[969] They undergo electrophilic substitution, for example, the Mannich reaction, in the 3-position. 1-Methoxyindole was also prepared by lithium aluminum hydride reduction of 1-methoxyoxindole.[969]

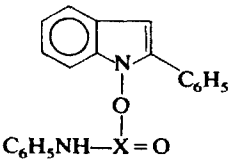
Saki and Katano have shown[970] that the structure **688c** put forward by Elks for the reaction product of ethyl 3-methylindole-2-carboxylate and sulfuryl chloride in HOAc is in error and that the actual product is 3-carbethoxy-3-methyloxindole, resulting by rearrangement of the ethoxycarbonyl group via a 3-acetoxyindolenine intermediate.

The uv irradiation of 1-methoxy- or 1-ethoxy-2-phenylindole in alcohols provided the 3-alkoxy isomers (18, 12% yields, respectively) as well as 2-phenylindole as the major products. The 1-methoxyindole also gave, as a minor product, a diindolyl methane, while the 1-ethoxyindole gave (3%) a benzene-ring-substituted (position unknown) isomer.[971]

Bristow and co-workers have oxidized 2-substituted indolines with four equivalents of *m*-chloroperbenzoic acid to the previously unknown 2-substituted (R = Me, *t*-Bu, C_6H_5) isatogens (30–60%) 1-hydroxyindole intermediates.[973]

Bond and Hooper have shown that other 2-substituted isatogens (R = C_6H_5, 2-pyridyl, 2-CO_2CH_3) can be prepared in 76–98% yield by oxidation of appropriate 1-hydroxyindoles with 4-nitroperbenzoic acid.[972]

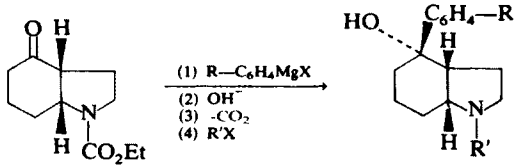
Bruni and Poloni have studied the decomposition of the adducts **1072** resulting from reaction of phenylisocyanate or phenylisothiocyanate with 2-phenyl-1-hydroxyindole. On refluxing in xylene these lose CO_2 and SO_2, respectively, to give the same mixture of products—namely, the 3,3′-dimer of 2-phenylindole, 2-phenylindole, 2-phenyl-3-anilinoindole, and 2-phenyl-3-anilidene-indolenine.[1057].



1072; X = C, S

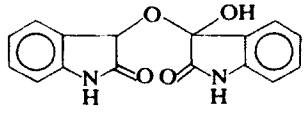
IX.A.2. Hooper and Pitkethly observed that the reduction of 1-alkyl-2-benzylidene-3-indolones with $NaBH_4$ to 2-benzylindoles proceeds via intermediate 3-indolinols.[976]

Berthold and Troxler prepared various cis octahydro-4-indolinols **1074** by reaction of substituted phenyl Grignard reagents with **1073**, followed by saponification and *N*-alkylation.[975]



1073 **1074;** R = various substituents
R' = complex alkyl–aryl groups

IX.A.3. Roth and Lausen found that 1-piperidinomethylisatin on lithium aluminum hydride reduction gave a 2,3-indolinediol, and $NaBH_4$ reduction gave a dimeric product **1075** in addition to the rearranged product, 3-piperidinomethyldioxindole.[974]



1075

IX.B.1.a. Fauran and co-workers have prepared a number of 3-hydroxymethylindoles by Vilsmeier formylation of 1-aryl-2-methyl-5-methoxyindoles followed by $NaBH_4$ reduction.[977] One derivative was reported to triple the blood flow in the guinea pig heart at a concentration of only 1 μg/ml.

Golubev and Golubeva have reported syntheses of glycerol ethers of indole-3-methanol and its 5-methoxy derivative. These were prepared (38%) by reaction of the gramine methiodides with the sodium salt of glycerol 2,3-acetonide or, less satisfactorily, by reaction of the indole-3-methanols with glycerol acetonide and NaOH catalysis.[989]

IX.B.1.b. A series of 5-substituted (Me, MeO, EtO, $C_6H_5CH_2O$, Cl, Br, H) 3-phenylindole-2-methanols were synthesized as intermediates for isotryptamine preparations.[983] Indole-2-methanols with 5-, 6-, and 7-methoxy substituents and either 3-H or 3-CH_3 substituents were similarly prepared, by $LiAlH_4$ reduction of the ethyl-2-carboxylates.[1061]

Heerdt and co-workers have reported[978] the synthesis of 12 indole-2-methanols including the 5-methoxy derivative by hydrogenation of ethyl indole-2-carboxylates.

Mudry and Frasca report the synthesis of 2-hydroxymethyl-3-methyl-5-nitroindole by $NaBH_4$ reduction of the 2-formyl compound which is obtained (2–48%) on photooxidation of 2,3-dimethyl-5-nitroindole in acetic acid.[987]

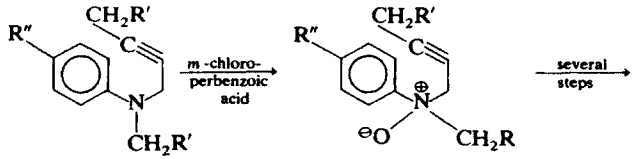
Sundberg and co-workers have prepared[953,979] a series of aryl-substituted indole-2-carbinols by reaction of *N*-protected (CH_2OCH_3, Cbz, Ts, Me_3Si, etc) 2-lithioindoles with aromatic aldehydes. These could be converted to 2-acylindoles by oxidation.[979]

IX.B.1.c. Skvortsova and co-workers have prepared various *N*-(α-alkoxyethyl)indoles by reaction of *N*-vinylindole with alcohols at 100–150° and the catalyst system $Cu(OAc)_2$–HOAc–boric acid.[1008]

Derivatives of indole-2,3-dimethanol **1080–1084** result in high yield from oxidation of *N*-propargyl-substituted anilines **1076** and **1077** with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature[980] (Scheme 91). This fascinating and potentially very important interconversion, discovered by Thyagarajan and co-workers, proceeds through the *N*-oxide **1078** and carbinolamine **1079** intermediates. An intriguing Claisen-type rearrangement is proposed for the conversion of **1078** to **1079**. The complex derivatives **1084** arise from bis(4-aryloxy-2-butynyl)anilines.[981] The ethers **1081** and alcohol **1082** arise from the alcoholysis or alkaline hydrolysis, respectively, of the primary product **1080**.[980] Makisani and Takada have extended this reaction to the preparation of thiophenyl ethers, nitriles, and azides **1083** by conducting the oxidation of **1077** in the presence of the nucleophiles thiophenol, cyanide ion, or azide ion.[982a,b]

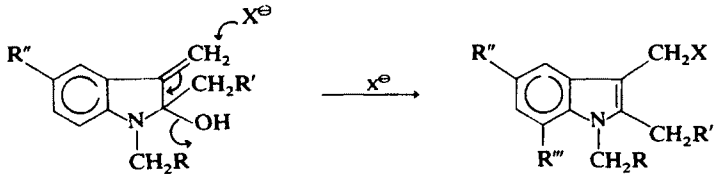
IX.B.2.a. Tryptophol (70%)[986,1042] and 2-methyl-[986] and 5-benzyloxytryptophol[986] were prepared by $NaBH_4$ or $LiAlH_4$ reduction of the appropriate indoleglyoxylic esters or halides.

Grandberg and co-workers have developed a new synthesis of tryptophols from phenylhydrazine hydrochlorides and various furan derivatives (γ-hydroxybutyraldehyde or -pentan-2-one equivalents) in dioxane or isopropanol (Scheme 92). Appropriately substituted phenylhydrazines with 2,3-dihydrofuran **1089** provide 20–70% yields or tryptophol or its 1-methyl, 1-phenyl, or 1-benzyl derivatives or the ring-substituted 5-methyl-, 7-methyl-, and 7-methoxytryptophol **1087**[991] 2-Hydroxy-[996a] or



1076; R = R'' = H R' = *p*-ClC$_6$H$_4$O—
1077; R = C$_6$H$_5$, R' = H, CH$_3$, CN,
R'' = H, Cl, CH$_3$O

1078



1079

X⊖ = 3-ClC$_6$H$_4$CO$_2$, C$_6$H$_5$S,
CN, N$_3$

1080–1084

R = H, R' = 4-Cl-C$_6$H$_4$O
R'' = R''' = H

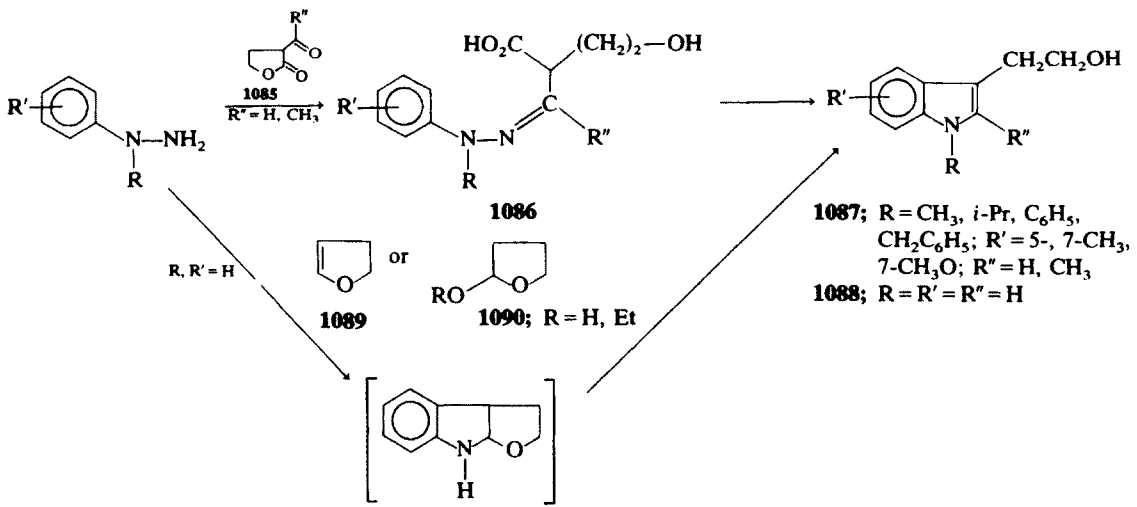
1080; X = 3-Cl—C$_6$H$_4$CO$_2$
1081; X = OCH$_3$, OC$_2$H$_5$
1082; X = OH
1083; R = C$_6$H$_5$, R' = H, CH$_3$, CN,
R'' = H, Cl, CH$_3$O, R''' = H
X = SC$_6$H$_5$, CN, N$_3$
1084; R = C≡C—CH$_2$—OC$_6$H$_4$—*p*-Cl(OCH$_3$),
R' = 3-Cl—C$_6$H$_4$CO$_2$, CH$_3$O, C$_2$H$_5$O
R'' = Cl, Br[6], CH$_3$, CH$_3$O
R''' = H or CH$_3$, X = 3-Cl—C$_6$H$_4$CO$_2$—

Scheme 91

2-ethoxytetrahydrofuran[993] **1090** and phenylhydrazine hydrochloride also provided tryptophol **1088** 1-Substituted and 1,2-disubstituted tryptophols **1087** (R' = H) also result (41–58%) from *N*-substituted phenylhydrazines and α-formyl-[992,995,996b] or α-acetyl-γ-butyrolactone,[992,994,996c] respectively. This reaction generates the phenylhydrazones of α-(2-hydroxyethyl)-β-ketoacids **1086** which decarboxylate to phenylhydrazones of γ-hydroxybutyraldehyde or γ-hydroxypentan-2-one, respectively. Fischer cyclization gives the 2-H[992,995] or 2-methyltryptophols[992,994] **1087** (R' = H) in 50–60% yield.

IX.B.2.b. α-Methyl- or α-isopropyltryptophol result in 32 and 37% yield, respectively, on direct lithium aluminum hydride reduction of Tacconi's intermediates **485** (R = H, R' = Me, *i*-Pr). Some cleavage to skatole and ethanol or isobutanol also occurs.[984]

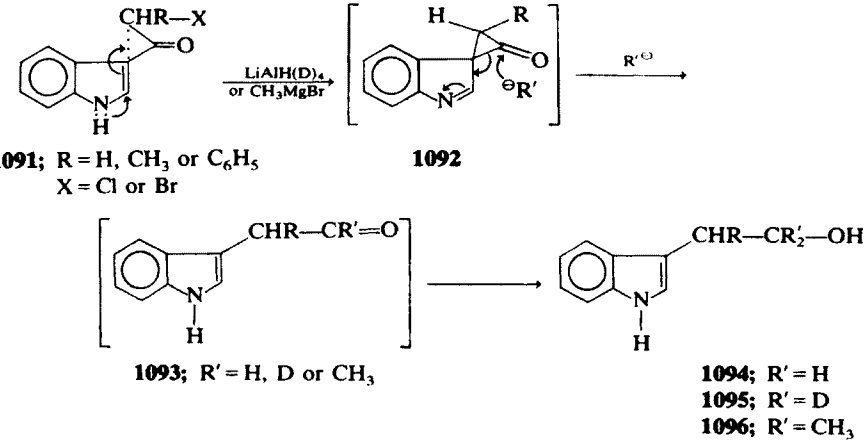
McElvoy and Allen have prepared[985] 1-acetyl-2,3-dihydrotryptophol


R″
1085
R″ = H, CH3
HO2C
(CH2)2—OH
R′
N—NH2
R
N—N
C
R″
1086
CH2CH2OH
1087; R = CH3, i-Pr, C6H5, CH2C6H5; R′ = 5-, 7-CH3, 7-CH3O; R″ = H, CH3
1088; R = R′ = R″ = H
R, R′ = H
or
1089
RO
1090; R = H, Et
N
H
O

Scheme 92

by diborane reduction of 1-acetylindoline-3-acetic acid. Surprisingly, no amide reduction occurs here. They have also prepared (49–79% yield) 1-acetyl derivatives of 5,6-dimethoxy- and 5,6-methylenedioxytryptophol by diborane reductions of oxindole-3-ethanol derivatives or oxindole-3-ethyl acetate derivatives followed by acetylation.

Bergman and Baeckvall have reported an interesting new route to tryptophols (67–73%) **1094** by action of lithium aluminum hydride on 3-(α-haloacyl)indoles **1091**[988a,b] (Scheme 93). The reaction was shown to proceed via indolenine spirocyclopropanones **1092** and indole-3-acetaldehydes **1093**. Consistent with the Favorskii-type rearrangement proposed is the observation that reduction of **1091** (R = H) with $LiAlD_4$ produces α,α-dideuterotryptophol **1095** (R = H). When 3-chloroacetylindole is treated with methylmagnesium bromide, α,α-dimethyltryptophol **1096** (R = H) results, also via the intermediate **1092** (R = H).[988a]



1091; R = H, CH_3 or C_6H_5
X = Cl or Br

1092

1093; R' = H, D or CH_3

1094; R' = H
1095; R' = D
1096; R' = CH_3

Scheme 93

Grandberg and Dashkevich report[1059] the syntheses of a number of new methyl- and dimethylphysovenine analogues from phenylhydrazones of appropriate γ-hydroxyketones. The 5-benzyloxy analogue of **790** was among the compounds prepared.

IX.B.3. The Grandberg tryptophol procedure has been applied to the synthesis of homotryptophols by substituting pyran derivatives in place of the furans. 2,3-Dihydro-4*H*-pyran and the appropriate phenylhydrazines were employed in the following syntheses (% yield): homotryptophol (35); 1-methyl- (72), 1-phenyl- (56), 5-methyl- (35), 7-methyl- (24), and 7-methoxyhomotryptophol[993a,c] (25). *N*-benzylphenylhydrazine and 2-methyl-2,3-dihydropyran provided 1-benzyl-α-methylhomotryptophol.[990] The reaction failed with 2,3-dialkyldihydropyrans.[990] Grandberg and

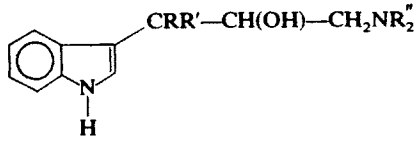
Moskvina prepared the following homotryptophols from 2-hydroxytetrahydropyran and the appropriate phenylhydrazine hydrochlorides in benzene: 1-methyl-, 5-methyl-, and 7-methylhomotryptophol.[993b,996a] A Japanese patent applies the Grandberg method to the syntheses of 4- and 6-fluorohomotryptophol in a product ratio of 1:3 from *m*-fluorophenylhydrazine.[997]

Homotryptophol and indole-3-butanol, employed as intermediates for the related alkyl bromides, were prepared by lithium aluminum hydride reduction of methyl esters.[1005]

IX.B.5. Plasvic and co-workers have prepared[999,1000] β-hydroxytryptamine (45%) and β-hydroxyserotonin (10%) by reaction of 3-(α-chloroacetyl)indole or its 5-benzyloxy derivative with dibenzylamine, followed by lithium aluminium hydride reduction, then debenzylation by hydrogenolysis.

Archibald has reported the related preparation of various β-hydroxytryptamines by aminolysis of 3-(α-bromoacetyl)indole followed by borohydride reduction.[998]

Starostina and co-workers have prepared indole-3-glycerol *N,N*-dialkylamino analogues (50–91%) **1098** by $NaBH_4$ reduction of the Mannich bases **1097**.[1003] Lithium aluminum hydride reduction of **1097** resulted in hydrogenolysis to the amino alcohols **1099** (70–90% yield).



$R'' = CH_3$, C_2H_5, $-(CH_2)_5-$, $-(CH_2)_6-$

1097: R,R' = O=

1098; R = H, R' = OH

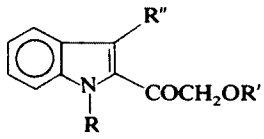
1099; R = R' = H

Preobrazhenskaya and co-workers have reduced oximes of **829** and the ethyl or benzyl ether oximes with aluminum amalgam or hydrogenations with Raney nickel or palladium–carbon catalysts to prepare β-aminotryptophol or the β-aminotryptophol ethers.[1001] β-Aminotryptophol was also prepared by lithium aluminum hydride reduction of the oxime of methyl indole-3-glyoxalate.[1001]

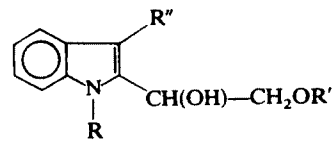
IX.B.6. Iyer and co-workers have convincing evidence that electrophilic substitution in 6-methoxyindoles can occur directly in the 2-position without initial 3-substitution. They find labeled 6-methoxyindole-3-butanol (cf. **821**) with BF_3 gives 7-methoxycarbazole (cf. **823**), where the label is not evenly distributed but rather indicates that some

5% of the cyclization occurs to give the tetrahydrocarbazole directly while 95% proceeds through the intermediate analogous to **824**. Similar results were obtained on solvolysis of the 6-methoxyindole-3-butanol tosylate. 6-Methoxyindole-3-butanol was prepared by Japp–Klingemann reaction of diazotized *m*-anisidine and 2-carbethoxycyclohexanone followed by steps of cyclization (HCl/EtOH), saponification, and decarboxylation to 6-methoxyindole-3-butyric acid, which was reduced with $LiAlD_4$ or B_2D_6 to the alcohol.[1004]

IX.B.7. Kost and co-workers have prepared a series of indole-2-ethylene glycol derivatives by acetolysis of 2-diazoacetylindole derivatives to the 2-(α-acetoxyacetyl)indoles **1100** followed by alkaline hydrolysis to the acyloin **1101**. The diazoketones on alcoholysis with BF_3 gave the ethers **1102** (24–81%). Lithium aluminum hydride reduction of the acyloin or alkoxyketones gave the glycols or glycol ethers (78–92%) **1103**, some of which were active as antibacterials.[1007]



$LiAlH_4$



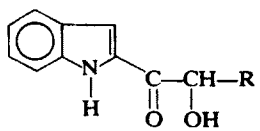
R = H, CH_3 or $CH_2C_6H_5$
R'' = H or CH_3

1100; R' = Ac
1101; R' = H
1102; R' = CH_3, C_2H_5, *i*-Pr, $CH_2C_6H_5$

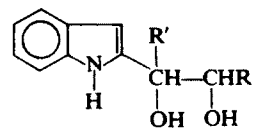
1103; R' = H, CH_3, C_2H_5, *i*-Pr, $CH_2C_6H_5$

Preobrazhenskaya and co-workers have reduced the acyloins **1104** with $LiAlH_4$ or $NaBH_4$ to the indole-2-propane or -butane glycols **1105**. A mixture of erythro and threo isomers formed with the propyl glycol, whereas the homologue gave only the erythro isomer. Methyl- or ethylmagnesium bromide on **1104** gave the glycols **1106**. The ethyl Grignard with the butyl acyloin gave solely the threo isomer, while erythro-threo mixtures occurred in the other reactions.[1006]

X.A.1.c. Wieland and co-workers have prepared[1013] the two diastereomeric 2-ethylthio-L-tryptophan sulfoxides from L-tryptophan and



R'MgX or $NaBH_4$



1104; R = CH_3, C_2H_5

R = CH_3, C_2H_5

1105; R' = H
1106; R' = CH_3, C_2H_5

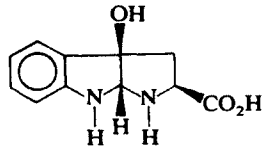
ethylsulfenyl chloride followed by oxidation with hydrogen peroxide in acetic acid. These were separated, and the sulfoxide with a positive Cotton effect between 280 and 360 nm was shown by X-ray diffraction to have the *R*-configuration, the same configuration as the naturally occurring toxin amanin (**928**) and *O*-acetyl-γ-amanitin, and interestingly, the same configuration as the toxic sulfoxide diastereomer produced on H_2O_2 oxidation of phalloidin. The phalloidin (*S*) sulfoxide is nontoxic. Furthermore, they demonstrated[1014] that only one of the pair of synthetic sulfoxide epimers resulting from hydrogen peroxide oxidation of deoxo-*O*-methyl-α-amanitin was toxic, and this epimer likewise possesses the *R*-configuration. The deoxoamatoxin was prepared by methylation of the indole 6-hydroxy group of **924**, followed by Raney nickel reduction.

Hino and co-workers find[1012] that 3-alkyl-or 3-arylindoles on treatment with S_2Cl_2 in ether or CH_2Cl_2 provide mixtures of 2,2′-disulfides with minor yields of 2,2′-mono- and trisulfides. These could be smoothly reduced with $NaBH_4$ to thiones. Interestingly, minor amounts of 2-chloro-substituted products were detected in reactions of 1-acetyl-3-methylindole and 3-*p*-tolylindole with S_2Cl_2.

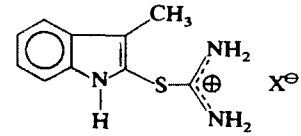
Indole-3-acetonitrile or 5-methoxyindole-3-acetonitrile with SCl_2 or S_2Cl_2 produced the indole 2,2′-sulfides or 2,2′-disulfides, respectively.[1028]

Bourdais and Obitz have prepared[1029] 2-methylthiotryptamines by amidation of 2-methylthioindole-3-acetic acid with various secondary amines followed by reduction.

Savige and Fontana have reported[1043] the facile synthesis of 2-(*S*-cysteinyl)-L-tryptophan ("tryptathione") in 80% yield by reaction of the tryptophan–peracetic acid oxidation product **1107** with cysteine in 25% TFA for two days at room temperature. Savige (see Ref. 1043) has reported other 2-alkylthiotryptophan syntheses from thiols with **1107**.



1107

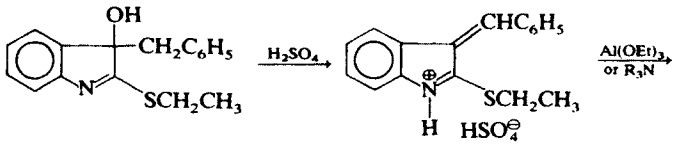


1108

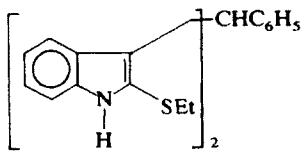
In contrast to the simple reaction of indole with iodine and thiourea [see Section X.B.1.(b).(1)] Hino and co-workers found[1010] skatole to yield six products: 3-methyl-3-isothioureidooxindole (23%), skatole-2-isothiouronium iodide (12%) (**1108**, X = I), and a sulfur-free oxindole (3-2′)indole dimer (13%) were the major products with 3-methyloxindole

(3%), 3-methyl dioxindole (6%), and 3-methylindolyl 2,2′-sulfide **896** (2%) detected as minor products. Compound **1108** (X = Br) was synthesized independently by reaction of thiourea with 2-bromoskatole.[1010]

X.A.2.a. Hino and Nakagawa have studied[1044] the hydrogen-acceptor reactions of the 3-benzylidene-2-ethylthioindolenine salt **1110** produced along with the sulfoxide of the starting material by autoxidation of 2-ethylthio-3-benzylindole (cf. ref. 1015) to the 3-hydroxyindolenine **1109** followed by dehydration with concentrated H_2SO_4. On treatment of **1110** with the Hantzsch ester in acetonitrile, aromatization of the latter to the pyridine occurs and **1110** is converted to 2-ethylthio-3-benzylindole. When **1110** is treated with aluminum ethoxide or tertiary amines, the diindolylmethane **1111** resulted, indicating the free base of **1110** is unstable.



1109 **1110**

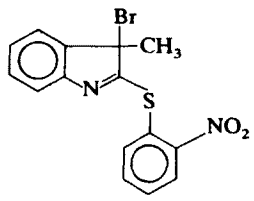


1111

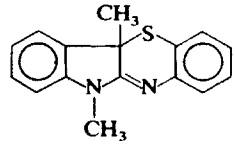
Hino and co-workers have studied[1045] the reactions of 2-ethylthio-3-alkylindoles with *N*-bromosuccinimide to form 3-bromoindolenine (cf. **1109**). These rearrange on heating to mixtures of 5-and 6-bromo-2-ethylthio-3-alkylindoles.

Fontana and Spande had earlier prepared a stable 3-bromoindolenine from 2-*o*-nitrophenylthioskatole and *N*-bromosuccinimide.[1053a] This compound (**1112**), now commercially produced (as "BNPS-skatole"), contains a mildly reactive positive bromine atom and is used as a reagent, more selective than the traditional *N*-bromosuccinimide, in cleaving tryptophyl bonds in peptides or proteins.[1053b]

X.A.2.f. 2-Methylthioindole or the ethyl homologue on treatment with tosyl azide gives, in 50% yield, a product comprised of two indole thioethers linked together with an azo bridge in the 3,3′-positions.[1016] 1-Methyl-2-methylthioindole gave a poor yield of the related product.



1112



1113

Hino and co-workers have reported details on their oxidative rearrangement of 2-ethylthioindoles to sulfone oxindoles (cf. Ref. 791).[1019] 2-Ethylthio-3-phenylindole oxidations, reported for the first time, were analogous to those previously reported (cf. **929** → **933**).

Jackson and co-workers have studied the deoxygenation of 1,3-dimethyl-2-(*o*-nitrophenylthio)indole with triethyl phosphite to the indolobenzothiazine **1113**.[1018]

X.B.1.a. Gassman and co-workers have prepared[1022a,b,1023] in good yield, 3-methylthioindoles as intermediates in a general indole synthesis (cf. Section X.B.1.(a).(1)]. From methylthio-2-propanones and the appropriate *N*-chloroaniline, the following 2-methyl-3-methylthioindoles were prepared: 5-acetoxy-, 5-methyl-, 5-chloro-, 5-nitro-, 5-ethoxycarbonyl-, 7-methyl-, 6-methyl-, 4-methyl-, 1-methyl-, and 4-nitro-. From methyl phenacylsulfide, 2-phenyl-3-methylthioindole, and methylthioacetaldehyde diethyl acetal, the following 2-unsubstituted 3-methylthio indoles were prepared: 5-methyl-, 5-chloro-, 5-ethoxycarbonyl-, 4-nitro-, and 3-methylthioindole itself.[1022a] Using a variation on the original procedure, whereby chlorine complexes of β-ketosulfides are employed in the case where the *N*-chloroanilines were too unstable, they prepared 5- and 7-methoxy-2-methyl-3-methylthioindole,[1022c] as well as some of the above. When α-methylthioketones [$CH_3SCH(R)COR'$] were employed with *N*-chloroanilines, 2(R')-3(R)-dialkyl-3-methylthioindolenines resulted which could be reduced with lithium aluminum hydride to 2,3-dialkylindoles.[1049]

X.B.1.b. A detailed procedure for Harris's synthesis of indole-3-thiol (65% overall yield) has appeared.[1012]

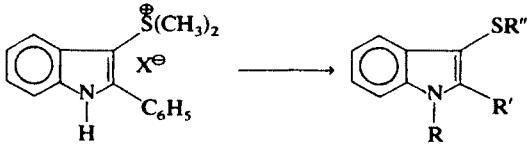
Bourdais and Lorre have prepared a series of indole-3-thiols and *S*-alkyl ethers by the thiourea–iodine reaction on various 2- and/or 5-substituted indoles and *S*-alkylation.[1024]

Haas and Niemann have prepared 3-trifluoromethylthioindole by reaction of indole with trifluoromethylsulfenyl chloride.[1021]

Hocker and co-workers report an interesting reaction of 2-phenylindole with DMSO in HCl to give the *S*-methylsulfonium chloride

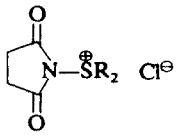
1114. On heating this loses methyl chloride and **1116** is produced. If **1114** is converted to the hydroxide **1115** using anion exchange resin, a spontaneous rearrangement to the *N*-methyl derivative **1117** occurs.[1025]

Tomita and co-workers have prepared indole-3-sulfonium chlorides by reaction of indole or 1-methylindole with *N*-chlorosuccinimide–dialkyl sulfide adducts **1120**.[1026a,b,c] On pyrolysis, 3-alkylthioindoles **1118** result.[1026a,b,c] Succinimidodiallylsulfonium chloride with indole gave, after pyrolysis, the 2-allyl-3-*S*-allylindoles **1119**.[1026d,e]



1114; X = Cl
1115; X = OH

1116; R = H; R′ = C_6H_5, R″ = CH_3
1117; R = CH_3; R′ = C_6H_5, R″ = CH_3
1118; R = H, CH_3; R′ = H, CH_3, R″ = various alkyl
1119; R = H, R′ = R″ = CH_2—CH = CH_2, $CH(CH_3)$ – CH = CH_2, $C(CH_3)_2$—CH = CH_2 CH_2—CH = CH—CH_3



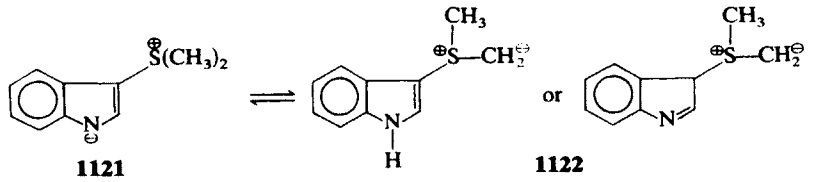
1120

Tomita and co-workers[1026a,d] have reduced various 2-allyl-3-allylthioindoles **1119** with zinc in acetic acid to 2-allylindoles or with Raney nickel to the 2-alkylindoles.

Gassman has reported[1022a,b,1023] many Raney nickel desulfurizations of 3-methylthioindoles. Jackson and co-workers, using triethyl phosphite, have deoxygenated the 3-(*o*-nitrophenylthio) derivatives of 1-methyl- and 1,2-dimethylindole to interesting tetracyclic products with central thiazine or thiazepine rings, respectively.[1018]

X.B.2.b. Daves and co-workers have made the interesting observation that indole-3-methylsulfonium iodide, prepared by methylation (CH_3I/DMF) of 3-methylthioindole, gives (71%) with aqueous KOH, a stable, crystalline ylid of structure **1121**. The ylid incorporates deuterium into the methyl groups from CD_3OD or even $CDCl_3$ via the ylid in equilibrium with **1122**.[1027] On heating over 100°, the ylid **1121–1122** slowly rearranges to 1-methyl-3-methylthioindole.

Jackson and co-workers have observed that 1-methyl-3-phenylthioindole on nitrosation gives a complex mixture of products which can be explained by initial attack of NO^+ at the 3-position.[1017] They isolated



1121 **1122**

1-methyl 2,3-diphenylthioindole (2.5%), 1-methyl-2-nitro-3-phenylthioindole (13%), 1-methyl-3-nitroindole (6%), and 1-methyl-3,3-bis(phenylthio)indolin-2-one (8%) in addition to 23% diphenyl disulfide. 3-Phenylthioindole was converted to the 2-nitro derivative with benzoyl nitrate, then methylated for an alternative synthesis of 1-methyl-2-nitro-3-phenylthioindole.

Plieninger and co-workers have studied[1020] the thio-Claisen rearrangement with 3-*S*-(allyl) indole or 3-*S*-(γ,γ-dimethylallyl)indole. The former, at 150°, rearranges smoothly to the expected 2-allyl-indole-3-thiol **1125**, whereas the latter forms the tricyclic thiatane **1126** and the sulfur-free product **1123**. When the *S*-dimethylallylindole was treated with methyl fluorosulfonate ("magic methyl"), the rearranged 2-allyl 3-methylthioindole **1124** resulted, via the *S*-methylsulfonium salt. An attempt to generate this intermediate with 3-methylthioindole and γ,γ-dimethylallyl bromide gave, instead, the product of *N*-alkylation. Plieninger and co-workers used the calcium–hexamine complex to cleave the *S*-methyl ether to indole-3-thiol, which could be reduced with zinc in acetic acid to indole.

1123: R = H, R′ = CH_3
1124; R = SCH_3, R′ = CH_3
1125; R = SH, R′ = H

1126

X.C.1. Roth and Lepke have prepared 2,3-dimethyl-6-methylthioindole (81%) by a modified Bischler reaction.[888]

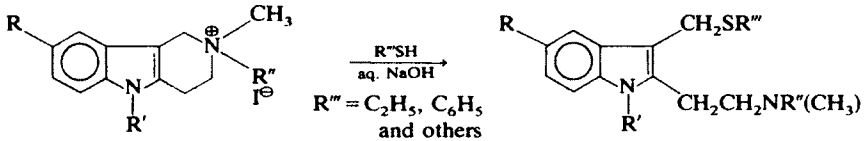
X.C.2. Rosenmund and co-workers have introduced a thiocyano group into the 5-position of 1-methyl-2,3-dihydroindole-3-acetic acid (cf. **995**) using cupric thiocyanate in heated methanol–benzene.[1030]

X.C.4. Keglevic and Goles prepared 5-benzylthiotryptamine (29% yield, overall) by reaction of *p*-benzylthiophenylhydrazine with 4-aminobutyraldehyde diethyl acetal and Fischer cyclization.[1050]

X.E.1.b. Posner and Ting prepared 1-methyl-3-phenylthiomethylindole in 72% yield on attempted demethylation of 1-methylgramine methiodide with cuprous phenyl mercaptide in refluxing pyridine.[1031]

X.E.1.d. Keglevic and Goles prepared[1050] 4- and 6-benzyloxy-3-benzylthiomethylindole by Fischer cyclization of the phenylhydrazone from *m*-benzyloxyphenylhydrazine and β-benzylthiopropionaldehyde diethyl acetal.

X.E.1.—. Zinnes and Schwartz have prepared[1032a,b] a series of 3-alkylthio or 3-arylthio isotryptamines **1128** as CNS depressants by thiolysis of carboline methiodides **1127**.

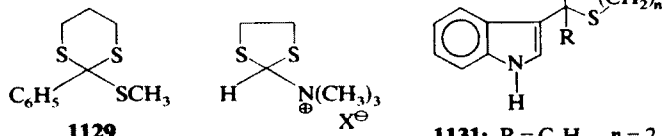


1127

R = H, Br, CH_3
R′ = H or alkyl
R″ = CH_3 or C_2H_5

1128

Two new electrophilic dithiolanating reagents **1129**[1033] and **1130**[1035] have been developed which substitute indole in the 3-position to give the derivatives **1131** and **1132**, respectively, in good yield. The former can be reduced with $LiAlH_4$ or hydrolyzed to 3-benzyl- or 3-benzoylindole,[1033] respectively, whereas the latter on hydrolysis affords indole-3-aldehyde in 80% overall yield, an alternative procedure to the Vilsmeier formylation.[1035]



1129

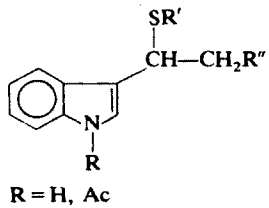
1130

1131; R = C_6H_5 $n = 2$
1132; R = H $n = 1$

X.E.4.b. 4- and 6-benzyloxy-*S*-benzylthiotryptophol resulted in poor yield by Fischer cyclization of the *m*-benzyloxyphenylhydrazones of 4-benzylthiobutyraldehyde diethyl acetal.[1050] *S*-Debenzylation was accomplished with sodium in ammonia to give the thiotryptophols accompanied by some of the related sulfides. The preparation of 4,5- and 5,6-dimethylthiotryptophols by the above sequence was more satisfactory.[1050]

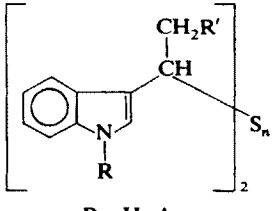
X.E.5. Gadaginamath and Siddappa have prepared[1034] various 1-substituted 4-phenylthiomethyl-5-hydroxy-2-phenyl-3-benzoylindoles by action of thiophenol and substituted thiophenols upon a 4-dimethylaminomethyl (Mannich) intermediate.

Shalygina and co-workers have reported[1036,1037] the syntheses of β-alkylthiotryptamine derivatives **1134** by triethylamine-catalyzed Michael addition of thiols or thiolacetic acid in DMF to 3-(β-nitrovinyl)indoles followed by $SnCl_2$ reduction. Zinc in acetic acid reduction gave the N^{ω}-hydroxytryptamines **1135**. Hydrogen sulfide at 0° could also be added[1036] to the nitrovinylindoles to give the sulfide (76%) **1136** via the unstable β-sulfhydryl derivative **1133** (R′ = H). Compound **1133** could, however, be prepared in methanol and oxidized to the disulfide **1137** (85%) with ferric chloride. Sodium dithionite in acetic acid gave,[1038] with 1-acetyl-3-(β-nitrovinyl)indole, a mixture of **1137** (R = Ac) and **1138**. Reduction[1039] of the sulfide **1136** (R = Ac) and disulfide **1137** with $SnCl_2$ gave the related amino sulfide **1139** (R = Ac) and disulfide **1140** (R = Ac), and reduction of **1138** gave 1-acetyl-β-sulfhydryltryptamine (**1134**, R = Ac, R′ = H).



R = H, Ac
R′ = H, Ac, CH_3, $C_6H_5CH_2$

1133; R″ = NO_2
1134; R″ = NH_2
1135; R″ = NHOH



R = H, Ac

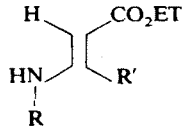
1136; R′ = NO_2 $n = 1$
1137; R′ = NO_2 $n = 2$
1138; R′ = NO_2 $n = 3$
1139; R′ = NH_2 $n = 1$
1140; R′ = NH_2 $n = 2$

XIII. Appendix of tables

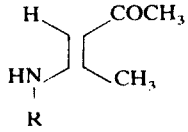
Compounds are arranged in *increasing carbon content* with the melting or boiling points of each compound listed in increasing order. The notation *n.c.* indicates the particular compound was not characterized by a melting or boiling point in the reference cited. Derivatives of a particular compound are indented below it. Hydroxy, methoxy, ethoxy, and benzyloxy derivatives are tabulated in that order for 4-, 5-, 6-, 7-, di-, and trisubstituted indoles in that order. Tryptamines are covered

similarly with 2-substituted and side-chain-substituted derivatives considered separately in each section. In the latter, α refers to the position adjacent to the side-chain nitrogen (N^{ω} in text); whereas β refers to the position adjacent to the indole ring. The tryptamine tables cover pyrrolidino-, piperidino-, piperazino-, and morpholino-substituted ethyl side chains but no more complex derivatives.

TABLE I. ENAMINES USED IN THE NENITZESCU CONDENSATION



R	Ref.
219	
H	93, 151a–d, 154–156, 158, 161, 163, 165, 166, 172
CH_3	156, 165
Et	151c,d, 164–166
n-Pr	151, 173
i-Pr	151a–d
n-Bu	151a–d, 173, 174
C_6H_5	154, 175
$CH_2C_6H_5$	162, 169, 172, 175
CH_2CO_2Et	154, 176
CH_2CH_2CN	164, 165
Various aryl	166, 170, 175
220	
H	167
n-Bu	159
$CH_2C_6H_5$	159



R	Ref.
221	
Et	151c,d
222	
CH_3	171
Et	171
$CH_2C_6H_5$	171
223	
H	163, 165
n-Bu	169
CH_2CO_2Et	169
C_6H_5	163, 165, 170
Various aryl	166, 169, 170

TABLE II. 4-HYDROXYINDOLE AND DERIVATIVES

Substituent(s)	mp or bp (mm) (°C)	Ref.
None	97	11
	98	68
	97–99	80
	97–100	203
Picrate	ca. 180	68
O-Acetate	99–100	11
	100	68
1-CH_3	90	211

TABLE II. *(Continued)*

Substituent(s)	mp or bp (mm) (°C)	Ref.
1-CH_3, 2,3-H_2	137	211
HCl	170	211
Methiodide	175	211
Ethiodide	146	211
2-CH_3	112–115	750
3-CH_3	122–123	197
	123	234a,b
3-CH_3, 2,3-H_2	205–206	234a,b
5-CH_3	126–131	384
7-CH_3	110–115	384
	113–116	750
2,3-$(CH_3)_2$	100–104	750
	106.5	197
3-C_2H_5	71	197
1-C_2H_5, 2,3-H_2	115	211
HCl	184	211
Ethiodide	153	211
1-C_2H_5, 2-CH_3	98–102	74, 205
2-CH_3, 3-C_2H_5	119–121	197
3-*n*-C_3H_7	62–63	197
1-C_2H_5, 2,5-$(CH_3)_2$	110–112	205
O-Acetate	61–63	507
1-C_2H_5, 2,6-$(CH_3)_2$	141–143	201b, 205
1-C_2H_5, 2,5,6-$(CH_3)_3$		
O-Acetate	113–114.5	507
3-C_6H_5	77–78	197
3-$CH_2C_6H_5$	129	197
2-C_6H_5,3-CH_3	109	197
2-C_6H_5,3-C_2H_5	108	197
2,3-$(C_6H_5)_2$	148–150	197
	149.5–151	33
	168[a]	126
7-Cl	174–175	33
1-CH_3, 2,3-$(C_6H_5)_2$	199–200[a]	126
2,3-$(C_6H_5)_2$, 5-CH_3	188[a]	127
2-CH_3, 5,6-$(CH_2C_6H_5)_2$	149–151	533
O-CH_3	69.5	52
	69.5–70.5	43
Picrate	159–160	43, 52
O-CH_3, 2,3-H_2		
HCl	200	215
Oxalate	165	211
1-Acetyl	112	215
1-CH_3, *O*-CH_3	89	26
Picrate	153	26

TABLE II. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
1-CH_3, *O*-CH_3, 2,3-H_2	95–97 (10.5)	26
	110 (11)	211
Picrate	162	211
	163–164d	26
Oxalate	118–119	211
1-C_2H_5, *O*-CH_3, 2,3-H_2	135–140 (12)	211
Picrate	135	211
2,3-$(CH_3)_2$, *O*-CH_3	145[a]	31
Picrate	162–165[a]	29
2-CH_3, 3-C_2H_5, *O*-CH_3	73[a]	31
2,3-$(C_6H_5)_2$, *O*-CH_3	147–148	33, 125
	202–203[a]	126
1-$CH_2C_6H_5$, *O*-CH_3, 2,3-H_2		
Oxalate	129	211
2,3-$(C_6H_5)_2$, *O*-CH_3,7-Cl	67–69[a]	126
	129	125
1-CH_3, 2,3-$(C_6H_5)_2$, *O*-CH_3	152[a]	126
2,3-$(C_6H_5)_2$, *O*-CH_3, 5-CH_3	189[a]	127
	108–109.5	533
O-$CH_2C_6H_5$	72–74	80
2-CH_3, *O*-$CH_2C_6H_5$	88–90; 170–175 (0.05)	750
3-CH_3, *O*-$CH_2C_6H_5$	83–84	234a,b
5-CH_3, *O*-$CH_2C_6H_5$	55–60	384
7-CH_3, *O*-$CH_2C_6H_5$	69–71	384

[a] Most probably the 6-hydroxy or 6-methoxy isomer was made (see Section III.E.2).

TABLE III. 5-HYDROXYINDOLE AND DERIVATIVES

Substituent(s)	mp or bp (mm) (°C)	Ref.
None	106–107	181, 353
	107	11, 68
	107–108	25, 80
	107.5–108	110
	108–108.5	85a,b
	107–109	78
Picrate	167	68
O-Acetate	113–115	11
	116–117	181
2,3-H_2	83–84; 120–122 (1)	50
HCl	200–201	50

TABLE III. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
Picrate	154–155	50
O-3,5-dinitrobenzoate	203–205	193
1-Acetyl	249–250	193
O-CONH(CH_3)	95.5–96.5	50
HCl	152–153	50
Picrate	138–139	50
Methiodide	205–206	50
1-CH_3	42–45	25
	131–132	182
1-CH_3, 2,3-H_2	83–84	50
HCl	200–201	50
Picrate	154–155	50
O-CONH(CH_3)	95.5–96.5	50
2-CH_3	131–133	81
	132–134	155
	133–134	68
	134–136	25
	132–137	161
	188	154
Picrate	157–158	68
O-Acetate	128–130	68
	130–132	81
7-Cl	152–154	155
4-CF_3	80–82	55
3-CH_3	108–109	23b
	114	234a,b
	114–115	233
	116	232a,b
4-CH_3	100–101	384
6-CH_3	154–156	384
1,3-$(CH_3)_2$ (physostigmol)	98–100	643
	102–103	1a,b
1,3-$(CH_3)_2$, 2,3-H_2	99	50
HCl	169–170	50
Picrate	165–166	50
O-CONH(CH_3)	75–76	50
HCl	168–168.5d	50
Methiodide	178–178.5	50
Picrate	127	50
O-CON(CH_3)$_2$		
HCl	188.5–189.0	50
Methiodide	206–207	50
Picrate	123.5–124.0	50
2,3-$(CH_3)_2$	154–155	355
3,4-$(CH_3)_2$	n.c.	384

TABLE III. *(Continued)*

Substituent(s)	mp or bp (mm) (°C)	Ref.
2,6-$(CH_3)_2$	183–184	151c,d
Picrate	162d	93
2,7-$(CH_3)_2$	145–147	151c, 341
4-Cl	111–113	341
3-C_2H_5	78–79	65a
1,2,3-$(CH_3)_3$	144.5–146	38
1,2,3-$(CH_3)_3$, 2,3-H_2	107–109	38
O-$CON(CH_3)_2$		
HCl	173.5–174.5	38
Methiodide	187.5–191.5	38
1,3,3-$(CH_3)_3$,2,3-H_2	109; 130(0.5)	353
HCl	238–239	353
HBr	212–212.5	353
Picrate	161–162	353
O-$CONH(CH_3)$	122–124	356
	144.5–145.0	353
HCl	174–175	353
Methiodide	194–195d	353
	196–197	356
O-$CON(CH_3)_2$		
HCl	111–112	356
Methiodide	172–176	356
1,2,6-$(CH_3)_3$	124–126	74
	130–132	151c,d
1,2,7-$(CH_3)_3$	133–135	151c
1,2,3,3-$(CH_3)_4$, 2,3-H_2	104–109	356
O-$CONH(CH_3)$	110–112	356
Methiodide	168–171	356
O-$CON(CH_3)_2$		
HCl	138–140	356
Methiodide	180–181	356
1,2-$(CH_3)_2$, 3-C_2H_5	150–152	3
Picrate	115–118	3
1,3-$(CH_3)_2$, 3-C_2H_5	Oil	357
HCl	174.5–175.5	357
HBr	164–165	357
Picrate	150–150.5	357
O-$CONH(CH_3)$	99–100	357
Picrate	147–148	357
1-C_2H_5, 2,6-$(CH_3)_2$	81–82	151c,d
	90–92: 113–117 (double)	74
	90–92: 120–122 (double)	150
1,2-$(C_2H_5)_2$, 6-CH_3	88–90	151c,d
1-*n*-C_3H_7, 2,6-$(CH_3)_2$	127–128	151c,d
1-*n*-C_3H_7, 2,7-$(CH_3)_2$	120–122	151c

TABLE III. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
1-*i*-C_3H_7, 2,6-$(CH_3)_2$	94–95	151c,d
2-C_6H_5	237–238	167
	238	23b
	236–239	214
	240–241	346
1-CH_3, 2-C_6H_5	150–152	268
1-*n*-C_4H_9, 2-C_6H_5	140	159
1-$CH_2C_6H_5$, 2-C_6H_5	178	159
2-CH_3, 4,6-$(CH_2C_6H_5)_2$	113	532
Picrate	154–155	532
O-CH_3	51–52	44
	52–53	193
	53–54	61
	54–55	25
	55	45, 52, 70
	55.5–56	43
	57	62
	57–57.5	187
Picrate	142–144	206
	143–143.5	43
	144	70
	145	52
	145–148	207
1-Acetyl	82	52
O-CH_3, 2,3-H_2	Oil	27
HCl	175–175.5	27
	179–180	193
1-Acetyl	135–136	193
6-NO_2	72–74	196
1-Acetyl	250–252	196
7-NO_2	118–119	56
2,3-H_2, *O*-CH_3 6-NH_2		
1-Acetyl	222–224	196
7-NH_2	120–122	56
7-$NHCOCH_3$	159–160	56
O-CH_3, 4,7-H_2	65–68	526–528
	66.5	358
O-CH_3, octahydro HCl	131	358
1-CH_3, *O*-CH_3	100.5–101	361
	103–104	49
	104–105	187
Picrate	97–98	25
	98–100	187

TABLE III. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
	111–112	49
1-CH_3, *O*-CH_3, 2,3-H_2		
Picrate	171–173d	49
2-CH_3, *O*-CH_3	82–84.5	867
	85	360
	85–86	25, 27
	89–90	24, 154, 163
4-CF_3	118–121	155
3-CH_3, *O*-CH_3	62–64	118
	66	52
Picrate	151–152	52
6-CH_3, *O*-CH_3	119–120	74
1,2-$(CH_3)_2$, *O*-CH_3	67–68	178
	76.5–77.5	39
	n.c. (abstr.)	171
1,2-$(CH_3)_2$, *O*-CH_3, 2,3-H_2		
Picrate	171–172	27
1,3-$(CH_3)_2$, *O*-CH_3 (physostigmol methyl ether)	59–60	27
	60	20, 115
	59–60.5	39
	60–61; 159–162 (14)	50, 116
	60–61	1a,b, 26
	61–62	65a
Picrate	112–113	115
	116–117	27, 50, 116
1,3-$(CH_3)_2$, *O*-CH_3, 2,3-H_2	99	26
Picrate	128–129	27
	165–166	26
HCl	169–170	26
2,3-$(CH_3)_2$, *O*-CH_3	108–110	57
	108–112.5	831
	111–112	117
	112–113	31
	114–115	53
Picrate	161–162	117
1-NO	74–76	369
2,4-$(CH_3)_2$ *O*-CH_3	54–55	155
2,7-$(CH_3)_2$ *O*-CH_3	76–77	341
4-Cl	139–140	341
3-C_2H_5, *O*-CH_3	27–28	2
Picrate	112	2
	116–117	388
1,2,3-$(CH_3)_3$, *O*-CH_3	93–95	38
1,2,6-$(CH_3)_3$, *O*-CH_3	75–77	74

TABLE III. *(Continued)*

Substituent(s)	mp or bp (mm) (°C)	Ref.
1,3,3-$(CH_3)_3$, *O*-CH_3, 2,3-H_2	118 (5)	359
	118–120 (6)	357
HCl	203–203.5	357
	207–208	359
Picrate	151.5–152	357
2-CH_3, 3-C_2H_5, *O*-CH_3	100	31
1-C_2H_5, 2-CH_3, *O*-CH_3	20–21	174
	n.c. (abstr.)	171
Picrate	104–104.5	174
1,2-$(CH_3)_2$, 3-C_2H_5, *O*-CH_3	62–64	3
1,3-$(CH_3)_2$, 3-C_2H_5, *O*-CH_3, 2,3-H_2	120–125 (1.5)	357
HCl	178–178.5	357
Picrate	125–126	357
1-C_2H_5, 2,6-$(CH_3)_2$, O-CH_3	56–57	74, 158
2-CH_3, 3-*i*-C_3H_7, *O*-CH_3	110–113	831
1-*n*-C_4H_9, 2-CH_3, *O*-CH_3	156–157 (3.5)	174
Picrate	90	174
1-$CH_2C_6H_5$, *O*-CH_3	74–75	267
	79–80	243
1-$CH_2C_6H_5$, 2-CH_3, *O*-CH_3	115.5–116	152
	115	243
1-$CH_2C_6H_5$, 2-*n*-C_3H_7, *O*-CH_3	65–66	174
2-C_6H_5, *O*-CH_3	158–160	124
	167–167.5	123[a]
	170	120b
	n.c.	35
1-C_6H_5, 2-CH_3, *O*-CH_3	79–80	178
	199–200 (5)	179a,b[b]
1-CH_3, 2-C_6H_5, *O*-CH_3	128–129	268
2-C_6H_5, 3-CH_3, *O*-CH_3	115	121
	120	37
2-CH_3, 3-C_6H_5, *O*-CH_3	84–85	37
2-CH_3, 4-$CH_2C_6H_5$, *O*-CH_3	160–190 (2)	531
Picrate	127–128	531
1-*p*-CH_3-C_6H_4, 2-CH_3, *O*-CH_3	65–66	179a
2-*p*-CH_3-C_6H_4, *O*-CH_3	185–185.5	123[a]
2-*p*-CH_3O-C_6H_4, *O*-CH_3	214–215.5	123[a]
	215	120a
	218–221	124[a]
2-*p*-Cl-C_6H_4, *O*-CH_3	200–201	123[a]
2-*p*-CH_3O-C_6H_4, 3-CH_3, *O*-CH_3	139	120b
1,3-$(CH_3)_2$, 2-C_6H_5, *O*-CH_3	65	121
Picrate	108	121
2,3-$(C_6H_5)_2$, O-CH_3	155–156	29, 37

TABLE III. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
2-CH_3, 4,6-$(CH_2C_6H_5)_2$, *O*-CH_3	135–136.5	532
O-C_2H_5	35–36	281
	39–40	47
	162 (4), 192 (11)	394
1-CH_3, *O*-C_2H_5	85–86, 145–148 (7)	50
	86–87	186
Picrate	95–96	186
	96–96.5	50
1-CH_3, *O*-C_2H_5, 2,3-H_2		
Picrate	142–144d	186
3-CH_3, *O*-C_2H_5	65–66	58, 59
2,3-$(CH_3)_2$, *O*-C_2H_5	114–115	58
1,3-$(CH_3)_2$, *O*-C_2H_5 (physostigmol ethyl ether)		
Picrate	95	54
1-C_2H_5, 2-C_6H_5, *O*-C_2H_5	112–113	40
3-NO	136–137.5	40
O-C_6H_5	118–119	209
O-$CH_2C_6H_5$	94–96	63
	96–97; 107 (double)	77, 84
	102	79
	102–103	105
	103–105	80
	104	289
	104–106	85a,b
	100–106	85c
	105–107	64
Picrate	142–143	85a,b
1-Acetyl	129–130	77, 84
4-Cl	75	83
Picrate	151–152	83
1-CH_3, *O*-$CH_2C_6H_5$	127	267
	130–131	222a,b
	131–131.5	361
2-CH_3, *O*-$CH_2C_6H_5$	81–82	105, 222a,b
3-CH_3, *O*-$CH_2C_6H_5$	115–116	234b
	117–118	34
	118	232b
Picrate	164	232b
4-CH_3, *O*-$CH_2C_6H_5$	72–73	384
6-CH_3, *O*-$CH_2C_6H_5$	59–61	384
	78–81	81
Picrate	143–145	81
7-CH_3, *O*-$CH_2C_6H_5$	71–72	57
1-C_2H_5, *O*-$CH_2C_6H_5$	68.5–70	267
3-C_2H_5, *O*-$CH_2C_6H_5$	78–79	34, 65a

TABLE III. (*Continued*)

Substituent(s)	mp or bp (mm)(°C)	Ref.
1,3,3-$(CH_3)_3$, *O*-$CH_2C_6H_5$, 2,3-H_2	46–48	356
1,2,3,3-$(CH_3)_4$, *O*-$CH_2C_6H_5$, 2,3-H_2		356
1-$CH_2C_6H_5$, *O*-$CH_2C_6H_5$	108–109	243, 267
1-CH_3, 2-C_6H_5, *O*-$CH_2C_6H_5$	159–160	268

[a] Other 2-aryl derivatives are also reported.
[b] Other 1-aryl derivatives are also reported.
[c] Other 2-alkyl derivatives are also reported.

TABLE IV. 6-HYDROXYINDOLE AND DERIVATIVES

Substituent(s)	mp or bp (mm) (°C)	Ref.
None	125.5	68
	124–126	80
	126	11
	125–127	195a,c
Picrate	154–156d	68
O-Acetate	81–82	11
2,3-H_2	112–113	193
	118–119	195a,c
1-Acetyl	282–284	193
1-Benzoyl	228–230	195a,c
1-NO	157–159	195a
1-CH_3	209–210	868a,b
1-CH_3, 2,3-H_2	97; 168–172 (12)	868a,b
Methiodide	173	211
Benzyl iodide salt	175	211
O-$CONHCH_3$	98	868a,b
Methobromide	158–170	868a,b
O-$CON(CH_3)_2$	63–64	868a,b
Methobromide	158–164	868a,b
O-$CON(C_6H_5)_2$	158–164	868a,b
3-CH_3	162	234a,b
O-SO_3K	>330	363
7-CH_3	179–180	384
3-CH_3, 2,3-H_2	180 (2)	234b
3,7-$(CH_3)_2$	n.c.	384
1-C_2H_5, 2,3-H_2	95	211
ethiodide	168	211
1-CH_3, 5-NH_2	220–222	212
N,*O*-Diacetyl	205–206	212
2,3-$(C_6H_5)_2$	166–167	125
	168	33

TABLE IV. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
$\frac{1}{2}$HOAc complex	145–148	125
O-Acetate	190	125
1-CH_3, 2,3-$(C_6H_5)_2$	198–199	33
O-CH_3	91	72
	91–92	51, 55, 87, 193
	91.5–92	89, 90a,c
	92	69, 796
	92.5	43
Picrate	118–120d	207
	132	43
	137	51, 55
5-Cl	109–110	238a–c, 284a
O-CH_3, 2,3-H_2	130–140 (18)	211
	135–137 (14)	364
	145–146 (15)	195a
HCl	202	215
	232–233	193
1-Acetyl	105	215
	105–106	193
1-Acetyl, 5-NO_2	210–211	196
5-NO_2	173–175	196
1-Acetyl, 5-NH_2	170–172	196
1-CH_3, *O*-CH_3	Oil	55
	30	212
	30–32	213
Picrate	123	55, 212, 213
5-Cl	117–118	188
1-CH_3, *O*-CH_3, 2,3-H_2	155 (1)	211
HCl	157	211
2-CH_3, *O*-CH_3	102	796
	102–103	27
	103	213
2-CH_3, *O*-CH_3, 2,3-H_2	142–145 (10)	868c,d
3-CH_3, *O*-CH_3	125	51, 55, 234a,b
	127	756
7-CH_3, *O*-CH_3	118–120	384
1,2-$(CH_3)_2$, *O*-CH_3	78–79	213
Picrate	125–126	213
1,2-$(CH_3)_2$, *O*-CH_3, 2,3-H_2		
Picrate	144–145	27
1,7-$(CH_3)_2$, *O*-CH_3	93	213
2,3-$(CH_3)_2$, *O*-CH_3	142–143	28
1-C_2H_5, *O*-CH_3, 2,3-H_2	165 (18)	211
HCl	153	211
2(or 3)-CH_3, 3(or 2)-C_2H_5,		

TABLE IV. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
O-CH_3	81–82	365
1-*i*-C_3H_7, *O*-CH_3	Oil	213
Picrate	96	213
1-$CH_2C_6H_5$, *O*-CH_3	70–71	243
2-C_6H_5, 3-CH_3, *O*-CH_3	164	121
1,3-$(CH_3)_2$, 2-C_6H_5, *O*-CH_3	83	121
Picrate	98	121
2-*p*-CH_3O-C_6H_4, 3-CH_3, *O*-CH_3	136	32, 120a,b
2-*p*-CH_3O-C_6H_4, 3-C_2H_5, *O*-CH_3	164–165	32
2,3-$(C_6H_5)_2$, *O*-CH_3	203	33
	206–207	125
	208	366
5-Cl	217	33
2-*p*-HO-C_6H_4, 3-C_6H_5, *O*-CH_3	204	366
1-CH_3, 2,3-$(C_6H_5)_2$, *O*-CH_3	149	33
O-C_2H_5	55	61
	57–58	73a,b
O-$CH_2C_6H_5$	111–112	77
	115–117	195c
	117–118	79, 86
	118–120	80
O-$CH_2C_6H_5$, 2,3-H_2	67–69	195a
1-Benzoyl	110–113	195a
3-CH_3, *O*-$CH_2C_6H_5$	148	234a,b
2,3-$(C_6H_5)_2$, *O*-$CH_2C_6H_5$	158	125

TABLE V. 7-HYDROXYINDOLE AND DERIVATIVES

Substituent(s)	mp or bp (mm) (°C)	Ref.
None	96	11, 68
	96.5	194
	97–98	181
	100–100.5	85a,b
Picrate	176d	85a,b
O-Acetate	55	11, 181
2,3-H_2	182–183	193
HCl	232–234	193
1-Acetyl	112–114	193
3-CH_3	82.5	234a,b
O-CH_3	Oil	70
	108–110 (0.2)	91

TABLE V. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
	110 (0.9)	193
	119 (6)	194
	157 (17)	52
Picrate	148–153d	207
	150–151d	70
	152–153	193
	154–155	43, 91
	156	52
O-CH_3, 2,3-H_2		
HCl	230–231	193
1-CH_3, O-CH_3	54.5–55.5	26
1-CH_3, O-CH_3, 2,3-H_2		
Picrate	145–148	26
2-CH_3, O-CH_3	79–81	867
	83–83.5	26
	83–85	111
Picrate	153	111
	157–158	26
3-CH_3, O-CH_3	150 (15)	26
	170 (20)	52
Picrate	156	52
	158.5–159	26
1,3-$(CH_3)_2$, O-CH_3	68–69	191
	74–75	115
Picrate	163–164	191
1,3-$(CH_3)_2$, O-CH_3, 2,3-H_2		
Picrate	135–136	191
2,3-$(CH_3)_2$, O-CH_3	155 (11)	31
	166 (14)	36
Picrate	171–172	36
3-C_2H_5, O-CH_3		
Picrate	136–137	388
2-CH_3, 3-C_2H_5, O-CH_3	160 (10)	31
Picrate	144	31
2-C_6H_5, O-CH_3	98	119a,b
1-CH_3, 2-C_6H_5, O-CH_3	89	122
Picrate	124	122
1-CH_3, 2-p-CH_3O-C_6H_4, O-CH_3	151	122
O-$CH_2C_6H_5$	67–68	105
	68	85a,b
Picrate	149–150	105
O-$CH_2C_6H_5$, 2,3-H_2		
Picrate	128–129	85a,b
3-CH_3, O-$CH_2C_6H_5$	160 (0.2)	234b

TABLE VI. 5,6-DIHYDROXYINDOLE AND DERIVATIVES

Substituent(s)	mp or bp (mm) (°C)	Ref.
None	138–139	99
	140	135b
	140d	92a,b, 93, 94 183, 334a,b
	140–142	333
	143–144d	337
7-I	108–108.5	137
5-(or 6)*O*-Acetate	150d	334a,b
O,O-Diacetate	134–136	334a,b
	135–136	92a,b, 93
	139–140	137
3-Br	126	97
7-I	125–126.5	137
2,3-H_2		
HCl	234–236	352
	235–236	217
2,3-H_2, *O,O*-Diacetate	223–224	217
Picrate	244	217
2,3-H_2, *O,O,N*-Triacetate	223–225	352
1-CH_3	133–134	138, 139
	134	134a,b
	134–135	137, 138
	135–136	133a
	136	135a,b
	136d	133b
7-Br	121–123d	133b
O,O-Diacetate	164	133b
7-I	88–90d	135a,b
	105–106	142
O,O-Diacetate	146–147	135a,b
	151–152.5	142
	153–155	141
O,O-Diacetate	95–100	354
	100–101	141
	101	133a
	101–102	134a,b
	104–105	133b
	109.5–110.5	137
	110	139
1-CH_3, 2,3,3a,4-H_4		
O,O-Diacetate	174	134b
2-CH_3	172–174	99
	ca. 180d	94, 334a,b
	180–200d	92a,b, 93
7-I	128d	99

TABLE VI. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
O,O-Diacetate	134	92a,b, 93
	140–141.5	99
7-I	164–165	99
3-CH_3	151	234b
	152	42
4-CH_3	146–149	146
7-CH_3	108–109	146
1,2-$(CH_3)_2$, *O,O*-Diacetate	134–135	148
7-I	170–172	148
2,3-$(CH_3)_2$	189d	42
	190d	94
1,4-$(CH_3)_2$	140–141	147
7-I	140–180d	147
O,O-Diacetate	135–136	147
7-I	192–193	147
1,7-$(CH_3)_2$	155	147
O,O-Diacetate	137–138	147
4,7-$(CH_3)_2$	170d	146
1-C_2H_5	Gum	137
O,O-Diacetate	107–108.5	137
7-I		
O,O-Diacetate	157.5–158.5	144
2,4,7-$(CH_3)_3$	168	93
1-C_2H_5, 2-CH_3		
O,O-Diacetate	137–138	148
7-I	158–160	148
1-*i*-C_3H_7	Gum	137
O,O-Diacetate	89.5–90.5	137
7-I	111–113	144
3-CH_3, 4-*n*-C_3H_7	112	67
3-CH_3, 7-*n*-C_3H_7	106–107	67
3-C_6H_5	256d	42
Picrate	Oil	42
6-OCH_3	110–111	368a,b
	113	92a,b
	113–114	337
6-OCH_3, 2,3-H_2		
1-Acetyl	254–256	196
2-CH_3, 6-OCH_3	128	93
Picrate	150	93
1-C_2H_5, 6-OCH_3	Oil	368a,b
5-OCH_3	111	92a,b, 100
	111–112	337
6-*O*-Acetate	135	92a,b
5-OCH_3, 2,3-H_2		

TABLE VI. *(Continued)*

Substituent(s)	mp or bp (mm) (°C)	Ref.
1-Acetyl	286–289	196
2-CH_3, 5-OCH_3	136	93
5,6-OCH_2O	110	336
	110–111	73a,b
Trinitrobenzene adduct	142	372
1-CH_3, 5,6-OCH_2O	70–71	112
2-CH_3, 5,6-OCH_2O	150	336
	150–151	112
Trinitrobenzene adduct	160	372
1,2-$(CH_3)_2$, 5,6-OCH_2O	95–97	112
Picrate	143–144	112
2,3-$(CH_3)_2$, 5,6-OCH_2O	115–116	112
	132–133	41
1,2,3-$(CH_3)_3$, 5,6-OCH_2O	200–201	112
5,6-$(OCH_3)_2$	142	76
	150–151	114
	150–152	196
	151–152	100
	152–153	88
	154	99
	154–155	75, 92a,b
	155	106a,b, 92a
	154–156	107
	155–156	217
	156	289
1-Acetyl	150–152	75
	151–153	107
7-I	130–131	99
5,6-$(OCH_3)_2$, 2,3-H_2	108.5	217
HCl	212	217
Picrate	197	217
1-Acetyl	175–176	196
	176	217
1-Tosyl	142	217
1-CH_3, 5,6-$(OCH_3)_2$	138–139	354
2-CH_3, 5,6-$(OCH_3)_2$	90	99
	91	94, 129
4-I	127	99
7-I	130–131	99
3-CH_3, 5,6-$(OCH_3)_2$	133–136	88
	150	42
2,3-$(CH_3)_2$, 5,6-$(OCH_3)_2$	110.5	42
3-C_6H_5, 5,6-$(OCH_3)_2$	137	92a,b
1-$CH_2C_6H_5$, 5,6-$(OCH_3)_2$	95–96	243
3-$CH_2C_6H_5$, 5,6-$(OCH_3)_2$		

TABLE VI. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
Hemihydrate	140–142	107
3-*p*-Dimethylaminobenzyl, 5,6-$(OCH_3)_2$	144–145	108
5-OCH_3, 6-OC_2H_5	117–118	95
	118–120	196
	123	97
5-OCH_3, 6-OC_2H_5, 2,3-H_2	48–50	97
Hydrate	66–67	97
1-Acetyl	130–130.5	97
	130–131	196
5-OC_2H_5, 6-OCH_3	142.5	97
	143–144	196
5-OC_2H_5, 6-OCH_3, 2,3-H_2	57–58	97
1-Acetyl	108–109	196
	110	97
5-$OCH_2C_6H_5$, 6-OCH_3	95–96	337
	96–99	81
5-OCH_3, 6-$OCH_2C_6H_5$	146	98
	148–150	337
	155	100, 114
5,6-$(OCH_2C_6H_5)_2$	113–114	337
	115	100
	115–115.5	82
3-CH_3, 5,6-$(OCH_2C_6H_5)_2$	122	234b
	123	230

TABLE VII. OTHER DIHYDROXYINDOLES

Substituent(s)	mp or bp (mm) (°C)	Ref.
4,7-$(OH)_2$	143–144	750
Dioxo tautomer	185	323a
2,3-$(CH)_3$, 4,7-$(OH)_2$	205–206d	339
Dioxo tautomer	210–213d	753
O,O-Diacetate	138	339
6-OH, 7-OCH_3	85–86	93
O-Acetate	81	93
6-OCH_3, 7-OH	89	93
2-CH_3, 6-OH, 7-OCH_3	114	93
O-Acetate	118–119	93
2-CH_3, 6-OCH_3, 7-OH	93	93
4,5-$(OCH_3)_2$	157	95
4,6-$(OCH_3)_2$	119–120.5	349

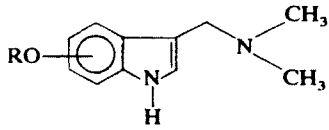
TABLE VII. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
4,7-$(OCH_3)_2$	131	96
4,7-$(OCH_2C_6H_5)_2$	158–159	750
5,7-$(OCH_3)_2$	82	378
	83–84	335
	159–160	208a,b
6,7-$(OCH_3)_2$	102	338
	102–103	113
1-CH_3, 5-Cl, 6,7-$(OCH_3)_2$	44–45	609
2,3-$(CH_3)_2$, 4,7-$(OCH_3)_2$	103–104, 135–140 (1–2)	339
Picrate	167	339
2,3-$(C_6H_5)_2$, 4,7-$(OCH_3)_2$	133.5	33
4-$OCH_2C_6H_5$, 5-OCH_3	84	98
6-$OCH_2C_6H_5$, 7-OCH_3	67	98

TABLE VIII. TRI- AND TETRAHYDROXYINDOLES AND DERIVATIVES

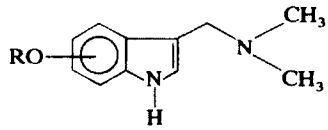
Substituent(s)	mp or bp (mm) (°C)	Ref.
4-OCH_3, 5-Br, 6,7-$(OH)_2$	139.5–141	367
4-OCH_3, 6,7-$(OCOCH_3)_2$	131–134	367
5-Br	149–151	367
4,5,6-$(OCH_3)_3$	101	189
4,5,7-$(OCH_3)_3$	124	102
5,6,7-$(OCH_3)_3$	71–72	103
	n.c.	104
5,6,7-$(OCH_3)_3$, 2,3-H_2	133–134 (0.7)	113
HCl	205–206	113
4-OCH_3, 5,6-OCH_2O	108	101
5,6-OCH_2O, 7-OCH_3	84–85	101
4,7-$(OCH_3)_2$, 5,6-OCH_2O	113	101
4,5-$(OCH_3)_2$, 6,7-OCH_2O	177–178	101
4,5-OCH_2O, 6,7-$(OCH_3)_2$	106–107	101

TABLE IX. HYDROXY- AND ALKOXYGRAMINES



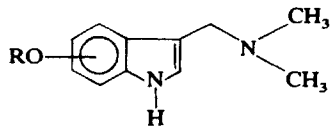
Substituent(s)	mp (°C)	Ref.
4-OH, HCl	187–189	227a,b
4-OCH_3	142–143	220
N,N-Diethyl analogue	132–134	71, 109
1-CH_3, 4-OCH_3	Oil	26
Methiodide	Hygroscopic	26
Picrate	160–161	26
4-$OCH_2C_6H_5$	194–198	80
Methosulfate	143–144	382
	144–145	408a,b
5-OH	197–198	227a,b
	198–199	233
2-CH_3, 5-OH, hydrate	>300	380
O-Acetyl	163–165	380
4-CH_3, 5-OH	157–158	384
1-$CH_2C_6H_5$, 5-OH	142	383
	145	243
5-OCH_3	124–125	49
	127.5–128	25
	128	218
Methiodide	>280	218
Picrate	164–165	49
	168	218
1-CH_3, 5-OCH_3	42–43	361
	43–45	49
Monopicrate	143–144d	49
Dipicrate	129–130	49
Methiodide	180–200d	49
2-CH_3, 5-OCH_3	112–114	25
	161–162	174
Picrate	136–137	174
1,2-$(CH_3)_2$, 5-OCH_3	113	174
Picrate	140–141	174
1-C_2H_5, 2-CH_3, 5-OCH_3, HCl	157–157.5	174
1-*n*-C_4H_9, 2-CH_3, 5-OCH_3	160–161	174
1-$CH_2C_6H_5$, 5-OCH_3, HCl	184–185	383
	185	243
1-$CH_2C_6H_5$, 2-CH_3, 5-OCH_3	63	174
	83–84	152
	83.5–84	276
HCl	185	243
Picrate	113–114	174

TABLE IX. *(Continued)*



Substituent(s)	mp (°C)	Ref.
Methiodide	>170d	152
	175d	276
1-C_6H_5, 2-CH_3, 5-OCH_3[a]		
HCl	195–196	240
Methiodide	210–212d	240
1-$CH_2C_6H_5$, 2-*n*-C_3H_7, 5-OCH_3, HCl		
2-CH_3, 4,6-$(CH_2C_6H_5)_2$, 5-OCH_3	156–157	174
	60.5	532
5-OC_2H_5	140	46
	146	373
HCl	150	373
5-$OCH_2C_6H_5$	134–139	235a
	138	80, 219a,b
	138.5–139.5	85b
4-NO_2	143–144	396
1-CH_3, 5-$OCH_2C_6H_5$	44–45	361
	48–50	222a,b, 231, 235a
Methiodide	173–175	231
2-CH_3, 5-$OCH_2C_6H_5$	150–153	222a,b
6-CH_3, 5-$OCH_2C_6H_5$	135–138	380
7-CH_3, 5-$OCH_2C_6H_5$	129–131	57
1-C_2H_5, 5-$OCH_2C_6H_5$		
HCl	162	243
	179–180	267
Methosulfate	151.5–153	267
1-$CH_2C_6H_5$, 5-$OCH_2C_6H_5$		
HCl	158–159	383
	162.5–164	267
Methosulfate	161.5–162.5	267
6-OH, HCl	184–185	227a,b
7-CH_3, 6-OH	153–155	384
6-OCH_3	85	221
	88–89	387
	93–94.5	57
	93.5–95	223
	94–95	90a,b
5-Cl	161	238a,b,c
1-$CH_2C_6H_5$, 6-OCH_3, maleate	141	243
6-$OCH_2C_6H_5$	136–137	86, 239
	136–138	80

TABLE IX. *(Continued)*



Substituent(s)	mp (°C)	Ref.
7-OH, HCl	178–180	227a,b
7-OCH_3	105–106	25
	112.5	220
	112–113	91
7-$OCH_2C_6H_5$	144.5–145.0	85b
Picrate	172–173	85b
4-$OCH_2C_6H_5$, 5-OCH_3	140–142	98
5,6-$(OCH_3)_2$	125–125.5	88
Methosulfate	154–161	88
1-$CH_2C_6H_5$, 5,6-$(OCH_3)_2$		
HCl	189	383
	192	243
5-$OCH_2C_6H_5$, 6-OCH_3	111–113	380
6-$OCH_2C_6H_5$, 5-OCH_3	135–136	242
Methosulfate	145–146	242
5,6-$(OCH_2C_6H_5)_2$	124	230
	125–126	224a,b
Methiodide	178–180	230
4,6-$(OCH_3)_2$	128–132	349
4,7-$(OCH_3)_2$	121	96, 190
Methopicrate	152	190
5,7-$(OCH_3)_2$	121–122	378

[a] And other 1-aryl-5-methoxygramines.

TABLE X. MISCELLANEOUS ALKOXYGRAMINE ANALOGUES

Compound	mp (°C)	Ref.
3-Phthalimidomethyl-5-methoxyindole	167–168.5	388
2-Methyl-3-piperidinomethyl-5-methoxy indole	134–136	174
1,2-Dimethyl-3-(*N*-anilinomethyl)-5-methoxyindole	112–113	174
3-Phthalimidomethyl-5-ethoxyindole	136–137	388
3-Phthalimidomethyl-5-benzyloxyindole	173–174	388
3-Phthalimidomethyl-7-methoxyindole	177–179	388

TABLE XI. NATURALLY OCCURRING 5-HYDROXYTRYPTAMINES*

5-Hydroxy-N^{ω}-methyl: found in mushrooms *Amanita citrina*,[416] *A. porphyria*.[416]

5-Hydroxy-N^{ω},N^{ω}-dimethyl (bufotenine): found in mushrooms *A. mappa*,[417] *A. muscaria*,[417†] *A. panterina*,[417‡] *A. tormentella*,[416,418,419] *A. porphyria*,[416,418,419] *A. citrina*[416,418,420]; toads *Bufo alvarius* (Ariz.),[414] *B. arenarum* (Argentina),[421,422] *B. chilensis* (Chile),[422] *B. crucifer* (Brazil),[422] *B. marinus*,[423] *B. paracnemis* (Argentina),[422] *B. viridis viridis*,[424†] *B. vulgaris*,[279,424b] and other *Bufo* sources[424a]; Indian plant *Desmodium pulchellum*,[425] South American hallucinatory *epená* snuff,[413b] *Lespedeza bicolor* var. *japonica*, (leaves and root bark)[426]; grasses *Phalaris tuberosa*,[427] *P. arundinacea*[427]; leguminous shrubs *Piptadenia excelsa* (seeds and pods),[428] *P. colubrina* (bark),[429] *P. macrocarpa* (seeds[415,428] and pods[428]), *P. peregrina* (seeds[415,430] and pods[415]).

5-Hydroxy-N^{ω},N^{ω}-dimethyl-N^{ω}-oxide: found in mushrooms *A. citrina*,[416] *A. porphyria*[416]; shrubs *Piptadenia excelsa* (seeds and pods),[428] *P. macrocarpa* (seeds),[415,428] *P. peregrina* (seeds).[415]

5-Hydroxy-N^{ω},N^{ω},N^{ω}-trimethylbetaine (Bufotenidine): found in toads *Bufo vulgaris*,[279] *Bufo bufo gargarizans*,[424b] *B. formosus*,[424b] *B. fowleri*,[424b] Chinese toad ch'an su[424†]; Chinese drug senso.[882]

5-Hydroxy-N^{ω},N^{ω}-dimethyl *O*-sulfate (bufoviridine): found in *Bufo alvarius* (Ariz.).[414]

Dehydrobufotenine (554): found in toads *Bufo arenarum* (Argentina),[422,424†] *B. crucifer* (Brazil),[422] *B. marinus*,[417,431] *B. paracnemis* (Argentina),[422] *B. spinulosis* (Peru),[422] *B. vulgaris*,[279] miscellaneous *Bufo* sources,[424a] Chinese toad ch'an su.[424†]

Dehydrobufotenine *O*-Sulfate (bufothionine): found in all of the above *Bufo* sources for dehydrobufotenine with the exception of *Bufo marinus* and ch'an su.[410,422]

5-Methoxy-N^{ω}-methyl: found in plants *Desmodium pulchellum*,[432] *Phalaris arundinacea*,[433] *Piptadenia macrocarpa* (bark),[428] *P. peregrina* (bark).[434]

1-Acetyl-5-methoxy: found in bovine pineal gland.[435]

5-Methoxy-N^{ω}-acetyl (melatonin): found in bovine pineal gland,[436] peripheral nerves in man, monkey, cow.[436]

1-Methoxy-N^{ω},N^{ω}-dimethyl (lespedamine): found in leaves of *lespedeza bicolor* var. *japonica*.[437]

5-Methoxy-N^{ω},N^{ω}-dimethyl: found in *Bufo alvarius* (Ariz.),[414] Brazilian tree *Dictyoloma incanescens* (bark),[429] *Epená* snuff,[413a,b] *Desmodium pulchellum*,[425] *Desmodium gangeticum*,[438] *Phalaris tuberosa*,[427] *Phalaris arundinacia*,[427] *Piptadenia peregrina* (bark),[434] mushrooms *Amanita citrina* and *A. porphyria*,[416] root bark of *Lespedeza bicolor* var. *japonica*.[426]

5-Methoxy-N^{ω},N^{ω}-dimethyl N^{ω}-oxide: found in *Desmodium gangeticum*,[438] *Desmodium pulchellum*,[432] *Lespedeza bicolor* var. *japonica* (root bark).[426]

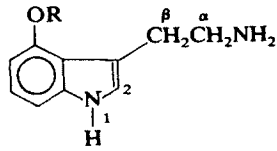
5,6-Dihydroxy: found in pericardial organs of crustacea (tentative structure).[265]

* This table excludes serotonin. A complete tabulation of its occurrence in a large number of plants and animals can be found in Appendix I of Ref. 400 and Refs. 441–443.

† This could not be verified; see Ref. 419.

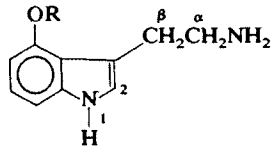
‡ This could not be verified; see Ref. 439.

TABLE XII. 4-HYDROXYTRYPTAMINE AND DERIVATIVES



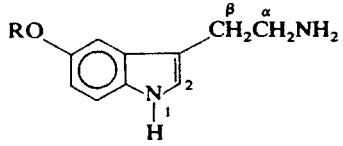
Substituent(s)	mp or bp (mm) (°C)	Ref.
None		
Oxalate	261–264	408a,b
	269–270	80
Creatinine sulfate	250–255	80
N-CH_3, oxalate	150–152	227a
N-C_2H_5, oxalate	218–222	227a
N-$(CH_3)_2$ (psilocin)	168–170	490
	169–170	408a,b
	173–176	227a, 259a,b, 483
1-Acetyl	178–185	227a
O-Acetate	92–95	227a
O-Phosphate (psilocybin)	219–222	227a
	220–228	259a,b
O-Benzoate	109–111	227a
O-Pivaloate	123–124	227a
O-Sulfate	251–252	227a
O-Tosylate	139–141	227a
O-$CONH(CH_3)$	141–145	227a
1-CH_3, *N*-$(CH_3)_2$	125–127	227a
O-Acetate, bismaleate	140–141	227a
O-Benzoate	69.5–71	227a
O-Pivaloate, bismaleate	137–138	227a
O-Phosphate	255–257	227a
O-Sulfate	277–279	227a
1-C_2H_5, *N*-$(CH_3)_2$	105–107	873
N-$(C_2H_5)_2$	104–106	227a
O-Phosphate	260–263	227a
1-CH_3, *N*-$(C_2H_5)_2$	195–200 (0.001)	874
O-Benzoate	167–168	874
O-Benzoate, bismaleate	122–124	874
N-$(CH_2)_5$	182–183	227a
O-Phosphate	260–262	227a
1-CH_3, *N*-$(CH_2)_5$	121–126	874
1-$CH_2C_6H_5$, *N*-$(CH_3)_2$	112–118	227a, 873
O-Benzoate, bismaleate	127–129	227a, 874, 875
O-CH_3	135	86
	135–137	71
HCl	217–218	86

TABLE XII. (*Continued*)



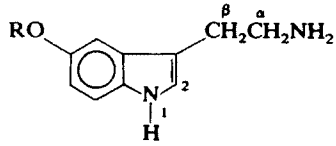
Substituent(s)	mp or bp (mm) (°C)	Ref.
1-*p*-CH_3-C_6H_4CO	107–109	71
O-CH_3, *N*-$(CH_3)_2$	89–92	227a
O-CH_3, 1-CH_3; *N*-$(CH_3)_2$	170 (0.005)	211
HCl	257	211
O-CH_3, 1-CH_3; *N*-$(CH_3)_2$, 2,3-H_2	165 (12)	211
HCl	169	211
O-$CH_2C_6H_5$	117–120	80
Acid oxalate	188–189	80
O-$CH_2C_6H_5$, *N*-CH_3	105–106	227a
O-$CH_2C_6H_5$, *N*-C_2H_5	96–97	227a
O-$CH_2C_6H_5$, *N*-$(CH_3)_2$	119–121	260a
	120–121	408a,b, 490
	121–123	227a
O-$CH_2C_6H_5$, 1-CH_3, *N*-$(CH_3)_2$	62–67	227a
O-$CH_2C_6H_5$, 1-$CH_2C_6H_5$, *N*-$(CH_3)_2$	87–88	227a, 247
O-$CH_2C_6H_5$, *N*-$(CH_2)_5$	126–128	227a
O-$CH_2C_6H_5$, 1-CH_3, *N*-$(CH_2)_5$	200 (0.001)	874
O-$CH_2C_6H_5$, *N*-$(C_2H_5)_2$	100–101	227a
α-CH_3	125–126	227a, 876
1-CH_3, α-CH_3	133–134	873
α-C_2H_5, dioxalate	136–140	876
β-OH, *N*-$(CH_3)_2$	180–181	227a
O(4)-Phosphate	219–221	227a
1-CH_3, β-OH, *N*-$(CH_3)_2$	161–165	227a
α-CH_3, *N*-$(CH_3)_2$	138–139	227a, 876
β-CH_3, *N*-$(CH_3)_2$	169–170	227a
O-$CH_2C_6H_5$, α-CH_3	148–149	227a, 877
O-$CH_2C_6H_5$, 1-CH_3, α-CH_3	109–110	877
O-$CH_2C_6H_5$, α-C_2H_5	134–137	877
O-$CH_2C_6H_5$, β-OH, *N*-$(CH_3)_2$	147–150	227a
O-$CH_2C_6H_5$, 1-CH_3, β-OH, *N*-$(CH_3)_2$	126–129	227a
O-$CH_2C_6H_5$, α-CH_3, *N*-$(CH_3)_2$	126	227a, 876
O-$CH_2C_6H_5$, β-CH_3, *N*-$(CH_3)_2$	Amorph.	227a

TABLE XIII. 5-HYDROXYTRYPTAMINE AND DERIVATIVES



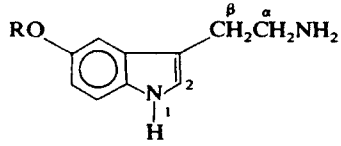
Substituent(s)	mp or bp (mm) (°C)	Ref.
None (serotonin)	150–150.5	872
HCl	167–168	219a,b
	200–201	309
Oxalate	195–197	185
	197–198	79
Bioxalate	198	299
Picrate	103–111; 185–189 (double)	219a,b
	105–110; 185–188 (double)	445
	184–187	85a,b
	196–197	185, 315a–d
	196–197.5	293
Creatinine sulfate, H_2O	209–211	309
	211–213	237
	212–214	444a,b, 290
	213–214	315a,c
	213–215	317a,b
	214–216	236, 305
	215–216	282
	216–218d	269a–e
	219–221	64, 316a,b
O-Carbamate	n.c. (abstr.)	869
O-Phosphate	260d	543, 870
O-Sulfate·$2H_2O$	n.c.	871
O-Acetate, HCl	213–214	540
O-Benzoate, HOAc	157–157.5	540
1-Acetyl	93–94	306
1-CH_3, picrate	197–198	65a
	201–202d	361
7-CH_3, creatinine sulfate $1.5H_2O$	ca. 245d	229
N-CH_3, bioxalate	153–156	80
	154–156	307
1-C_2H_5, picrate	200–201d	267
N-C_2H_5, oxalate	239–240	80
N-$(CH_3)_2$ (bufotenine)	86–90	251
	123–124	428
	125–126	253b
	138–140	80,227a

TABLE XIII. (*Continued*)



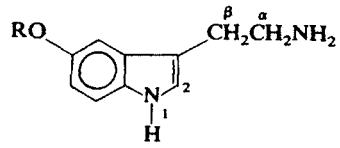
Substituent(s)	mp or bp (mm) (°C)	Ref.
	141–142	300
	146	425
	146–147	248, 279, 430
	166–167 (0.01)	253b
	320 (0.1)	279
CH_3I	210	279, 428
	210–211	253b
	213–214	430
	214–215	79, 80
Picrolonate	255	1062
Oxalate, H_2O	82–84	430
	84–88	417
	93–94	79
	96.5	279
Bioxalate	89–90	80
Picrate	176–177	430
	177d	80, 185, 227a, 248
	177–178	244a,b
	178	279, 426
Dipicrate	174–175	428
	175	426
	177–178	244a,b, 425
C_2H_5I	192–193	253b
Fumarate	228–230d	253b
Flavianate	194–195	79
Creatinine sulfate	147–149	80
Picrolonate	120–121	1062
	183–184	428
O-*m*-Nitrobenzoate	255–257	430
	258	279
O-Phosphate	237–242	227a
O,1-Diacetyl, HCl	226d	279
1-Oxide	158	425
N-Oxide	211–214	415
	212–214	428
1-CH_3, *N*-$(CH_3)_2$, HCl	191–192	252
N-*i*-C_3H_7 HCl	193–195	547

TABLE XIII. *(Continued)*



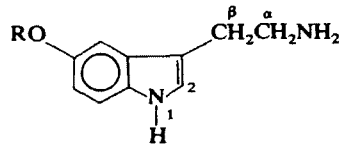
Substituent(s)	mp or bp (mm) (°C)	Ref.
Acetate	138–139d	547
Oxalate	257	547
Benzoate	188–190	547
N-$(C_2H_5)_2$	147–149	80
	150–151	258
HCl	169.5–170	253b
Oxalate	230–232	80
N-$(CH_2)_5$	196–200	307
N-$(CH_2)_6$	201–203	80
	204–206	258
Oxalate	243–244	80
N-(*n*-$C_3H_7)_2$, HCl	204–205	253b
N-(*i*-$C_3H_7)_2$, HCl	109–111	253b
1-$CH_2C_6H_5$, picrate, H_2O	165	267
N-trityl	107–110	540
O-Acetate	143.5–144.5	540
O-Benzoate	195–196	540
O-CH_3	115–116	314a
	118 ± 1	61
	118	62
	119–120	73b, 539
	119.5–120.5	256
	120	288, 321a, 878a,b
	120–121	294a,b, 301, 316b
	121–122	255, 279, 291
	121.5–122.5	275
	122–123	303
HCl	215	272
	239–240	539
	245d	303
	247.5–248.5	255
	249–250	73b
CH_3I	183–184	279
CH_3I, picrate	84	279
Picrate	202–203	539
	212–213d	314a
	214–215	301
	219	312d

TABLE XIII. (*Continued*)



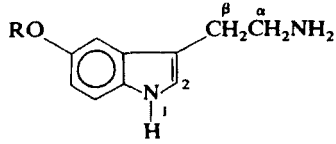
Substituent(s)	mp or bp (mm) (°C)	Ref.
	219d	34, 294a,b
	220	291, 292
	220d	279
	220–221	303
Carbonate	114d	878a,b
Benzoate	161–162	303
Flavianate	233	279
Octanoate	114–115	551
Stearate	94–97	551
Sulfate	230–232	316b
N-Phthaloyl	156–158	316b
N-Acetyl (melatonin)	115–116	15, 34, 312d
	116–118	255, 275, 539
	117	550
N-Chloroacetyl	125–127	272, 495
7-Cl	131.5–133.0	322
HCl	246–248	322
N-Acetyl	142–143	322
O-CH_3, 1-CH_3		
HCl	176–177	65a,b
	181.5–183.0	361
Picrate	189–190	65a,b
O-CH_3, 7-CH_3	163–164	324
O-CH_3, *N*-CH_3	99–102	434
	102–102.5	256
	205	251
HCl	164–166	434
	165–166	62
	166–167	433
Oxalate	223–226	434
Picrate	220–221d	433
	216–222	434
	216.5–217	256
N-Acetyl	97–99	361
	125	550
N-*p*-Tosylate	116–118	434
	118–119	433
O-CH_3, *N*-$(CH_3)_2$	66–67	244a,b

TABLE XIII. (*Continued*)



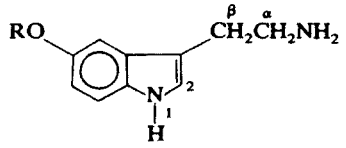
Substituent(s)	mp or bp (mm) (°C)	Ref.
	67–68	434
	67.0–67.5	256
	67.5–68.0	414
	69	425
	208–210 (4)	244a,b
HCl	145–146	252
	169–170	307
CH_3I	181–182	425
	183	244a,b
	185–186	256
	186–188	434
CH_3I, picrate	170–171	244a,b
CH_3I, dipicrate	103–104	244a,b
Oxalate	172–175	434
Picrate	168	438
	172	425
	173–175	434
	175.5–177.0	256
	176–177	244a,b
N-Oxide, picrate	158	432, 438
O-CH_3, *N*-C_2H_5	84–88	546
	85	62
	168–174 (0.08)	61
HCl	150	62
O-CH_3, 1-CH_3, *N*-$(CH_3)_2$, HCl	189–190	65a,b
O-CH_3, *N*-*n*-C_3H_7, HCl	145	62
O-CH_3, *N*-*i*-C_3H_7, HCl	185	62
O-CH_3, *N*-$(C_2H_5)_2$		
HCl	190–191	62
Picrate	134–136	307
O-CH_3, *N*-$(CH_2)_4$	167	62
Oxalate	150–158	257
Picrate	154–157	257
	182–184	307
O-CH_3, *N*-$(CH_2)_5$		
HCl	164–167	258
	192	62
Oxalate	143–146	257

TABLE XIII. (*Continued*)



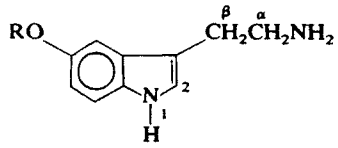
Substituent(s)	mp or bp (mm) (°C)	Ref.
Picrate	148–150	307
	190–191	257
O-CH_3, N-(n-C_3H_7)$_2$		
HCl	188	62
Picrate	179–180	307
O-CH_3, N-(i-C_3H_7)$_2$, HCl	180–181	62
O-CH_3, 1-$CH_2C_6H_5$, HCl	156–159	328, 329
	166–167	65a,b
Picrate	167–168	329
O-CH_3, 1-p-CH_3O-$C_6H_4CH_2$, HCl	162–164	328, 329
O-CH_3, N-CH_3, N-$CH_2C_6H_5$, picrate	153–154	307
O-CH_3, 1-$CH_2C_6H_5$, N-$(CH_3)_2$		
HCl	189–191	328, 329
	191–192	65a,b
O-CH_3, 1-p-CH_3O-$C_6H_4CH_2$, N-$(CH_3)_2$		
HCl	174–176	328, 329
O-CH_3, 1-$CH_2C_6H_5$, N-$(C_2H_5)_2$, HCl	135	327, 328
O-CH_3, 1-p-CH_3O-$C_6H_4CH_2$, N-$(C_2H_5)_2$		
Picrate	88–89	329
O-CH_3, 1-$CH_2C_6H_5$, N-$(CH_2)_5$, HCl	202–204	328, 329
O-CH_3, 1-p-CH_3O-$C_6H_4CH_2$, N-$(CH_2)_5$, HCl	180–183	329
O-CH_3, 1-p-CH_3O-$C_6H_4CH_2$, N-C_6H_5		
HCl	147–149	327
O-CH_3, 1-p-CH_3O-$C_6H_4CH_2$, N-CH_3, N-$CH_2C_6H_5$, HCl	159–160	328, 329
O-C_2H_5	108–109	281
	113–114	303
HCl	247–249	73a–d
	262–263	303
	263	310
Benzoate	202–203	303

TABLE XIII. (*Continued*)



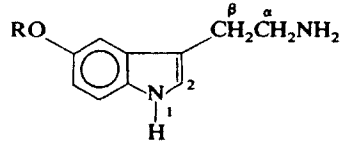
Substituent(s)	mp or bp (mm) (°C)	Ref.
Picrate	231–233	73a–d
O-C_2H_5, *N*-CH_3	99–100, 179–184 (2–3)	304
Benzoate	119–120	304
Picrate	209–210	304
Flavianate	217–219	304
N-*p*-Tosylate	63–64	304
O-C_2H_5, *N*-$(CH_3)_2$	230–232 (5)	244a
Picrate	144–145	244a
Dipicrate	124–125	244a
O-*n*-C_3H_7, HCl	256–257	310
O-*n*-C_4H_9, HCl	249–252	310
O-$CH_2C_6H_5$		
HCl	245–247	290
	248–250	305
	248–250d	236, 282
	250–251	34
	253–255	317a,b
	257–258	269a,d
	263–264	85b
	265	219a,b, 288, 299
	265–266	79
Oxalate	162	299
Bioxalate	197	299
Benzoate	153–154	315b,c
Salicylate	174–175	315b,c
Picrate	231–232	315a
	231.5–232d	290
$\frac{1}{2}H_2SO_4$, hydrate	187–189	316a,b
	230–232	64
N-Formyl	99–101	545
N-Acetyl	132–133	306
N-Phthaloyl	176–178	317a,b
	181–182	316a,b
N-Trityl	145–145.5	540
N-$CO(OCH_3)$	94–95	315a–c
N-$CO(OC_2H_5)$	87–88	315a–c
N-$CO(OCH_2C_6H_5)$	72–73	315a–c
O-$CH_2C_6H_5$, 1-CH_3, HCl	213–214d	361

TABLE XIII. (*Continued*)



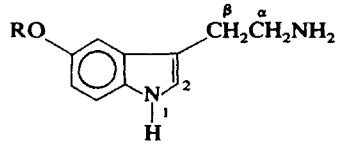
Substituent(s)	mp or bp (mm) (°C)	Ref.
O-$CH_2C_6H_5$, 7-CH_3, sulfate·$3H_2O$	233–234	229
O-$CH_2C_6H_5$, *N*-CH_3	84–86	80
Bioxalate	201–203	80
	203–205	545
O-$CH_2C_6H_5$, *N*-$(CH_3)_2$	87–89	80
HCl	154–155	248, 285b
	157–158	307
	159–161	253a
	162–163	252
CH_3I	212–213	79
Oxalate	178–179	79
Bioxalate	177–178	80
O-$CH_2C_6H_5$, 1-C_2H_5, oxalate	180–180.5	267
O-$CH_2C_6H_5$, *N*-C_2H_5	59–61	80
Bioxalate	187–189	80
O-$CH_2C_6H_5$, 1-CH_3, *N*-$(CH_3)_2$, HCl	182–183	252
O-$CH_2C_6H_5$, *N*-CH_3, *N*-C_2H_5, oxalate	165	545
O-$CH_2C_6H_5$, *N*-*i*-C_3H_7, HCl	201–202	548
O-$CH_2C_6H_5$, *N*-$(C_2H_5)_2$	Oil	80
HCl	171–172	253b
Oxalate	158–159	258, 307
	159–160	300
	161–162	79, 300
Bioxalate	161–162	80
O-$CH_2C_6H_5$, *N*-$(CH_2)_4$	198–199	258
O-$CH_2C_6H_5$, *N*-$(CH_2)_5$	136–138	80
O-$CH_2C_6H_5$, *N*-(*n*-$C_3H_7)_2$, HCl	209–211	253b
O-$CH_2C_6H_5$, *N*-(*i*-$C_3H_7)_2$		
HCl	215–218d	253b
Oxalate	103–106	307
O-$CH_2C_6H_5$, 1-$CH_2C_6H_5$		
Oxalate	177–178	267
Picrate	188–190	267
O-$CH_2C_6H_5$, *N*-CH_3, *N*-$CH_2C_6H_5$		
HCl	110–112	285b
Oxalate	155–158	307

TABLE XIII. (*Continued*)



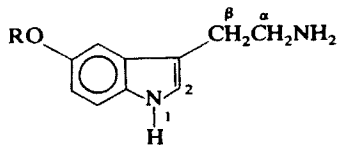
Substituent(s)	mp or bp (mm) (°C)	Ref.
O-$CH_2C_6H_5$, 1-$CH_2C_6H_5$, *N*-C_6H_5, HCl	151–154	327, 329
O-$CH_2C_6H_5$, *N*-$(CH_2C_6H_5)_2$	101–102	248, 285b
HCl	232–233	248, 285b
2-CH_3		
HCl	230–231	65a
Picrate	216–217	65a
2-CH_3, *N*-$(CH_3)_2$	167–168	254
2-CH_3, *N*-$(C_2H_5)_2$, HCl	254–255	254
2-CH_3, *N*-$(CH_2)_5$, HCl	253–254	254
2-CH_3, 1-*p*-CH_3O-$C_6H_4CH_2$, HCl	253–254	312b
2-CH_3, 1-*p*-CH_3O-$C_6H_4CH_2$, *N*-$(CH_3)_2$	258–259	312b
O-Acetate, HCl	177–178	312b
2-*p*-Cl-C_6H_4	144	313
2-*p*-Br-C_6H_4	142	313
2-CH_3, *O*-CH_3		
HCl	179–180	65a,b
	183–185	312c
Picrate	216–217	65a,b
N-Phthaloyl	182–183	312b
2-CH_3, 1-CH_3, *O*-CH_3		
HCl	230–232	65a,b
Picrate	197–198	65a,b
2-CH_3, *O*-CH_3, *N*-$(CH_3)_2$, picrate	147, 182 (double)	65a,b
2-CH_3, *O*-CH_3, 1-C_6H_5,[a] HCl	222–223	240
2-CH_3, *O*-CH_3, 1-$CH_2C_6H_5$ (benzyl anti-serotonin, "BAS")	57–58	314a
HCl	225–227	153
	228–230	152
	229–231	328, 329
	230	276
	230–231	65a,b
	231–232	314a
	239–241	312d
	243–244	312a,b
	243–244.5	312c
Picrate	182–184	314a

TABLE XIII. (*Continued*)



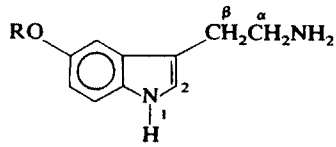
Substituent(s)	mp or bp (mm) (°C)	Ref.
N-Phthaloyl	155–157	312a–d
2-CH_3, *O*-CH_3, 1-*p*-$CH_3OC_6H_4CH_2$		
HCl	194–197	312b
N-Phthaloyl	131–132	312b
2-CH_3, *O*-CH_3, 1-$CH_2C_6H_5$, *N*-$(CH_3)_2$		
HCl	191–192	65a,b
	197.5–199	312d
2-CH_3, *O*-CH_3, 1-*p*-$CH_3OC_6H_4CH_2$, *N*-$(CH_3)_2$		
HCl	133–136	312b
2-CH_3, *O*-CH_3, 1-$CH_2C_6H_5$, *N*-C_2H_5, HCl	190–192	312d
2-CH_3, *O*-CH_3, 1-*p*-$CH_3OC_6H_4CH_2$, *N*-C_2H_5		
HCl	179–181	312b
2-CH_3, *O*-CH_3, 1-$CH_2C_6H_5$, *N*-*i*-C_3H_7, HCl	204–205	312d
2-CH_3, *O*-CH_3, 1-$CH_2C_6H_5$, *N*-$(CH_2)_5$, HCl	253–256	312d
2-CH_3, *O*-CH_3, 1,*N*-$(CH_2C_6H_5)_2$,[b]		
HCl	233	312d
2-CH_3, *O*-CH_3, *N*-$(CH_2C_6H_5)_2$,		
HCl	221–223	65a,b
2-CH_3, *O*-*n*-C_4H_9, *N*-$(C_2H_5)_2$,		
HCl	187	311
2-CH_3, *O*-$CH_2C_6H_5$	114–115	312c
HCl	207–208	65a,b
	209–211	312c
2-CH_3, *O*-$CH_2C_6H_5$, *N*-$(CH_3)_2$,		
HBr	157–159	254
2-CH_3, *O*-$CH_2C_6H_5$, *N*-$(C_2H_5)_2$,		
HBr	186–187	254
2-CH_3, *O*-$CH_2C_6H_5$, *N*-$(CH_2)_5$	122–123	254
HBr	175–176	254
2-CH_3, *O*-$CH_2C_6H_5$,		
1-*p*-$CH_3OC_6H_4CH_2$, HCl	203–205	312b
2-C_6H_5, *O*-CH_3,[c] HCl	150	313

TABLE XIII. (*Continued*)



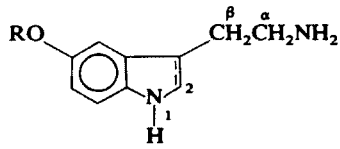
Substituent(s)	mp or bp (mm) (°C)	Ref.
2-C_6H_5, *O*-CH_3, *N*-$(CH_3)_2$[c]	124–125	287
HCl	160	313
2-C_6H_5, *O*-CH_3, *N*-$(C_2H_5)_2$, HCl[c]	165	313
α-CH_3		
Picrate	208–209	269a,e
	218–220d	64
Maleate	186–187	308
Creatinine sulfate	Amorphous	222, 235a
$\frac{1}{2}H_2SO_4$, hydrate	130–133	64, 270
α,*N*-$(CH_3)_2$, creatinine sulfate, hydrate	175–177	229
α,1-$(CH_3)_2$, creatinine sulfate, hydrate	n.c.	222, 235a
α,α-$(CH_3)_2$	74–84	222, 235a
creatinine sulfate	161	222
α-C_2H_5		
Picrate	183–184	269a,e
Dipicrate	176–177	64
$\frac{1}{2}H_2SO_4$	148–150	64
β-OH	n.c.	268
1-CH_3, β-OH, indole-3-acetate salt	160d	267
1-CH_3, 2-C_6H_5, β-OH, *N*-$(CH_3)_2$	153–155	268
O-CH_3, α-CH_3	100–101	326
	102	295
	187–190 (0.3)	298a,b
HCl	112–113	298a,b
	210	326
	220–221d	269a,d
	222–223	319
Picrate	196–197	295
	197	326
O-CH_3, β-CH_3, benzoate	120–123	246a
O-CH_3, 1,α-$(CH_3)_2$		
HCl	168.5–169	297
Picrate	182–185	297
N-Phthaloyl	154–155	297
O-CH_3, α,*N*-$(CH_3)_2$, maleate	125–127	229

TABLE XIII. (*Continued*)



Substituent(s)	mp or bp (mm) (°C)	Ref.
O-CH_3, α,α-$(CH_3)_2$	117–118	229
O-CH_3, α,β-$(CH_3)_2$	108–109	320
HCl	215–216	320
Picrate	194–195	320
O-CH_3, β,β-$(CH_2)_2$, acetate	142 ± 2	246b
O-CH_3, α-C_2H_5	106–107	229
	143–144	228
HCl	226–227	229
O-CH_3, β-C_2H_5, acetate	135–137	278c
O-CH_3, 1-CH_3, α-*i*-C_3H_7		
HCl	247–248	296
Picrate	193–194	296
O-CH_3, α-C_6H_5	103	296
Picrate	209	296
O-CH_3, β-C_6H_5	142–143	296
Picrate	186–187	296
O-CH_3, 1-CH_3, α-C_6H_5		
HCl	247–248	296
Picrate	200–201	296
O-CH_3, 1-CH_3, β-C_6H_5, *N*-phthaloyl	136	296
O-CH_3, 1-$CH_2C_6H_5$, α-CH_3, HCl	190–192	329
O-CH_3, 1-$CH_2C_6H_5$, β-CH_3	72	246a
HCl	168–173	328, 329
Benzoate	153	246a
O-CH_3, 1-$CH_2C_6H_5$, 2,β-$(CH_3)_2$, HCl	178–180	328
O-CH_3, 1-$CH_2C_6H_5$, β,β-$(CH_3)_2$, HCl	228–230	328, 329
O-CH_3, 1-$CH_2C_6H_5$, 2,β-$(CH_3)_2$, *N*-$(CH_3)_2$, HCl	193–194	328
O-CH_3, 1-$CH_2C_6H_5$, 2,α-$(CH_3)_2$, *N*-C_2H_5, HCl	197–198	312d
O-CH_3, 1-$CH_2C_6H_5$, 2,β-$(CH_3)_2$, *N*-$(C_2H_5)_2$, HCl	167–169	328
O-CH_3, 1-CH_3, β-OH	121–122	267
O-CH_3, α-CH_3, *N*-OH	162–163	245a,b
O-CH_3, α,α-$(CH_3)_2$, *N*-OH	162	245a

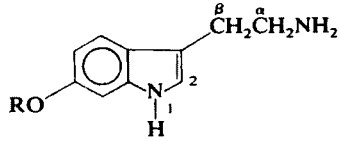
TABLE XIII. (*Continued*)



Substituent(s)	mp or bp (mm) (°C)	Ref.
O-$CH_2C_6H_5$, α-CH_3		
HCl	253–254	222, 235a
	257–258d	269a,d
Succinate	181–182	269a,d
$\frac{1}{2}H_2SO_4$	146–148d	64
$\frac{1}{2}H_2SO_4 \cdot 2H_2O$	128–131	64
O-$CH_2C_6H_5$, 1,α-$(CH_3)_2$	62–64	222, 235a
HCl	193–195	222
O-$CH_2C_6H_5$, α,α-$(CH_3)_2$	114.5–116.5	222
O-$CH_2C_6H_5$, α-C_2H_5		
HCl	243–244	269d
$\frac{1}{2}H_2SO_4$	190–191	64
$\frac{1}{2}H_2SO_4$, hydrate	185–188	64
O-$CH_2C_6H_5$, β-C_6H_5	150–151	300
Oxalate	209–210	300
O-$CH_2C_6H_5$, 1-CH_3, β-OH	113.5–114.5	267
O-$CH_2C_6H_5$, 1-CH_3, 2-C_6H_5, β-OH, *N*-$(CH_3)_2$	121–123	268

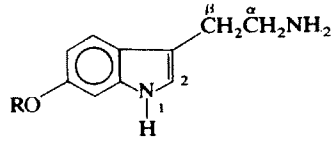
[a] Other 1-aryl analogues are also reported.
[b] Other *N*-substituted analogues are also reported.
[c] 2-*p*-Bromo- and 2-*p*-chloro-phenyl analogues are reported.

TABLE XIV. 6-HYDROXYTRYPTAMINE AND DERIVATIVES



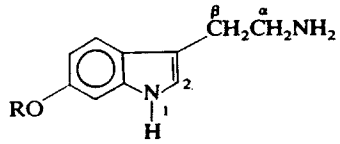
Substituent(s)	mp or bp (mm) (°C)	Ref.
None	191–193	183
HCl, hydrate	192	269a
Picrate	226–227d	269a
Creatinine sulfate	205–211	239
	209–212	183

TABLE XIV. (*Continued*)



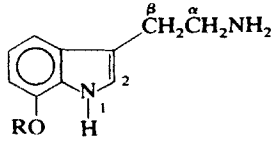
Substituent(s)	mp or bp (mm) (°C)	Ref.
	210–211	316b
	212–215	80
Creatinine sulfate, hydrate	210–213	86
N-$(CH_3)_2$	165–166	227a,c
Picrate	205–206d	267
O-Phosphate	233–235	227a
O-Dibenzylphosphate	240–242	227a
N-$CH_2C_6H_5$	n.c.	89
O-CH_3	139–140	90b,c
	139.5–141	90a
	140–141	87
	141–143	223
	142–143.5	318
	142.5–143.5	280
	144	321a
	145–146	228, 878a,b
HCl	219–221	90a
	221–223	87
CH_3I	182–183	279
Carbonate	150–155d	228, 878a,b
Picrate	221	318
N-Formyl	96.5–98.0	223
N-Acetyl	136	302
5-Cl	163–164	238a–c, 288 321a,c,f
7-Cl	149	238a–c, 288 321a,c,f
Carbonate	145–147	238a–c, 288 321a,c,f
O-CH_3, *N*-CH_3, HCl	169	62
O-CH_3, *N*-$(CH_3)_2$	75–76	62
	76–77.2	264
HCl	143	62
O-CH_3, *N*-C_2H_5, HCl	176–177	62
O-CH_3, *N*-$(C_2H_5)_2$, HCl	210–215	62
O-CH_3, *N*-$(CH_2)_5$	90–91	258
HCl	151–152	62
O-CH_3, *N*-$(C_3H_7)_2$, HCl	172	62
O-CH_3, *N*-$(CH_2)_6$, HCl	193	62

TABLE XIV. (*Continued*)



Substituent(s)	mp or bp (mm) (°C)	Ref.
O-CH_3, *N*-$CH_2C_6H_5$	n.c.	89
O-C_2H_5, HCl	242–247	73a,b,d
O-C_2H_5, *N*-C_2H_5	n.c.	61
O-*i*-C_3H_7	n.c.	881
O-*n*-C_4H_9	n.c.	881
O-$CH_2C_6H_5$	92–96	80
HCl	237–238	239
	255–256d	269a,d
$\frac{1}{2}H_2SO_4$	260–265	80
	263–265	86
	296–297	316b
N-Phthaloyl	203–205	316b
O-$CH_2C_6H_5$, *N*-$(CH_3)_2$	87–88	227a,c
Oxalate	178–179	79
α-C_2H_5, creatinine sulfate	87–90	228
O-CH_3, α-CH_3, picrate	227	273a,b
	242	273c
Benzoate	187 ± 2	273b
O-CH_3, β-CH_3		
Picrate	242	278a,b,e, 284a–d
Flavianate	155 ± 3	246b
O-CH_3, α-CH_3, *N*-CH_3, maleate	140–142	229
O-CH_3, α-CH_3, *N*-OH	Oil	245a,b
O-CH_3, α,α-$(CH_3)_2$, HCl	268–270	229
O-CH_3, β,β-$(CH_3)_2$, HOAc	142	246a
O-CH_3, 1-$CH_2C_6H_5$, β,β-$(CH_3)_2$, picrate	220	246a
O-CH_3, α-C_2H_5	144–145	228
Maleate	132–134	228
O-CH_3, β-C_2H_5, picrate	233	284a
O-$CH_2C_6H_5$, α-CH_3, sulfate, hydrate	ca. 270	229
O-$CH_2C_6H_5$, α-C_2H_5		
HCl	214.5–215	228
Sulfate	179–183	228
O-$CH_2C_6H_5$, β-C_6H_5, oxalate	125–126	300

TABLE XV. 7-HYDROXYTRYPTAMINE AND DERIVATIVES



Substituent(s)	mp or bp (mm) (°C)	Ref.
None		
HCl	145–148	85a,b
Picrate	340	85a,b
N-$(CH_3)_2$	185–188	227a,d
Picrate	183d	194
	188.5–189.0d	267
O-Phosphate	229–231	227a,d
O-CH_3	133–135	91
	135–136	301, 321a,c, 878a,b
HCl	208–209.5	310
Carbonate	125d	321a,c, 878a,b
Picrate	236–238	91
N-Phenylacetyl	190	554
4-Cl	156.5	321a–d
Carbonate	115–120	321a–d
6-Cl	113.5	321a–d
O-CH_3, *N*-$(CH_3)_2$	147 (0.18)	194
	77–78	91
HCl	204–205	91
Picrate	179–180	194
	181–182	91
O-CH_3, *N*-$(CH_2)_4$	87–88	258
O-CH_3, *N*-$(C_2H_5)_2$	180–185 (0.5)	91
Picrate	148–149	91
O-$CH_2C_6H_5$	167.5–168.5	85a,b
HCl, hydrate	214–216	85a,b
Picrate	241–242	85a,b
O-$CH_2C_6H_5$, *N*-$(CH_3)_2$	100–102	227a,d
O-CH_3, α-CH_3		
HCl	247–248	274
	255–256	91
Picrate	217–219	91

TABLE XVI. DI- AND TRIHYDROXYTRYPTAMINES AND DERIVATIVES

Substituent(s)	mp or bp (mm) (°C)	Ref.
4-OH, 5-OCH_3, HCl	228d	98
4-OH, 5-OCH_3, *N*-$(CH_3)_2$	146–147	98
4-$OCH_2C_6H_5$, 5-OCH_3	106	98
Fumarate	240d	98
4-$OCH_2C_6H_5$, 5-OCH_3, *N*-$(CH_3)_2$, fumarate	176	98
4-$OCH_2C_6H_5$, 5-OCH_3, *N*-$(C_2H_5)_2$, HCl	152	98
4,6-$(OCH_3)_2$, *N*-$(CH_3)_2$, dipicrate	155–160	349
4,7-$(OCH_3)_2$	135	96
HCl	258	96
Picrate	226	96
4,7-$(OCH_3)_2$, *N*-$(CH_2C_6H_5)_2$, HCl	222	96
5,6-$(OH)_2$		
HCl	212–214d	82
Oxalate	237–239	82
Creatinine sulfate, dihydrate	180–182d	82
	182–184	224b
N,O,O-Triacetyl	135–136	82
5,6-$(OH)_2$, *N*-$(CH_3)_2$, picrate	139–140d	185
5-OCH_3, 6-OH		
HCl	277–278	242
N-Acetyl	175	277
N-Acetyl, picrate	145–146	242
	146–147	277
5-OCH_3, 6-OH, N-$(CH_3)_2$, fumarate	140	98
5-OCH_3, 6-OH, *N*-$(C_2H_5)_2$, fumarate	208	98
5,6-OCH_2O	90	288
HCl	261–262	73a,b,d
Picrate	223–224	73a,b,d
5,6-$(OCH_3)_2$	90–92	88
Picrate	223–224	289
	225d	88
N-Acetyl	179–181	88
5,6-$(OCH_3)_2$, 1-$CH_2C_6H_5$, HCl	95–96 (hygroscopic)	328, 329
5,6-$(OCH_3)_2$, 1-*p*-$CH_3OC_6H_4CH_2$		
HCl	Hygroscopic	328, 329
Picrate	190–193	328, 329
5,6-$(OCH_3)_2$, *N*-$(CH_3)_2$		
HCl	Hygroscopic	107
Picrate	182–184	107
CH_3I	213–216	107
5,6-$(OCH_3)_2$, 1-$CH_2C_6H_5$		
HCl	Hygroscopic	328, 329
Picrate	172–174	328, 329
5-OCH_3, 6-$OCH_2C_6H_5$		
HCl	183–184	242

TABLE XVI. (*Continued*)

Substituent(s)	mp or bp (mm) (°C)	Ref.
N-Acetyl	148	277
	151–152	242
5-OCH_3, 6-$OCH_2C_6H_5$, *N*-CH_3	116	98
5-OCH_3, 6-$OCH_2C_6H_5$, *N*-$(CH_3)_2$	86	98
Oxalate	153–154	98
Fumarate	192	98
5-OCH_3, 6-$OCH_2C_6H_5$, *N*-$(C_2H_5)_2$, fumarate	175	98
5,6-$(OCH_2C_6H_5)_2$	84–87	224b
Picrate	183–185	224b
Sulfate	226–228d	224b
Oxalate	193–195	224b
5,6-$(OCH_2C_6H_5)_2$, *N*-$(CH_2C_6H_5)_2$	89–90	82
HCl	216–217d	82
Oxalate	208–209d	82
5,7-$(OCH_3)_2$, oxalate	170–171	378
5,7-$(OCH_3)_2$, *N*-CH_3, oxalate	197–198	378
5,7-$(OCH_3)_2$, *N*-$(CH_3)_2$	118–119	378
6-OH, 7-OCH_3, *N*-$(CH_3)_2$, HCl	174	98
6-OH, 7-OCH_3, *N*-$(C_2H_5)_2$, HCl	154	98
6-$OCH_2C_6H_5$, 7-OCH_3, *N*-$(CH_3)_2$, HCl	172	98
6-$OCH_2C_6H_5$, 7-OCH_3, *N*-$(C_2H_5)_2$	77	98
4,5,6-$(OCH_3)_3$	146	189
	146–147	321a,c,e, 325a,b
Sulfate	255–256	316b
N-Phthaloyl	175–177	316b
4,5,6-$(OCH_3)_3$, *N*-$(CH_3)_2$	97	189
5,6,7-$(OCH_3)_3$, *N*-$(CH_3)_2$	107	104

TABLE XVII. HYDROXYINDOLE COLOR REACTIONS

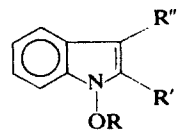
3-Substituent	Position of hydroxyl group	Color with van Urk–Ehrlich reaction	Color with $FeCl_3$ reaction
H	4	Blue[11]	Blue[11]
	5	Pink[25]; violet[11]	Brown-gray[11]; purple[25]
	6	Gray-blue[11]	Blue[11]
	7	Gray-blue[11]; lilac-pink[25]	Purple[25]; brown-red[11]
CH_3	4	Gray-blue[22]	
	5	Violet[22]	
	6	Cobalt-blue[22]	
	7	Gray[22]	

TABLE XVII. (*Continued*)

3-Substituent	Position of hydroxyl group	Color with van Urk–Ehrlich reaction	Color with $FeCl_3$ reaction
$CH_2N(CH_3)_2$	4	Salmon-pink[227]	Green-blue → blue[227]
	5	Violet[227]	Pink → brown-violet[227]
	6	Greenish[227]	Violet-gray[227]
	7	Greenish-blue[227]	Pink[227]
$(CH_2)_2NH_2$	4	Gray-blue[330b]; gray[330b*] blue[227]	Olive green → gray-blue[80]
	5	Blue[227,330b,330b*]; purple[505]	
	6	Blue[330b]; gray-blue[330b*]	Chrome green → olive-green[80]
	7	Blue-green[330b]; green[330b*]	
$(CH_2)_2N(CH_3)_2$	4(psilocin)	Gray-blue[227]; blue-violet[484]	Olive-green → blue[227] Blue-green[259b]
	5(bufotenine)	Blue[227]	Red-blue[80,227]
	6	Green-blue[227]	Olive brown[227]
	7	Green	Green-violet[227]
	4-*O*-phosphate (psilocybin)	Rose-brown[227]; red-violet[484]	Red-violet[227] violet[259b]
	5-*O*-phosphate	Rose[227]	Wine red[227]
	6-*O*-phosphate	Dark blue	Wine red[227]
	7-*O*-phosphate	Negative	Red-violet → brown-violet[227]

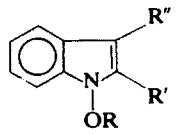
* Color with *p*-dimethylaminocinnamaldehyde.

TABLE XVIII. 1-HYDROXYINDOLES



R	R'	R''	mp (°C)	Ref.
H	CH_3	H	74–78	573
			78–79	589
p-ClC_6H_4CO	CH_3	H	88–92	573
C_2H_5	C_3H_7	H	Oil	570
CH_3	CH_2OH	H	47	562
H	H	C_6H_5	170–171	563
			172	574
			173	570
			175	560, 589
H	H	4-$CH_3OC_6H_4$	145	562

TABLE XVIII. (*Continued*)



R	R′	R″	mp (°C)	Ref.
H	H	4-$(CH_3)_2NC_6H_4$	165	562
C_2H_5	H	C_6H_5	Oil	570
C_6H_5CO	H	C_6H_5	100	563, 586b
			101	574
p-$O_2NC_6H_4CO$	H	C_6H_5	128d	571
H	CN	C_6H_5	195	574
CH_3CO	CN	C_6H_5	111	574
H	NO	C_6H_5	240	586b
C_2H_5	NO	C_6H_5	Oil	586b
CH_3CO	NO	C_6H_5	140	586b
C_6H_5CO	NO	C_6H_5	163	586b

TABLE XIX. 2-INDOLINOLS

Substituent(s)	mp or bp (mm) (°C)	Ref.
1-CHO	113–116	623
1-CHO, 5-CH_3	108–109	623
1-CHO, 5-OCH_3	151–152	623
1-CH_3CO	157–159	622
1,3,3-$(CH_3)_3$	80–92	611b
	95	612
	97–98	610, 614
1-CH_3CO, 3,3-$(CH_3)_2$	117–118	614, 617
O-CH_3	n.c.	614, 617
O-Acetate	60–61	614, 618
O-Benzoate	83–85	614, 618
1,3,3-$(CH_3)_3$, 5-OCH_3	155 (6)	357
Picrate	155–156	357
1,3-$(CH_3)_2$, 3-C_2H_5, 5-OCH_3	145–146 (1.5)	357
Picrate	138–138.5d	357
1,6-$(CH_3CO)_2$, 2,3-$(CH_3)_2$, 3-NO_2	185	620
1,3,3-$(CH_3)_3$, 2-*t*-C_4H_9	58–61	611a,b
1-C_6H_5CO, 3,3-$(CH_3)_2$	202–204	617, 618
O-CH_3	71–72	614, 617
O-C_6H_5	125–127	618
O-Acetate	156–157	614, 617

TABLE XIX. 2-INDOLINOLS

Substituent(s)	mp or bp (mm) (°C)	Ref.
1-C_6H_5CO, 2,3-$(CH_3)_2$, 3-NO_2	103	619
1,3,3-$(CH_3)_3$, 2-C_6H_5	107–108	614
	108–109	611a,b
1,2-$(C_6H_5)_2$, 3,3-$(CH_3)_2$	156d	615
O-CH_3	118	615
1,3-$(CH_3)_2$, 2,3-$(C_6H_5)_2$	110	613

TABLE XX. 3-INDOLINOLS

Substituent(s)	mp (°C)	Ref.
None	92–93	627
	96	624, 625
CH_3I	201.5d	627
1-CH_3	88 (sinters), 111–131	626
2-CH_3	92–94	630
2,2-$(CH_3)_2$	138	625
1,2,2-$(CH_3)_3$	64	626
1-CH_3CO, 2,3-$(CH_3)_2$	Oil (crude)	629
1-CH_3, 2,2-$(C_6H_5)_2$	124–126	628
HCl (unstable)	85–105	628
1-CH_3CO, 2,3-$(C_6H_5)_2$	56–72	629

TABLE XXI. 2,3-INDOLINEDIOLS

Substituent(s)	mp (°C)	Ref.
cis-1-CH_3CO, 2,3-$(CH_3)_2$	130–133	631a,b
cis-1-CH_3CO, 2,3,5-$(CH_3)_3$	102–108	631a,b
cis-1-C_6H_5CO, 2,3-$(CH_3)_2$	104–105	633
	215–218	631a,b
cis-1-CH_3CO, 2,3-$(C_6H_5)_2$	206–208	631a,b
trans-1-CH_3CO, 2,3-$(CH_3)_2$	132–134	632
	133–134	633
trans-1-C_6H_5CO, 2,3-$(CH_3)_2$	168	633

TABLE XXII. HYDROXYMETHYLINDOLES (INDOLE METHANOLS)

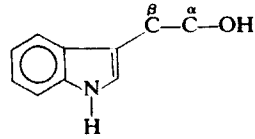
Substituent(s)	mp or bp (mm) (°C)	Ref.
2-Hydroxymethylindoles		
None	75	656
	75–76	657
	75–77	655
O-Acetate	110–112	656
2,3-H_2	57.7–59.1	662a
1-NO	130–133	662a
1-CH_3	108–110	658
O-Acetate	63.5–64	661
2-CH_3, 2,3-H_2, HCl	179	662a
3-CH_3	122	619
	123–124	656
O-Acetate	92	656
1-Acetyl	88–90.5	659
5-NO_2	n.c.	752
4-OH	135–136	750
3-Hydroxymethylindoles		
None	89–91[a]	644
	90	635a,b
	90–91[a]	641
	95–96	647
	99–100	637, 640
	100–101	638
	158[b]	645
O-CH_3	94–95	637
	97–98	642
	98–99	636
	99–100	635a,b
O-C_2H_5	62–63	640
	63–64	636, 637, 642
	93–94	635a,b
O-*i*-C_4H_9	120 (0.0005)	642
Trinitrobenzene adduct	103–104	642
1-Acetyl	137–139	644
1,*O*-Diacetyl	89–90	637
	90–90.5	636
	95	645
None(*Cont.*)		
Ether dimer	133–134	638
1-CH_3	150–160 (2)	644
	160 (0.001)	642
Trinitrobenzene adduct	139–141	642
2-CH_3	112–114	642
	205–206	645
	225	619

TABLE XXII. *(Continued)*

Substituent(s)	mp or bp (mm) (°C)	Ref.
1,*O*-Diacetyl	140–142	645
Trinitrobenzene adduct	169–170	642
4-CN	140–146	639
O-CH_3	119–120	639
1,*O*-Diacetyl	162.5–163.5	639
1-CH_3, 5-Br	100–101	643
1,2-$(CH_3)_2$	100–101	642
2-C_6H_5	129–130	642
O-C_2H_5	116–117	642
Trinitrobenzene adduct	140–141	642
1-CH_3, 2-C_6H_5	129–130	642
Trinitrobenzene adduct	104–105	642
Side-chain-substituted derivatives		
3-(1-Hydroxyethyl)indole	Oil	644
1-Acetyl	Gum	644
3-(1-Methoxyethyl)indole	78–79	652
3-(1-Ethoxyethyl)indole	95–97.5	652
3-(1-iso-Propoxyethyl)indole	94–96	652
3-(1-Methyl-1-hydroxyethyl)indole	105–115d	649
3-(α-Ethoxybenzyl)-2-methylindole	118–120	652
	123	654
Other hydroxymethylindoles		
4-Hydroxymethylindole	56–57	655
	59–61	664a,b
5-Hydroxymethylindole	73–75	664a,b
6-Hydroxymethylindole	62–63	664a,b
7-Hydroxymethylindole	55–56	664a,b

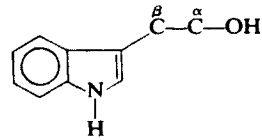
[a] The mp depends on rate of heating.
[b] The mp was revised to 88 °C (see Ref. 646).

TABLE XXIII. TRYPTOPHOL AND DERIVATIVES



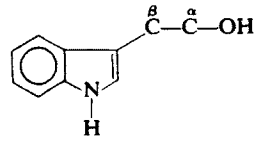
Substituent(s)	mp or bp (mm) (°C)	Ref.
None	56–57	698
	56–58; 150–154 (?)	72, 692a,b
	57	690
	57–58	684
	58–59; 170–173 (2)	244a, 680
	59	666, 694
	59–60	69
Picrate	94–96	666
	98–99	694
	101	680
Trinitrotoluene adduct	72.5	694
O-C_2H_5	147 (1.25)	698
O-$CH_2C_6H_5$	n.c.	701
O-Tosylate	79	690
	79–81d	710
5-Br	84–85	697
5-NO_2	97–98	403
2,3-H_2	156–164 (3)	880
O-Acetate	140–145 (2)	880
Octahydro	120–122 (0.05)	678
1-CH_3	120–124 (0.1)	658
Picrate	92–95	361
O-*p*-Nitrobenzoate	181–182	658
1-CH_3, octahydro	90–92 (0.01)	678
2-CH_3	52–55; 202–204 (7–8)	699
	55–56; 198 (3.5)	244a
	56.5; 202–204 (20)	694
	143–144 (0.01)	685
Picrate	132	699
	134.5	244a
Trinitrobenzene adduct	91–92	694
O-Acetate	196–204	699
Picrate of above	131.5	699
1,*O*-Diacetyl	96–97	244a
5-Cl, 1-*p*-Cl-C_6H_4CO	168–171	700
5-NO_2	158–159	879
5-NH_2	186–188	879
2-CH_3, 5-$N(CH_3)_2$	101–102	879
1,2-$(CH_3)_2$, octahydro	92–94 (0.5)	678
1-C_2H_5, octahydro	108–109 (0.2)	678

TABLE XXIII. (*Continued*)



Substituent(s)	mp or bp (mm) (°C)	Ref.
2-C_6H_5	144–146	686
O-Acetate	180–184 (0.02)	268
1-$CH_2C_6H_5$	53	690
O-3,5-Dinitrobenzoate	165	690
O-Tosylate	64	690
5-OH	105–107	673
	111–113	231
Picrate	151	435
5-OCH_3	Oil	687, 688
	50–51	690
	194 (4)	244b
Picrate	113	435
	116	690
	116–116.5	687, 688
	117–118	244b
O-Acetate	Oil	688
Picrate	95–95.5	688
O-Tosylate	66	690
	96–97	741
1-CH_3, 5-OCH_3	128–129	361
2-CH_3, 5-OCH_3		
1-*p*-ClC_6H_4CO	160–160.5	700
1-$CH_2C_6H_5$, 5-OCH_3	47	690
	47–48; 172–178 (0.05)	329
O-*p*-Nitrobenzoate	122	690
O-3,5-Dinitrobenzoate	158–161	329
O-Tosylate	95	690
1-*p*-$CH_3OC_6H_4$, 5-OCH_3	185–195 (0.05)	329
O-3,5-Dinitrobenzoate	169–171	329
5-OC_2H_5	75	244a
5-$OCH_2C_6H_5$	93–95	673
	98–100	231
6-OCH_3	96–97	691a,b
O-Tosylate	81–82	740
7-OCH_3		
O-Tosylate	Oil	741
2-CH_2OH	83–84	656
5-OCH_3, 6-OH	Oil	688
Picrate	138.5–139d	688
1-Acetyl, picrate	114–114.5	688

TABLE XXIII. (*Continued*)



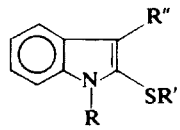
Substituent(s)	mp or bp (mm) (°C)	Ref.
5-OCH_3, 6-$OCH_2C_6H_5$	122–123	688
1-Acetyl	89–89.5	688
1-$CH_2C_6H_5$, 5,6-$(OCH_3)_2$	95–96	329
O-Tosylate	107	690
1-*p*-$CH_3OC_6H_4$, 5,6-$(OCH_3)_2$	81–82	329
α-CH_3	37.5; 146–147 (0.35)	693
	37.5; 140–145 (0.05)	689
	142–145 (0.1)	681
	145 (0.15)	696
	162–164 (0.75)	698
O-3,5-Dinitrobenzoate	185–186	681
	186–188	689
1,α-$(CH_3)_2$	75–76	689
O-3,5-Dinitrobenzoate	174–175	689
α,α-$(CH_3)_2$	92–93	702
	93–94	689
β-CH_3	145–155 (0.05)	689
O-C_2H_5	158 (1)	698
O-3,5-Dinitrobenzoate	187–188	689
1,β-$(CH_3)_2$	125–135 (0.05)	689
O-*p*-Nitrobenzoate	146–147	689
O-3,5-Dinitrobenzoate	184–186	689
β,β-$(CH_3)_2$	Oil	689
O-3,5-Dinitrobenzoate	176–178	689
α,β-$(CH_3)_2$	152–164 (0.5)	698
α-C_2H_5	42; 134–152 (0.2)	689
β-C_2H_5	155–160 (0.01)	689
O-3,5-Dinitrobenzoate	144	689
1-$CH_2C_6H_5$, β-CH_3		
O-3,5-Dinitrobenzoate	151	690
O-Tosylate	Oil	690
1-$CH_2C_6H_5$, 2,β-$(CH_3)_2$	89	329
1-$CH_2C_6H_5$, β-C_2H_5	Oil	689
O-3,5-Dinitrobenzoate	96–100	689
α-CH_3, 5-OCH_3		
O-3,5-Dinitrobenzoate	202–203	681
1-$CH_2C_6H_5$, β-CH_3, 5-OCH_3		
O-*p*-Nitrobenzoate	95	690
O-Tosylate	69–70	690

TABLE XXIV. MISCELLANEOUS INDOLE ALCOHOLS[a]

Compound	mp or bp (mm) (°C)	Ref.
3-(3-Indolyl)propanol (homotryptophol)	ca. 0	711, 712
Picrate	101	711
Trinitrobenzene adduct	119–121	712
O-Tosylate	105–108	712
O-CONH(C_6H_5)	94	711
2-Methyl homotryptophol	190–192 (4)	714
Picrate	94–95	714
4-(3-Indolyl)butanol	32–33	711
	189–202 (2)	698
Picrate	102	711
O-Tosylate	62–64	703
O-CONH(C_6H_5)	88	711
L-Tryptophanol	155–165 (0.65); $[\alpha]_D^{17} = -2.77$	716
	$[\alpha]_D^{15} = -18.7$	721a,b
Oxalate	204–205; $[\alpha]_D^{18} = -25.34$	716
Bioxalate	206.5d $[\alpha]_D^{18} = 25.1$	721a,b
DL-Tryptophanol	180–185 (0.1)	719
	85–86	717
Oxalate	209–210d	719
Picrate	203d	720
N-2,4-Dinitrophenyl	153–154	718
5-Methoxy-DL-tryptophanol		
Picrate	192–194	65a
5-Benzyloxy-DL-tryptophanol	108–109	231

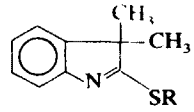
[a] See Sections IX.B.4–8 for other compounds. See also Table XIII under side-chain derivatives of 5-hydroxy- and 5-alkoxytryptamines for a few alcohols.

TABLE XXV. INDOLE-2-THIOETHERS[a]



R	R'	R''	mp (°C)	Ref.
H	CH_3	H	48–49	772
			50–51	789
CH_3	CH_3	H	16	789
		Picrate	83–84	772
H	C_2H_5	H	32.5–33.5	773
			36–37.5	774
H	$COCH_3$	H	184	784
CH_3	CH_3	CH_3	Oil	772
H	C_2H_5	CH_3	33–33.5	773, 774
			33–34	757
		Sulfoxide	126d	757
			136–137	773, 774
		Sulfone	77–78	791
			113.5	757
CH_3	C_2H_5	CH_3		
		Sulfoxide	92	757
			97–97.5	791
		Sulfone	84–85	791
H	C_2H_5	CH_3		
		6-CH_3O–	138	756
		Sulfoxide	130	757
		Sulfone	113	757
H	C_6H_5CO	H	128	784
H	$CH_2C_6H_5$	H	76	789
H	2,4-Dinitrophenyl	CH_3	194–196	761
			199–203	810
H	C_6H_5CO	CH_3	90–100	785
CH_3	CH_3	C_6H_5	96	765
CH_3	CH_3	*m*-Tolyl	Oil	765
		Picrate	84	765
CH_3			57.5–58	770
			65	766
HI			165	766
			167–168d	770
CH_3CO			39–40	766
C_6H_5CO			80	766

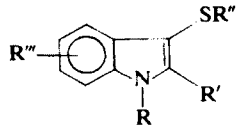
TABLE XXV. (*Continued*)



Related compounds	mp (°C)	Ref.
1-Benzoyl-2-ethylthio-3,3-dimethylindoline	165–166 (0.01)	756
Diskatyl 2,2′-trisulfide	145	785
Picrate	152	785

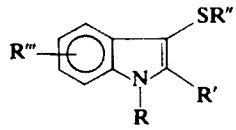
[a] "Indole-2-thiols" are excluded from this table because they are more properly represented as thiones. See Ref. 764.

TABLE XXVI. INDOLE-3-THIOETHERS



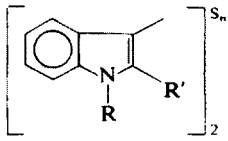
R	R′	R″	R‴	mp or bp (mm) (°C)	Ref.
H	H	H	H	99–100	805
				100–101	802
H	H	CN	H	73–76	805
				76.5–78	804
CH_3	H	H	H	104–106	805
H	H	CH_3	H	112.5–113.0 (0.15)	799, 866
H	H	CH_3	4-NO_2	123–124	866
H	H	CH_3	5-Cl	134.5–135.5 (0.20)	799, 866
H	H	C(=NH)NH_2	H	n.c.	802
CH_3	H	CN	H	85–86	805
H	CH_3	CH_3	H	56.5–58.3	798, 867
				58–59; 140–142 (0.85)	798, 866
H	CH_3	CH_3	4-NO_2	148–150	866
H	CH_3	CH_3	5-NO_2	197.5–198.5	866
H	CH_3	CH_3	5-Cl	62–63.5	867
				64.0–65.5	798, 866
H	H	$COCH_3$	H	208–211	784
H	H	C_2H_5	H	95(1.5)	797
			Picrate	−10–0	797
H	H	$CH_2CO_2^-$ NH_4^+	H	155–165	804
H	H	C(=NH)OCH_3	H	187–188	804
H	H	CO_2CH_3	H	124–124.5	804
H	CO_2H	CN	H	195d	804
CH_3CO	H	CN	H	122.5–123.5	804

TABLE XXVI. INDOLE-3-THIOETHERS



R	R′	R″	R‴	mp or bp (mm) (°C)	Ref.
H	CH_3	CH_3CO	H	311–312	785
CH_3	CH_3	CH_3	H	59.5–60	866
H	CH_3	CH_3	5-CH_3	110–111	798, 866
H	CH_3	CH_3	7-CH_3	59.5–60.5	866
H	CH_3	CH_3	5-OCH_3	109–111	867
H	CH_3	CH_3	7-OCH_3	58–59	867
H	CH_3	CH_3	5-$OCOCH_3$	129–129.5	798, 866
H	H	CH_3	5-$CO_2C_2H_5$	89.0–90.5	866
$COCH_3$	H	$COCH_3$	H	129–130	784
H	$CO_2C_2H_5$	C_2H_5	H	110	795
H	CH_3	$CH_2CO_2C_2H_5$	H	71	796
H	CH_3	$CH_2CO_2C_2H_5$	5-CH_3	71	796
H	CH_3	CH_3	5-$CO_2C_2H_5$	126–127	798, 866
				127–130	867
H	CH_3	$CH_2CO_2C_2H_5$	5-CH_3	111	796
H	CH_3	$CH_2CO_2C_2H_5$	6-OCH_3	83	796
H	CH_3	$CH_2CO_2C_2H_5$	6-CH_3	108	796
H	H	C_6H_5	H	154	796
H	H	C_6H_5	6-Cl	154	796
H	H	2,4-Dinitrophenyl	H	175	802, 810
				175–175.5	804
H	H	C_6H_5CO	H	142–143	802
				142–144	805
				157	784
H	C_6H_5	CH_3	H	106–107	798, 866
H	CH_3	C_6H_5	H	130	796
H	CH_3	C_6H_5	6-Cl	142	796
H	H	C_6H_5	5-CH_3	156	796
H	H	C_6H_5	6-CH_3	160	796
H	H	C_6H_5	6-OCH_3	76	796
H	CH_3	C_6H_5CO	H	237–238	785
H	CH_3	C_6H_5	5-CH_3	161–162	796
H	CH_3	C_6H_5	6-CH_3	162	796
H	CH_3	C_6H_5	7-CH_3	161	796
H	CH_3	C_6H_5	6-OCH_3	137	796

TABLE XXVII. 3,3'-DIINDOLYL MONO-, DI-, AND TRISULFIDES



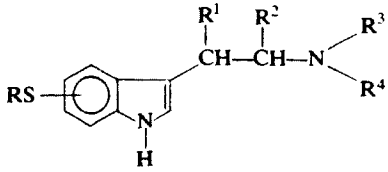
R	R'	*n*		mp (°C)	Ref.
H	H	1		232	814, 816
			Sulfoxide	157	814, 816
			Sulfone	151–152	814, 816
H	CH_3	1		225–226	816
				226	814
H	CO_2H	1		237–239	812
				242–244	811
H	$CONH_2$	1		336	812
H	$CO_2C_2H_5$	1		270–273	811
H	CO_2CH_3	1			
			Sulfoxide	178d	809
CH_3	$CONH(CH_3)$	1		239–240.5	809
CH_3	CO_2CH_3	1		150.5–152	809
H	H	2		217–218	804
				217–219	805
				217–222	786
				218–220	802
				227–229.5	801
				235[a]	784
CH_3	H	2		134–136	805
H	CH_3	2		230	819
				236–237	801
CH_3	CO_2CH_3	2		199–200	809
H	C_6H_5	2		161.8–162.4	801
C_6H_5CO	CH_3	2		100–105	819
H	CH_3	3		201	819
CH_3	CO_2CH_3	3		158.5–159.5	809

[a] Probable structure.

TABLE XXVIII. MERCAPTOINDOLES AND DERIVATIVES

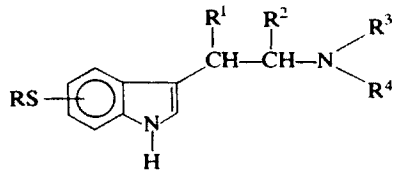
Substituent(s)	mp (°C)	Ref.
4-SH	Oil	822
4-SCH_3	44–47	823
4-$SCH_2C_6H_5$	32–35	823
	35–36	822
4-$SCH_2C_6H_5$, 1-CH_3	86–87	823
4-$SCH_2C_6H_5$, 1-$CH_2C_6H_5$	59–62	823
5-SH	75–76	822
5-SH, 1-CH_3		
Disulfide	101–102	825
5-SH, 1-CH_3, 2,3-H_2		
Disulfide	96.5–98	825
5-$SCH_2C_6H_5$	74–75	822
5-$SCOC_6H_5$, 1-CH_3	118.5–119.5	825
2,3-H_2	105-106.5	825
5-SCN	104–105	825
2,3-H_2	64.5–65	825
2,3-H_2, 1-CH_3CO	102.5–103.5	825
5-SCN, 1-CH_3	57–57.5	825
2,3-H_2	45–45.5	825
6-SH	70–71	822
6-$SCH_2C_6H_5$	106.5–107	822
7-SH	57–58	822
7-$SCH_2C_6H_5$	52–53	822

TABLE XXIX. MERCAPTOTRYPTAMINES



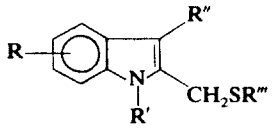
R	R^1	R^2	R^3	R^4	mp or bp (mm) (°C)	Ref.
4-H	H	H	CH_3	CH_3	218–219	828
4-CH_3	H	H	H	H	118–122	827
4-CH_3	H	H	CH_3	CH_3	105–107	833
4-CH_3	H	CH_3	H	H	143-145	829
				Methosulfate	222–227	829
4-C_7H_7	H	H	H	H	120–122	827, 829

TABLE XXIX. MERCAPTOTRYPTAMINES

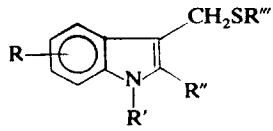


R	R^1	R^2	R^3	R^4		mp or bp (mm) (°C)	Ref.
4-C_7H_7	H	H	CH_3	CH_3		99–103	827
4-C_7H_7	H	CH_3	H	H		156–158	829
5-H	H	H	H	H			
					Picrate	220d	830, 831
					Hydrochloride	Oil	830, 831
5-CH_3	H	H	H	H			
					Picrate	240	73a–d
					Hydrochloride	252–254	73a–d
5-CH_3	H	CH_3	H	H		108	832
5-CH_3	H	CH_3	H	CH_3		180 (0.4)	833
5-CH_3	H	CH_3	CH_3	CH_3		200 (0.5)	832
5-CH_3	CH_3	H	H	H			
					Hydrochloride	212–215	832
5-CH_3	CH_3	H	H	CH_3		160 (0.3)	833
5-CH_3	CH_3	H	CH_3	CH_3		102	832
5-CH_3	CH_3	CH_3	H	H			
					Picrate	202–205	832
5-CH_3	CH_3	CH_3	H	CH_3			
					Bicarbonate	210	833
5-CH_3	CH_3	CH_3	CH_3	CH_3		180 (0.3)	832
5-C_7H_7	H	H	H	H			
					Hydrochloride	213–214	830, 831
5-C_7H_7	H	H	H	CH_3			
					Picrate	213d	833
					Hydrochloride	184–187	833
5-C_7H_7	H	CH_3	H	H			
					Picrate	200	832
					Hydrochloride	219	832
5-C_7H_7	H	CH_3	H	CH_3		200 (0.2)	833
5-C_7H_7	H	CH_3	CH_3	CH_3			
					Picrate	90, 125 (double)	833
5-C_7H_7	CH_3	H	H	H			
					Hydrochloride	210	832
5-C_7H_7	CH_3	CH_3	H	H		170 (0.3)	832
7-CH_3	H	H	H	H			
					Hydrochloride	188–191	73a–d
2-CH_3 derivatives							
1-Benzyl-2-methyl-5-methylthiotryptamine HCl						198–200	834
N-phthalimido derivative						149–151	834
1-*p*-Chlorobenzyl-2-methyl-5-methylthiotryptamine HCl						197.6–202.6	834

TABLE XXX. INDOLE METHYLENE THIOLS AND THIOL ETHERS



1

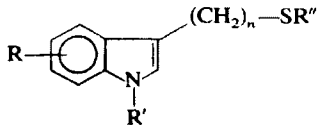


2

No.	R	R'	R''	R'''	mp or bp (mm) (°C)	Ref.
1	H	H	CH_3	2,4-Dinitrophenyl	194–195	848
1	5-CH_3O	CH_3	H	C_6H_5	143–144	846
1	5-CH_3O	CH_3	H	*p*-CH_3-C_6H_4[a]	149–151	846
2	H	H	H	H	125–127 (1)	843
				Disulfide	186–187	842
2	H	H	H	CH_3	87–88	840
2	H	H	H	C_2H_5	48–49	840
					51.5	837
2	H	H	H	*n*-C_3H_7	46.5	837
					47	840
2	H	H	H	*n*-C_4H_9	42.5	837
					43–44	840
2	H	H	H	*n*-C_5H_{11}	47–48	840
2	H	H	H	C_6H_5	84	837
2	H	H	H	$CH_2C_6H_5$	72.5	838
					74	837
					78	839
2	H	H	H	*p*-$CH_3C_6H_4CH_2$	107	838
					107–108.5	841
2	H	CH_3	H	*p*-$CH_3C_6H_4CH_2$	60.2–61	841
2	H	H	H	CH_2CO_2H	110–111	840
					116	839

[a] And other derivatives.

TABLE XXXI. THIOTRYPTOPHOLS AND HOMOLOGUES



n	R	R′	R″	mp or bp (mm) (°C)	Ref.
2	H	H	H	34–36	850, 851
				43–44.5	845
			Disulfide	119	845
				120–121.5	850, 851
2	H	CH_3	H	100–110 (0.01)	845
			Disulfide	Oil	845
2	H	H	2,4-Dinitrophenyl	90.5–92	845
2	H	CH_3	2,4-Dinitrophenyl	207–209	845
2	H	H	CH_3	Oil	850, 851
			S-Methylsulfonium iodide	109–111	850, 851
2	H	H	$CH_2C_6H_5$	27–29	845
				169–170 (0.01)	845
2	H	CH_3	$CH_2C_6H_5$	150–160 (0.01)	845
2	5-OH	H	H	Oil	845
			Disulfide	132–134	845
2	5-OH	H	2,4-Dinitrophenyl	226–228	845
2	5-OCH_3	H	H	38–41	850, 851
				45–46	845
			Disulfide	87–89	850, 851
				90.5–91.5	845
2	5-OCH_3	H	CH_3	46–49	850, 851
			S-Methylsulfonium iodide	118.5–119.5	850, 851
2	5-OC_2H_5	H	H	44–46	845
			Disulfide	82–83	845
2	5-OC_2H_5	H	$CH_2C_6H_5$	175–185 (0.01)	845
2	5-$OCH_2C_6H_5$	H	$CH_2C_6H_5$	63–65	845
2	7-OCH_3	H	H	72–74	845
			Disulfide	108–110	845
2	7-OCH_3	H	$CH_2C_6H_5$	150–160 (0.01)	845
3	H	H	H	—	850, 851
			Disulfide	69–71	850, 851
3	H	H	CH_3	42–43	850, 851
			S-Methylsulfonium iodide	93–95	850, 851
4	H	H	H	—	850, 851
			Disulfide	84–86	850, 851
4	H	H	CH_3	Oil	850, 851
			S-Methylsulfonium iodide	53–55	850, 851

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CHAPTER IX

Indole Aldehydes and Ketones

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I. Introduction

This chapter is concerned with indole aldehydes and ketones which have the carbonyl groups attached to the indole nucleus or in a side chain, with the exception of indoles with 2- or 3-carbonyl groups. Those compounds (oxindoles, indoxyls, and isatins) are covered in a subsequent chapter. Indoloquinones, adrenochromes, and tetrahydroindoles, hexahydroindoles, and octahydroindoles with carbonyl groups in the six-membered ring are included in this chapter.

Aldehydes and ketones containing other functional groups such as halogen, hydroxy, or nitro are reviewed in this chapter, but when carboxylic acid or derived functions are present the compounds are to be found in Chapter XX.

Since the physical and spectroscopic properties of indole aldehydes and ketones were discussed in detail in Chapter I, Part One, they are not reviewed in this chapter.

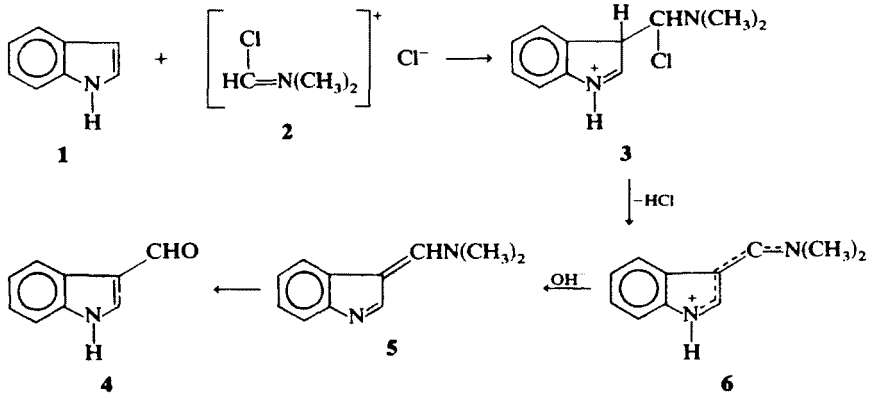
The literature through 1976 as found in *Chemical Abstracts* has been reviewed in this chapter. Some references from 1977 are included.

II. Indolecarboxaldehydes

A. Aldehyde Attached to the Nucleus

1. *Preparation*

a. FROM FORMAMIDES. The most important method for the preparation of indolecarboxaldehydes is the Vilsmeier–Haack formylation.[1] In this method, a formamide derivative such as dimethylformamide or *N*-methylformanilide is treated with phosphorus oxychloride. The resulting chloroimmonium ion complex **2**[2] effects electrophilic attack on the indole **1**, affording an intermediate **3** which loses HCl in going to a relatively stable mesomeric cation **6**. With indole itself this cation was identified spectroscopically, and upon careful neutralization it gave crystalline free base **5**. This free base was hydrolyzed to indole-3-carboxaldehyde (**4**) by boiling water[3] (Scheme 1).

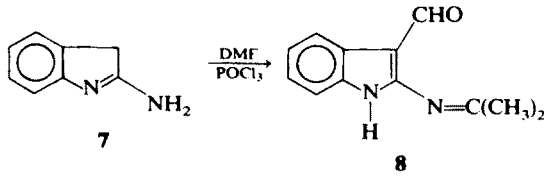


Scheme 1

In most synthetic procedures the free base is not isolated, but the cation is converted directly to the aldehyde by making the solution basic and warming it.[4]

For most 3-unsubstituted indoles the Vilsmeier–Haack method gives high yields of the corresponding 3-carboxaldehydes. Its mild conditions permit formylation of indoles which are unstable to acids. Electron-withdrawing groups such as phenyl, pyridyl, carbethoxy, or carboxamide at the 2-position do not prevent formylation.[5–7] However, 2-acylindoles are very difficult to formylate by this method or any other method.[8] Nitro or

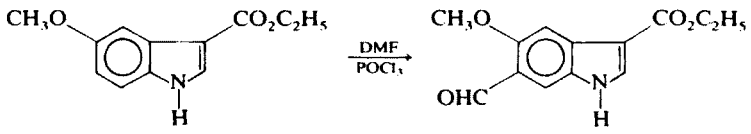
halogen substituents in the benzene ring are also compatible with 3-formylation.[9,10] Bulky substituents such as *t*-butyl and (3-methyl)butyl at position 2 do not prevent formylation.[11,12] The Vilsmeier–Haack method is compatible with 1-alkoxyindoles, which formylate at position 3.[13] 2-Aminoindole (**7**) also is formylated at position 3, but the amino group is converted into an *N,N*-dimethylamidine **8**[14] (eq. 1).



7 **8** (1)

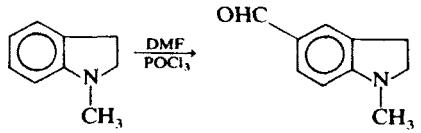
One interesting exception to the rule of preferential 3-substitution was encountered with 4,6-dimethoxyindole. This compound was formylated at the 7-position by $POCl_3$ and dimethylformamide.[15] In contrast, 5,7-dimethoxyindole, 6-benzyloxy-5-methoxyindole, and 4,5,6-trimethoxyindole reacted at the 3-position under similar conditions.[16–18] In another exception, 4-benzyloxyindole-2-carboxylic acid esters were formylated at the 6-position. However, the corresponding carboxylic acid amide gave its 3-formyl derivative.[19]

When the indole 3-position is substituted, for example, in skatole, formylation can occur at positions 1 and 2.[20] A combination of a 3-carbethoxy group and a 5-methoxy group on an indole nucleus resulted in formylation at position 6[21] (eq. 2). The corresponding 6-methyl compound could not be formylated.



9 **10** (2)

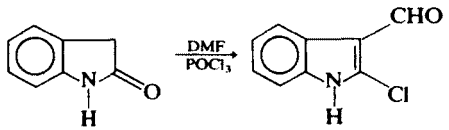
The benzene ring of indolines can be formylated at the 5-position under Vilsmeier–Haack conditions, as exemplified by the preparation of 1-methylindoline-5-carboxaldehyde (**12**)[22] (eq. 3). If the benzene ring is reduced, for example, in 1-phenyl-4,5,6,7-tetrahydroindole, then the pyrrole ring is substituted at position 2.[23,24] 2-Phenyl-4,5,6-7-tetrahydroindole is formylated at position 3,[23] whereas 4-oxo-4,5,6,7-tetrahydroindoles are substituted in either the pyrrole ring or next to the carbonyl group, depending on the *N*-substituent (Section III. C.3.d).



(3)

11 **12**

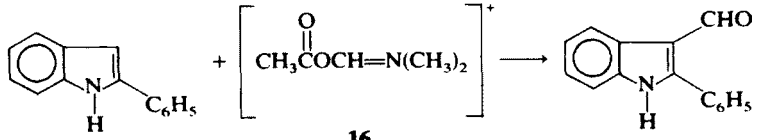
Oxindoles, for example, **13**, are converted into the corresponding 2-chlorindole-3-carboxaldehydes **14** by dimethylformamide and $POCl_3$[25-28] (eq. 4). In the cases of 5-nitrooxindole and 5,7-dibromooxindole, the intermediate *N,N*-dimethyliminomethyl derivatives were isolated from the reaction mixture.[25]



(4)

13 **14**

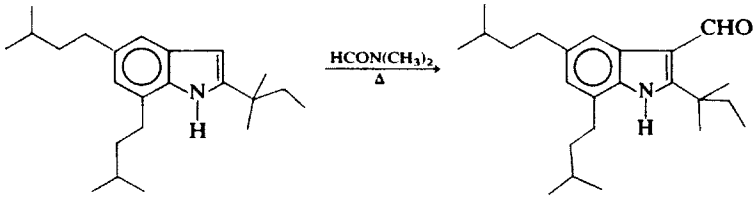
Although phosphorus oxychloride is usually employed in the Vilsmeier–Haack reaction, other reagents such as phosgene[29] and carboxylic acid halides[30] effectively activate the dimethylformamide. The proposed intermediate electrophiles of these reactions (e.g., **16**) appear to be less powerful than complex **2**. Thus 2-phenylindole (**15**) was formylated in 96% by acetyl bromide or benzoyl chloride and dimethylformamide, but the reaction required 2–4 days[30] (eq. 5). Methyl indole-2-carboxylate was not formylated by these reagents. Bromotriphenylphosphonium bromide and dimethylformamide were an effective combination for the formylation of indole.[31]



(5)

15 **16** **17**

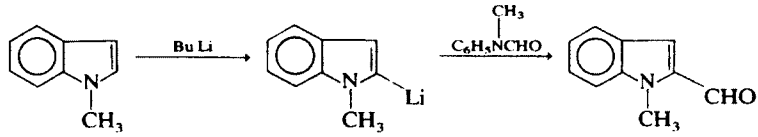
Certain electron-rich indoles such as **18** gave the corresponding 3-carboxaldehyde **19** simply by heating them with *N,N*-dimethylformamide[32] (eq. 6).



(6)

18 **19**

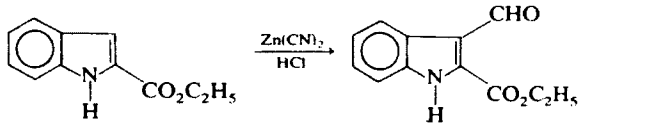
1-Methylindole-2-carboxaldehyde (**22**) has been prepared by treating the 2-lithio salt (**21**) of 1-methylindole (**20**) with *N*-methylformanilide[33] (eq. 7).



(7)

20 **21** **22**

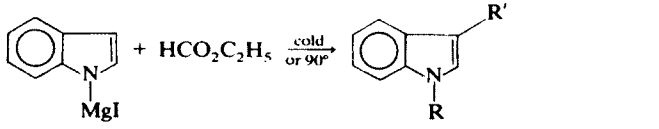
b. From Cyanides. The Gatterman reaction, which involves hydrocyanic acid or zinc cyanide and hydrochloric acid, is useful for the preparation of indole-3-carboxaldehydes, but is limited because its strongly acidic conditions destroy most indoles. Important examples of successful Gatterman reactions are the synthesis of **24** from ethyl indole-2-carboxylate (**23**) (eq. 8)[34] and 2-methylindole-3-carboxaldehyde from 2-methylindole (stabilized by steric hindrance to dimerization).[35]



(8)

23 **24**

c. From Formate Esters. Grignard reagents derived from indoles react with formate esters at low temperatures to give indole-1-carboxaldehydes, but at higher reaction temperatures the corresponding 3-carboxaldehydes are obtained.[36,37] Thus indolylmagnesium iodide (**25**)



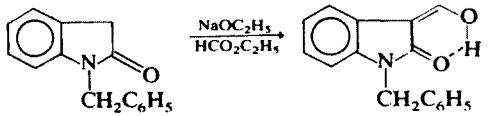
(9)

25

26; R = CHO, R' = H
27; R = H, R' = CHO

and ethyl formate at low temperatures gave 90% of 1-carboxaldehyde **26**, whereas 3-carboxaldehyde **27** was obtained (30–40% yield) at 90–95°[38,39] (eq. 9).

Oxindoles react with formate esters in the presence of strong bases to give 3-carboxaldehyde derivatives.[40] In these derivatives, the aldehyde group exists as the hydroxymethylene tautomer.[41] For example, 1-benzyloxindole (**28**), ethyl formate, and sodium ethoxide gave 1-benzyl-3-hydroxymethyleneoxindole (**29**)[42] (eq. 10).

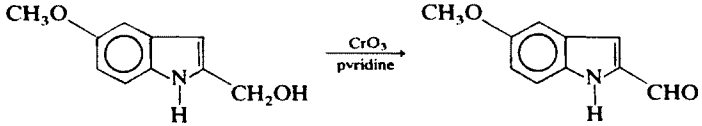


28 **29** (10)

d. Reimer–Tiemann Reaction. Indole-3-carboxaldehydes have been prepared from indoles, chloroform, and bases such as potassium hydroxide or sodium ethoxide.[43,44] However, the yields are generally low and quinoline derivatives are also obtained.[45] The complex mechanisms of these reactions, which are thought to involve dichlorocarbene, are discussed under indoles (Part One, Chapter I). A photochemical Reimer–Tiemann reaction of indoline gave mainly 1-formylindoline. However, 1-methylindoline gave a mixture of the corresponding 5- and 7-carboxaldehydes plus some 1-methylindole.[46]

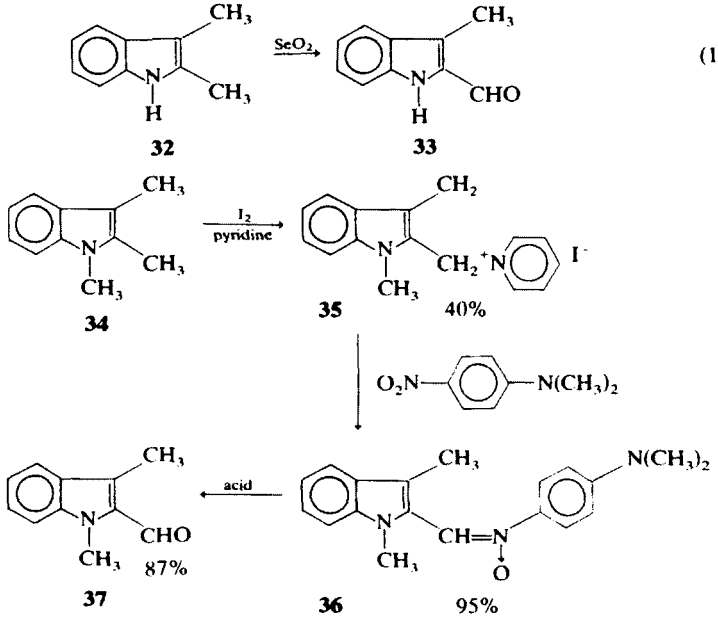
e. Oxidation of Hydroxymethylindoles. The oxidation of primary alcohols is a general method for the preparation of aldehydes. It is a useful route for indole-2-carboxaldehydes since the required alcohols are readily available from indole-2-carboxylates. A variety of oxidizing agents including manganese dioxide,[47–50] chromium trioxide–pyridine,[51,52] and potassium permanganate[53] have been used. Thus 2-hydroxymethyl-5-methoxyindole (**30**) was converted into the corresponding 2-carboxaldehyde (**31**) in 90% yield by chromium trioxide–pyridine[51] (eq. 11). This method also has been important for the preparation of indoles with aldehyde groups on the benzene ring.[53,54]

f. Oxidation of Methylindoles. The 2-methyl group of indoles is susceptible to oxidation under a variety of conditions, but the 3-methyl



30 **31** (11)

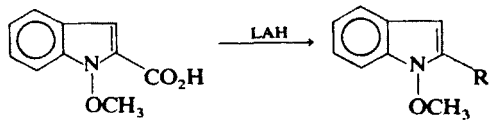
group is relatively resistant. Thus 2,3-dimethylindole (**32**) was converted into the corresponding 2-carboxaldehyde (**33**) by selenium dioxide[55] or by photochemical oxygenation[56] (eq. 12). A substantial number of substituted 2-methylindoles and 3-methylindoles gave aldehydes upon photochemical oxygenation, but more complex mixtures were obtained with the 3-methylindoles.[57] The conversion of 1,2,3-trimethylindole (**34**) into 2-carboxaldehyde derivative **37** by a route involving iodine in pyridine, followed by *p*-dimethylaminonitrobenzene and acid hydrolysis, was reported.[58] The intermediate pyridinium salt **35** and nitrone **36** were isolated. A low yield in the first step decreased the overall efficiency of this conversion (Scheme 2).



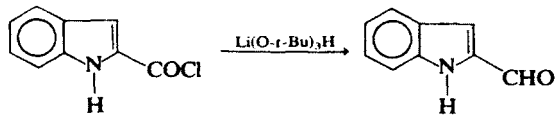
(12)

Scheme 2

g. Reduction of Indolecarboxylic Acids and Derivatives. Certain indolecarboxylic acids have been reduced to the aldehydes, although good yields were not obtained. Lithium aluminum hydride converted 1-methoxyindole-2-carboxylic acid (**38**) into a mixture of the aldehyde **39** and alcohol **40**[59] (eq. 13). In contrast, the reduction of indole-2-carboxylic acid by lithium tri-*t*-butoxyaluminum hydride gave only indole-2-carboxaldehyde.[60] This same reducing agent effectively converted the corresponding acid chloride **41** into indole-2-carboxaldehyde (**42**)[61] (eq. 14).

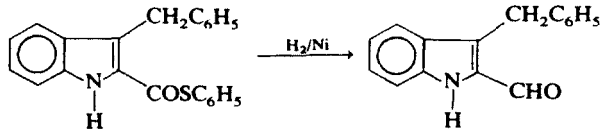


38 39; R = CHO 40; R = CH_2OH (13)

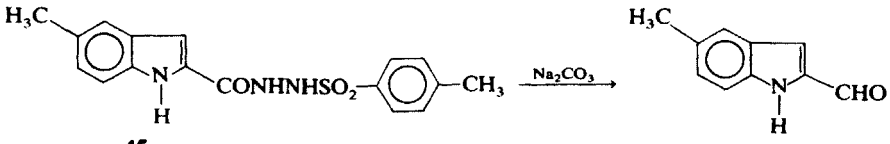


41 42 (14)

Reduction of 5-cyanoindole in the presence of Raney nickel with or without sodium hypophosphite gave indole-5-carboxaldehyde.[62] Raney nickel also was useful for the preparation of 3-benzylindole-2-carboxaldehyde (**44**) from the corresponding 2-carboxythiophenylate **43**[63] (eq. 15). Another method for the preparation of indolecarboxaldehydes is the McFayden–Stevens reaction with appropriate *N*-arylsulfonyl acid hydrazides.[64,65] For example, 5-methylindole-2-carboxylic acid *N*-*p*-toluenesulfonylhydrazide (**45**) afforded the 2-carboxaldehyde (**46**) in 90% yield[66] (eq. 16).



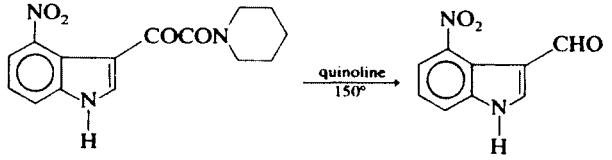
43 44 (15)



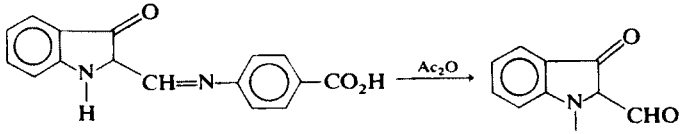
45 46 (16)

h. Miscellaneous Synthetic Methods. Heating the potassium salt of 2-methylindole with carbon monoxide in dimethylformamide at 150° and high pressure afforded the 3-carboxaldehyde in over 40% yield.[67] The Duff reaction between hexamethylenetetramine and indole or 2-phenylindole also gave the corresponding 3-carboxaldehyde.[20] Substituted gramines were converted into 3-carboxaldehydes by the Sommelet method.[68]

Certain 3-glyoxylic acid derivatives of indole gave the carboxaldehydes upon heating. Thus the anil of ethyl indole-2-glyoxylate gave indole-3-carboxaldehyde when heated at 140°.[65] Heating glyoxylamide **47** with quinoline at 150° furnished the corresponding carboxaldehyde **48** in moderate yield[69] (eq. 17). Cleavage of chrysanilic acid (**49**) by acetic anhydride gave indoxyl-2-carboxaldehyde (**50**)[70] (eq. 18).

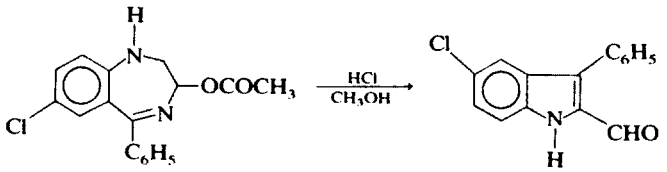


47 **48** (17)

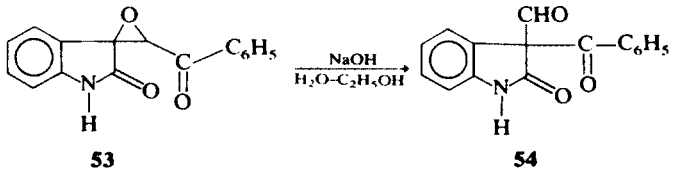


49 **50** (18)

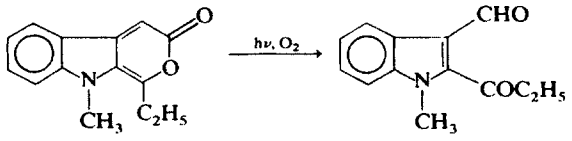
Unusual transformations which have given indolecarboxaldehyde derivatives include the acid- or base-induced rearrangement of certain 3-hydroxy- or 3-acetoxy-1,3-dihydrobenzodiazepines, for example, **51** to **52**[71,72] (eq. 19), the base-catalyzed rearrangement of isatylideneacetophenone oxide **53** to **54**[73] (eq. 20), and the photooxygenation of pyrano-[3,4-b]indol-3(9*H*)-ones **55** to **56**[74] (eq. 21).



51 **52** (19)



53 **54** (20)



(21)

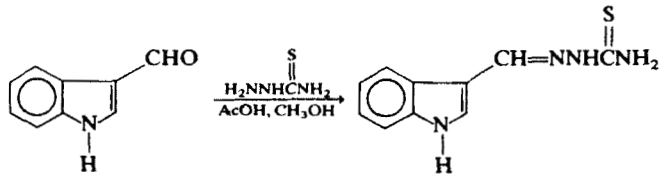
55 **56**

i. BIOLOGICAL FORMATION. Indole-3-carboxaldehyde has been detected as a metabolite of indole-3-acetaldehyde,[75] indole-3-acetic acid,[76,77] and D-tryptophan (but not L-tryptophan)[78] in various organisms. It also has been found in the urine of patients with untreated phenylketonuria.[79]

2. *Functional Group Derivatives*

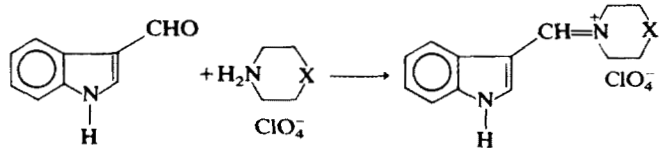
The most extensively prepared derivatives of indolecarboxaldehydes are the hydrazones, semicarbazones, and thiosemicarbazones. These compounds are usually prepared in alcohol–acetic acid solution (eq. 22). The discovery that the thiosemicarbazone (**58**) of indole-3-carboxaldehyde is active against *Mycobacterium tuberculosis* in mice[80,81] provided stimulus for the preparation of many related compounds. None of them have shown better antitubercular activity than **58**, although certain compounds have been reported to have antiviral[82] and antifungal[83] properties. A variety of biological activities has been claimed in patents for derivatives of indolecarboxaldehydes. Mostly they reflect the intrinsic activity of the derivatizing moiety. For example, the isonicotinylhydrazone of 1-benzylindole-3-carboxaldehyde is claimed to be antitubercular,[84] and the Schiff's base derivative of this aldehyde with erythromycylamine is stated to have antibacterial activity.[85] A variety of hydrazones prepared from 1-methylindole-2-carboxaldehyde was reported to be monoamine oxidase inhibitors,[86] whereas certain other indole hydrazones and oximes were claimed to have antihypertensive, diuretic, antiinflammatory, analgesic, and antiulcer properties.[87,88] Useful general procedures for the preparation of hydrazones,[89,90] acylhydrazones,[91,92] and imines[93–97] are available in the literature. Treatment of indole-3-carboxaldehyde (**59**) with morpholine perchlorate or piperazine monoperchlorate resulted in formation of the corresponding imminium perchlorates **60** and **61**, which gave azafulvene dimers on basification[98] (eq. 23).

Addition of aryldiazonium salts to 2-methyleneindolines affords hydrazones related to indolenine-2-carboxaldehydes.[99–101] For example, treatment of 2-methylene-1,3,3-trimethylindoline (**62**) with 4-benzylbenzenediazonium chloride gave **63** (eq. 24), which is a yellow dye



(22)

57 58

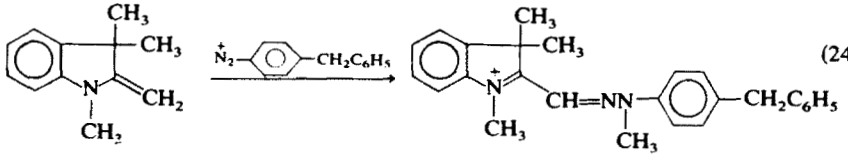


(23)

59

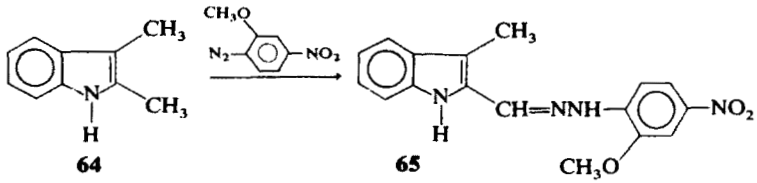
60; X = O
61; X = NH

suitable for acrylics.[100] Numerous analogues of **63** have useful properties as dyes. Diazonium salts also add to the 2-methyl group of 2,3-dimethylindole (**64**). Thus **64** and 2-methoxy-4-nitrobenzenediazonium ion gave hydrazone **65** (eq. 25). This process was thought to involve initial substitution of position 3 followed by rearrangement.[102]



(24)

62 63



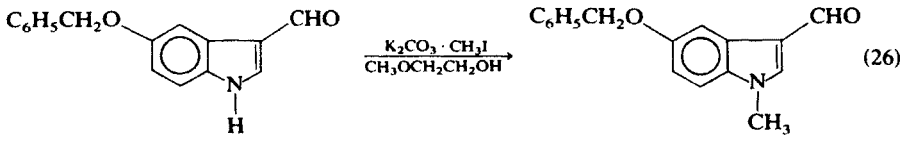
(25)

64 65

3. *Reactions*

a. Alkylation and Acylation on Nitrogen. The electron-withdrawing effect of the aldehyde group causes the N–H of indole-3-carboxaldehydes to become more acidic (pK_a 12) than that of indole itself (pK_a 17).[103] Consequently, the anion can be prepared and alkylated under relatively mild conditions. Dimethyl sulfate in aqueous sodium hydroxide has been used for the 1-methylation of indole-3-carboxaldehyde.[104,105] Even potassium carbonate is sufficiently basic to promote

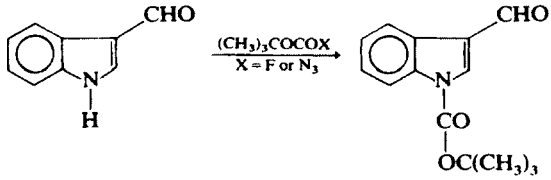
alkylation, as exemplified by the conversion of 5-benzyloxyindole-3-carboxaldehyde (**66**) into its 1-methyl derivative (**67**) by K_2CO_3 and methyl iodide in methyl Cellosolve[106] (eq. 26). Potassium *t*-butoxide has also been used as the base in methylations with methyl iodide.[107]



(26)

66 **67**

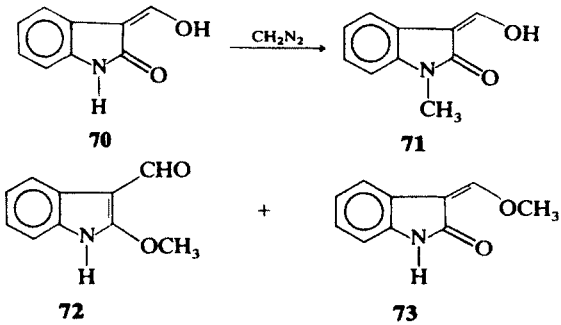
N-Acylation of indole-3-carboxaldehyde has been accomplished with a variety of acid chlorides, acid anhydrides, and sulfonyl halides.[108,109] Recently 1-(*t*-butyloxycarbonyl)indole-3-carboxaldehyde (**69**) has been advocated as a new reagent for linking peptide fragments.[110] It is prepared from indole-3-carboxaldehyde (**68**) and either *t*-butyloxycarbonyl fluoride or *t*-butyloxycarbonyl azide[111] (eq. 27).



(27)

68 **69**

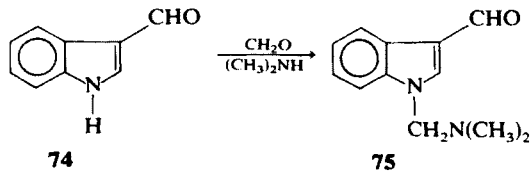
Treatment of oxindole-3-carboxaldehyde, which exists as enol **70**, with diazomethane gave a mixture of 1-methyl derivative **71**, 2-methoxyindole-3-carboxaldehyde (**73**), and 3-methoxymethyleneoxindole (**72**), all in low yields[112] (Scheme 3). 1-Aminomethylation of indole-3-carboxaldehyde (**74**) by a Mannich reaction gave **75**[113] (eq. 28).



70 **71**

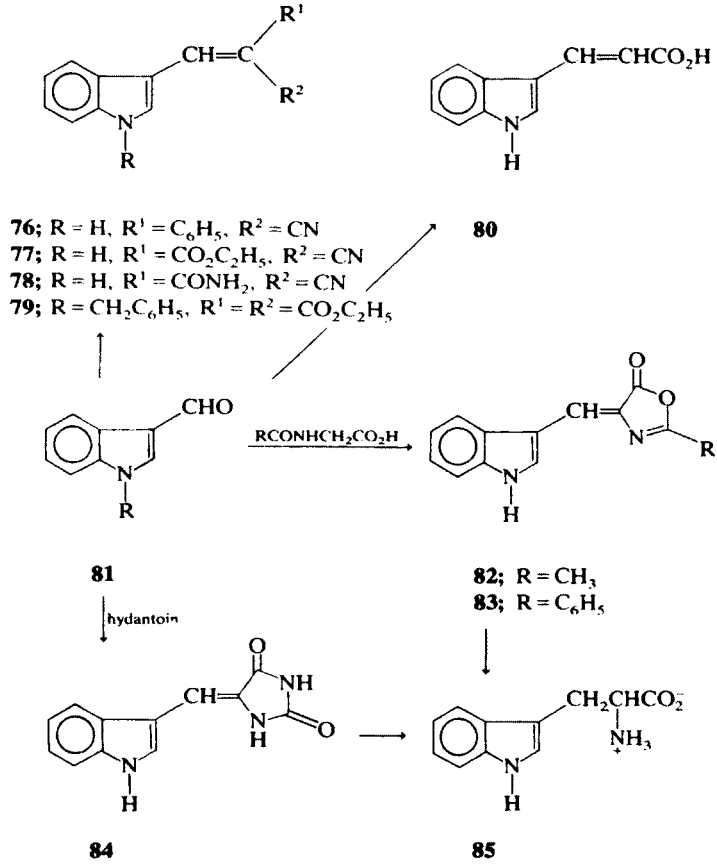
72 **73**

Scheme 3



74 75 (28)

b. Condensation with Active Methylene Compounds. Although the aldehyde group of indole-3-carboxaldehydes is less reactive toward nucleophiles than many aldehydes because of its conjugation with the indole nitrogen, it still undergoes condensation with a variety of active methylene compounds in the presence of mild bases like piperidine or sodium acetate. Thus indole-3-carboxaldehyde (**81**) readily reacted under Knovenagel conditions with phenylacetonitrile, ethyl cyanoacetate, and

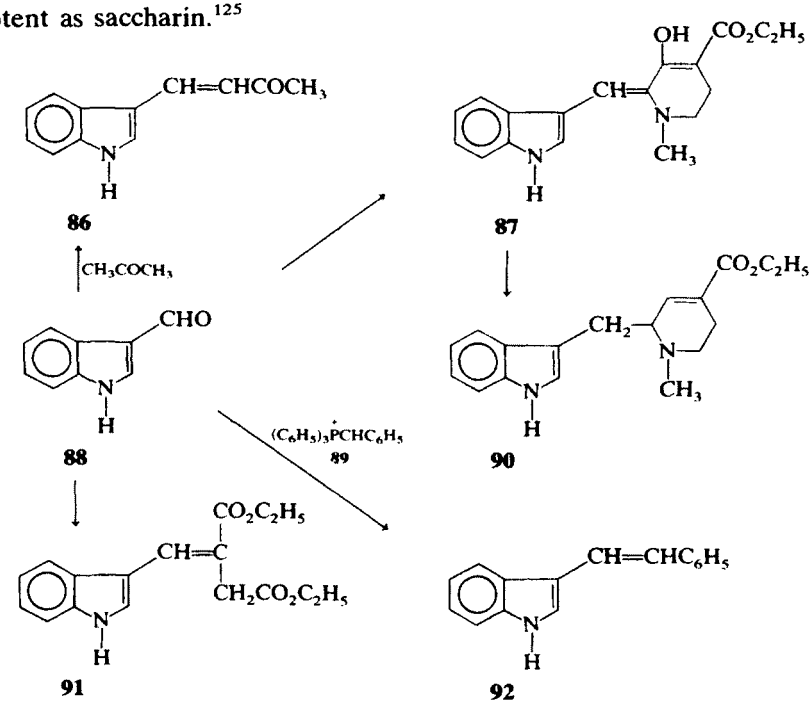


Scheme 4

cyanoacetamide to give the corresponding methylene derivatives **76–78**.[114] Similar reactions were obtained with 2-phenylindole-3-carboxaldehyde.[115] Condensation of diethyl malonate with 1-benzylindole-3-carboxaldehyde also gave the corresponding methylene compound **79** in good yield[116] (Scheme 4).

Perkin condensation between indole-3-carboxaldehyde and succinic anhydride with sodium acetate as the base resulted in a low yield of the 3-indolylacrylic acid **80**.[117] The use of acetylglycine or benzoylglycine in Perkin reactions led to azlactones **82** and **83**, which could be converted into tryptophan **85** by reduction and hydrolysis[118,119] (Scheme 4). An alternative route for tryptophen synthesis was based on the condensation of indole-3-carboxaldehydes with hydantoin followed by reduction and hydrolysis of the intermediate **84**[120,121] (Scheme 4).

Numerous 3-indolyl vinyl ketone derivatives were synthesized by Claisen condensation between indole-3-carboxaldehydes and a variety of ketones.[122–125] For example, indole-3-carboxaldehyde (**88**) and acetone gave a 54% yield of 3-indolylvinyl methyl ketone (**86**)[122] (Scheme 5). Condensation of **88** with ethyl 1-methyl-3-piperidone-4-carboxylate yielded an intermediate **87** that was converted by reduction and hydrolysis into **90** (Scheme 5). This product was an artificial sweetener twice as potent as saccharin.[125]

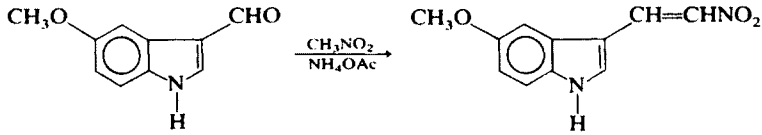


Scheme 5

The Stobbe condensation with indole-3-carboxaldehyde (**88**) also is facile. Thus dimethyl succinate gave derivative **91**, which was cyclized to a carbozole with acetic anhydride.[126]

A variety of Wittig reagents has been condensed with indole-2-carboxaldehydes and indole-3-carboxaldehydes.[127-129] For example, indole-3-carboxaldehyde (**88**) and ylid **89** gave 3-(ω-styryl)indole (**92**) in 38% yield[128] (Scheme 5).

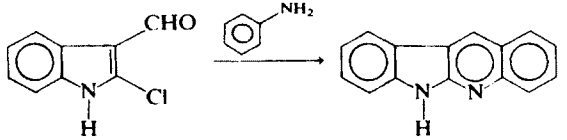
Condensations of indolecarboxaldehydes with nitroalkanes under Knovenagel conditions have been important in the synthesis of new tryptamine analogues.[130-133] In a typical process, 5-methoxyindole-3-carboxaldehyde (**93**) was treated with nitromethane and ammonium acetate to give the nitrovinyl derivative **94** in 94% yield[131] (eq. 29). Lithium aluminum hydride reduction of **94** then gave 5-methoxytryptamine.



(29)

93 **94**

A variety of other active methylene compounds has been condensed with indole-3-carboxaldehydes. They include rhodanine,[134] *N*-alkylbarbiturates,[123] pyrrazolinediones,[135] and thiohydantoins.[135] Indole-3-carboxaldehydes also have been used in the preparation of indoles substituted with or fused to heterocyclic rings.[136-139] Thus 2-chloroindole-3-carboxaldehyde (**95**) and aniline condensed at 150–190° to form indolo[2,3-*b*]quinoline **96**[137] (eq. 30). Treatment of 4,7-dimethylindole-3-carboxaldehyde (**97**) with 3,3-dimethoxypropylamine followed by cyclodehydration in orthophosphoric acid gave pyrido[4,3-*b*]indole **98**[136] (eq. 31). An example of heterocycle formation on the aldehyde carbon is



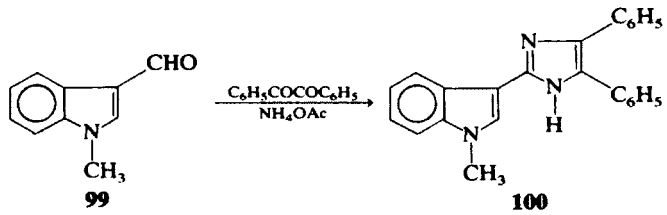
(30)

95 **96**

(31)

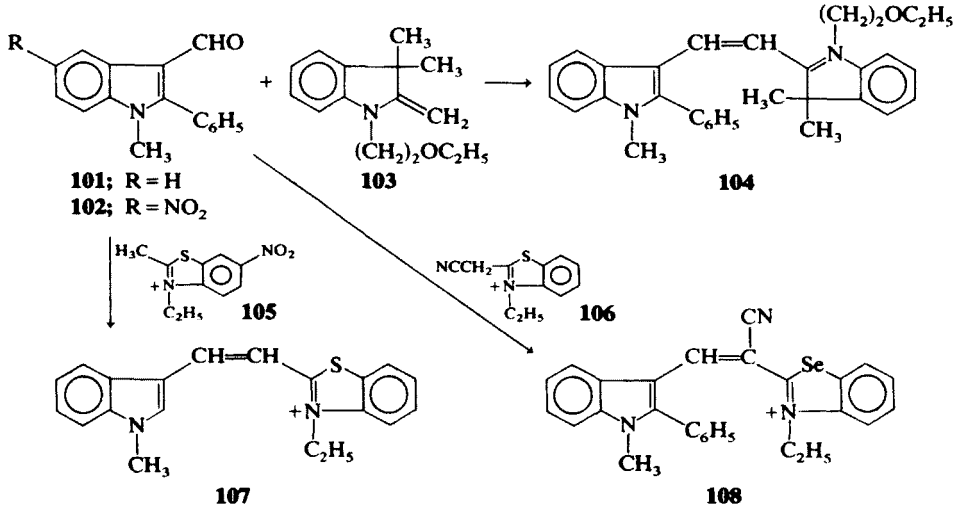
97 **98**

the condensation of 1-methylindole-3-carboxaldehyde (**99**) with benzil and ammonium acetate to give 3-(2-imidazolyl)indole **100** in 60% yield[138] (eq. 32).



99 **100** (32)

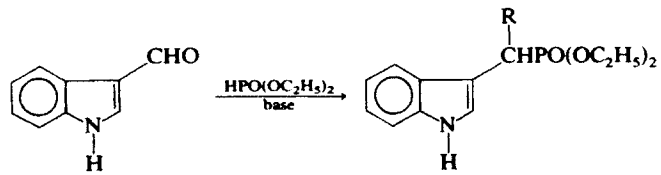
Another important use of indole-3-carboxaldehydes is in the synthesis of dyes and dye sensitizers.[140–149] Thus an orange dye **104** for acrylic fibers was prepared by heating indolecarboxaldehyde **101** and 2-methyleneindoline **103** in acetic anhydride–acetic acid[140] (Scheme 6). A cyanine dye sensitizer **107** (550 nm) for direct positive silver halide emulsions was obtained by condensing indolecarboxaldehyde **102** and 3-ethyl-2-methylbenzothiazolium salt **105** in hot acetic anhydride.[141] Furthermore, a photobleaching orange dye **108** useful for photocopying was synthesized from indolecarboxaldehyde **101** and benzoselenazolium compound **106**[146] (Scheme 6).



101; R = H
102; R = NO_2
103 **104**
105 **106**
107 **108**

Scheme 6

Phosphonates (e.g., **110**) have been prepared from indole-3-carboxaldehyde (**109**) and dialkyl phosphites.[150] If these reactions are run in the presence of secondary amines such as diethylamine, the product is an α-aminophosphonate such as **111**[151] (eq. 33).



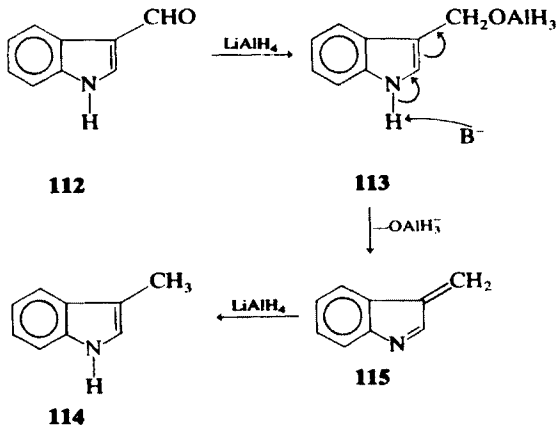
(33)

109

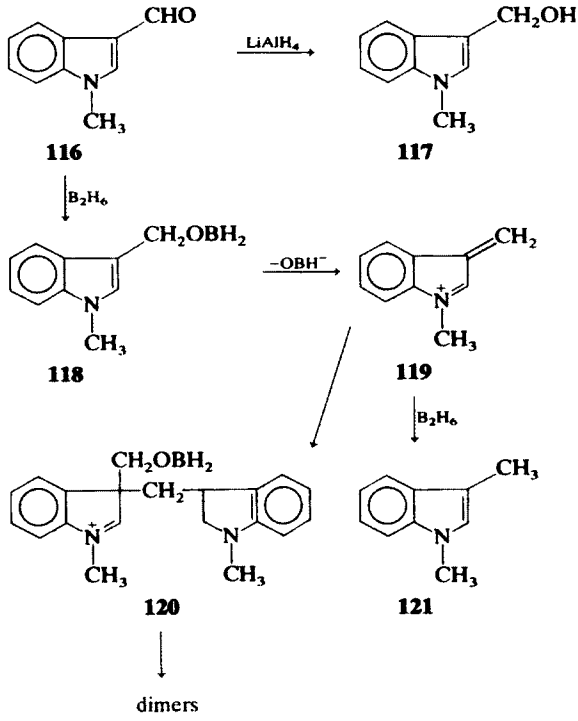
110; R = OH
111; R = $N(C_2H_5)_2$

c. Reduction of the Aldehyde Group. Indole-3-carboxaldehyde (**112**) has been reduced to 3-hydroxymethylindole by sodium borohydride or lithium borohydride.[152–154] Stronger reducing agents like lithium aluminum hydride (LAH)[152,153,155] or diborane[156] convert **112** into 3-methylindole (**114**) (Scheme 7). In addition to **114**, the diborane reduction gave significant amounts of dimers. For indole-3-carboxaldehydes with alkyl substituents on nitrogen (e.g., **116**), LAH reduction stops with the 3-hydroxymethyl derivative **117**[153,156]; however, diborane reduction gives the 3-methyl derivative (**121**) plus dimers.[156] This difference in products has been attributed to the relative stabilities of the intermediate aluminate and borate complexes (**113** and **118**, respectively). Thus the aluminate complex **113** forms methylene derivative **115** only when the N–H proton is removed (Scheme 7). In contrast, borate complex **118** can give methylene derivative **119** even when the nitrogen is alkylated[156] (Scheme 8).

3-(Aminomethyl)indoles have been prepared by diborane reduction of the methoximes of indole-3-carboxaldehydes.[157]

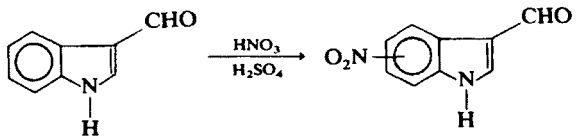


Scheme 7

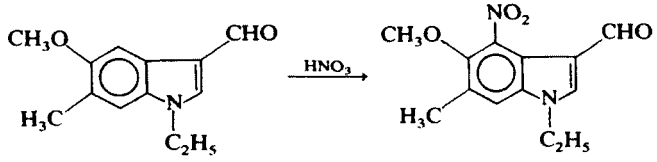


Scheme 8

d. ELECTROPHILIC SUBSTITUTION. Electrophilic substitution constitutes the most important group of reactions for electron-rich molecules such as indole. The presence of a strong electron-withdrawing group such as the 3-carboxaldehyde diminishes the reactivity of an indole toward electrophiles; however, it also decreases the chances of acid-catalyzed or oxidative decomposition of the indole, so that certain electrophilic substitutions can be made under moderately strong conditions. These substitutions generally take place in the benzene ring at the 5- or 6-position. Thus indole-3-carboxaldehyde (**122**) gave upon nitration in sulfuric acid at 10° a mixture (high yield) which contained 66% 5-nitro derivative **123** and 34% 6-nitro derivative **124**[158,159] (eq. 34). Similar ratios were obtained with the 1- and 2-methyl and 1,2-dimethyl homologues of **122**.[160] Nitration of **122** with nitric acid in acetic acid at 80° gave low yields of the mononitro derivatives **123** and **124**. The major reaction was nitration at the 3-position accompanied by cleavage of the carboxaldehyde group and formation of nitroisatins and nitroanthranilic acids.[161] When the indole-3-carboxaldehyde has a 5-methoxy group, nitration can take place at the 4-position, as in formation of **126** from **125**[162] (eq. 35).

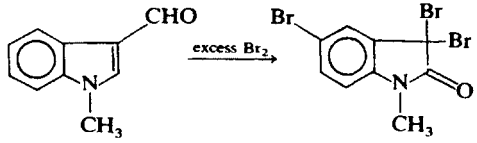


122 123; 5-NO_2 124; 6-NO_2 (34)



125 126 (35)

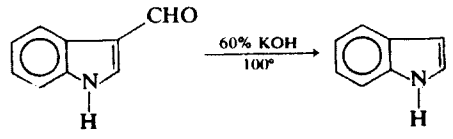
Bromination of **122** afforded a mixture of the corresponding 5- and 6-bromo derivatives under a variety of conditions, with the 5-bromo isomer predominating. Excess bromine gave the expected 5,6-dibromo derivative.[163] In contrast to this result was the report that bromination of 1-methylindole-3-carboxaldehyde (**127**) with excess bromine gave 3,3,5-tribromooxindole (**128**)[164] (eq. 36).



127 128 (36)

e. Cleavage of the Aldehyde Group. Indolecarboxaldehydes are relatively stable compounds which do not readily undergo cleavage. Nevertheless, strong bases or acids will cleave the formyl group. Thus treatment of indole-3-carboxaldehyde (**129**) in 60% potassium hydroxide at 100° resulted in the formation of indole (**130**) (eq. 37). This cleavage did not occur in dilute alkali.[165] Acid-catalyzed cleavage occurs in the presence of perchloric acid or sulfuric acid. In this reaction formic acid is eliminated and the product is urorosein (**131**)[166] (eq. 38). Cleavage of a carboxaldehyde group during nitration was described in the preceding section. The photodecarbonylation of 1,3-dimethylindoline-3-carboxaldehyde (**132**) gave 93% of 1,3-dimethylindoline (**133**) and 7% of the corresponding indole[167] (eq. 39).

f. Miscellaneous Reactions. Indole-3-carboxaldehydes have been converted into the corresponding nitriles under a variety of conditions.



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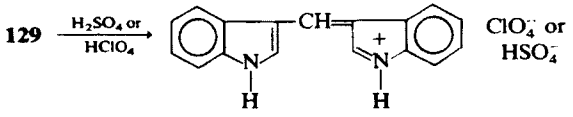
129 130



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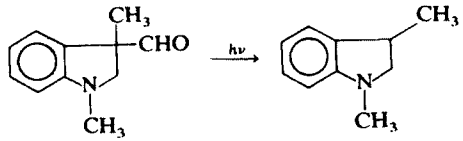
131



(39)

132 133

One of the simplest procedures for this conversion is to heat the aldehyde with hydroxylamine hydrochloride in boiling dimethylformamide for 10 minutes.[168] 4-Fluoroindole-3-carboxaldehyde was oxidized directly to the corresponding 3-carboxylic acid by potassium permanganate.[169] Treatment of indole-3-carboxaldehyde under conditions of the Dakin reaction gave a quantitative yield of indigo.[170]

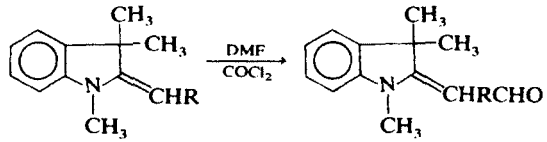
B. Aldehyde in the Side Chain

1. *Preparation*

Most of the syntheses have been directed toward indole-3-acetaldehyde. This compound has been identified as a tryptophan metabolite.[171] It has potent activity against ATPases in rat brain synaptosomes.[172] Storage of indole-3-acetaldehyde is difficult because of its instability; however, it was reported that stability is greatly increased by making the 2,4,7-trinitro-3-fluorenone complex.[173]

a. Formylation of 2-Methyleneindolines. The Vilsmeier–Haack reaction effectively formylates the enamine system of 2-methyleneindolines, affording the corresponding α,β-unsaturated aldehydes.[174] For example, treatment of 1,3,3-trimethyl-2-methyleneindoline (**134**) with

phosgene and dimethylformamide gave **136**[175] (eq. 40). Related 2-cyanomethyleneindolines such as **135** also can be formylated in the same manner to give **137**.[176,177]

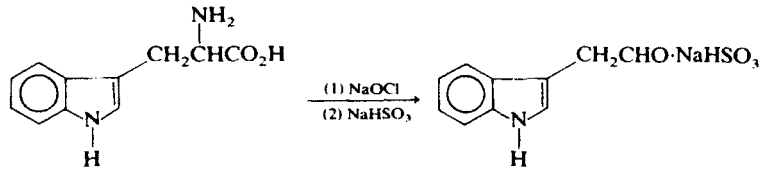


(40)

134; R = H
135; R = CN

136; R = H
137; R = CN

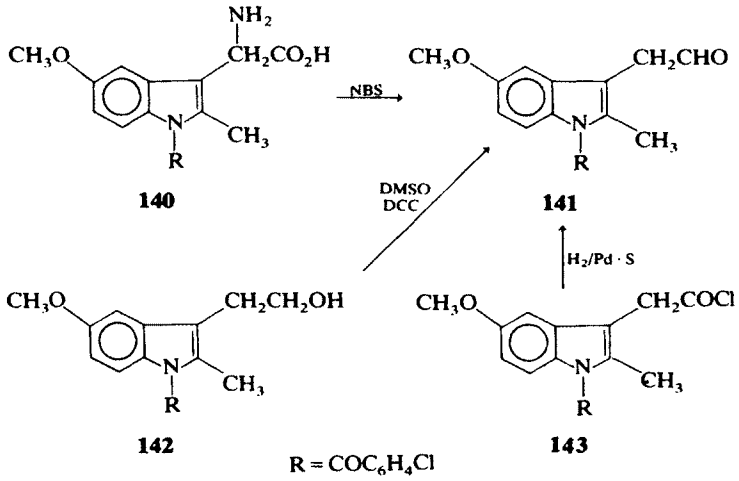
b. Oxidation of Tryptophan Derivatives. One route to indole-3-acetaldehyde involves careful oxidation of tryptophan (**138**) by sodium hypochlorite in a two-phase system. The indole-3-acetaldehyde is isolated as its bisulfite addition compound (**139**) because it is unstable[178] (eq. 41). This method has also been used in preparing 2-methylindole-3-acetaldehyde[179] and 5-benzyloxyindole-3-acetaldehyde.[180] 1-*p*-Chlorobenzoyl-5-methoxy-2-methylindole-3-acetaldehyde (**141**) was synthesized by a variety of routes (see below), one of which involved oxidation of the corresponding tryptophan derivative **140** with *N*-bromosuccinimide in water (Scheme 9). Compound **141** had 0.6–0.7 times the antiinflammatory activity of indomethacin in the rat foot edema assay when given orally, but it was much less active by the subcutaneous route. This result suggested metabolism to indomethacin.[182]



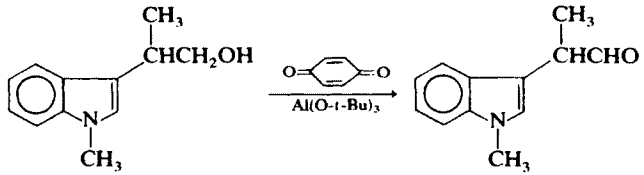
(41)

138 **139**

c. Oxidation of Primary Alcohols. This method has been successful for indoleacetaldehydes with branched chains. Thus **144** was converted in good yield to **145** by an Oppenauer oxidation[183] (eq. 42). The acetic anhydride–dimethyl sulfoxide method was used for the oxidation of 2-(1,1-dimethyl-2-hydroxyethyl)indole (**146**) to the corresponding aldehyde **147**[184] (eq. 43). A route to compound **141** involved the oxidation of the corresponding tryptophol (**142**) with dimethyl sulfoxide and dicyclohexylcarbodiimide[182] (Scheme 9).



Scheme 9



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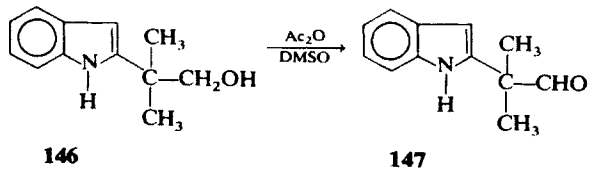
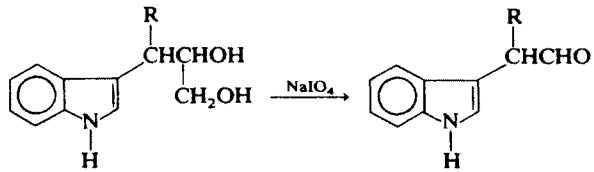


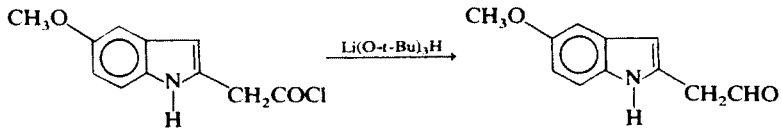
(43)

d. Oxidative Cleavage of Glycols. Sodium periodate cleavage of a 3-propyleneglycol derivative (**148**) of indole gave indole-3-acetaldehyde (**150**).[185] The homologous glycol **149**, which was obtained by degradation of indolmycin, gave α-methylindole-3-acetaldehyde (**151**) upon similar cleavage[186] (eq. 44).



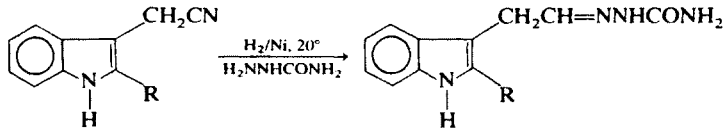
(44)

e. Reduction of Indoleacetic Acid Derivatives. Indoleacetaldehyde derivatives have been prepared by reduction of the corresponding acid chlorides, amides, and nitriles. For 5-methoxyindole-2-acetaldehyde **153**, lithium tri-*t*-butoxyaluminum hydride reduction of the acid chloride **152** was an effective procedure[187] (eq. 45). Rosenmund reduction of the corresponding acid chloride (**143**) was utilized in an alternative preparation of compound **141**.[188] Another preparation of this compound involved reduction of the corresponding nitrile with Raney nickel in the presence of Girard's reagent T.[188] Catalytic hydrogenation of nitriles **154** and **155** afforded syntheses of indole-3-acetaldehyde and its 2-methyl homologue which were isolated as their semicarbazones **156** and **157**[188,189] (eq. 46). Lithium aluminum hydride (LAH) reduction of pyrazole derivative **158** afforded 5-hydroxyindole-3-acetaldehyde (**159**), an unstable compound that was characterized as its 2,4-dinitrophenylhydrazone[190] (eq. 47).



(45)

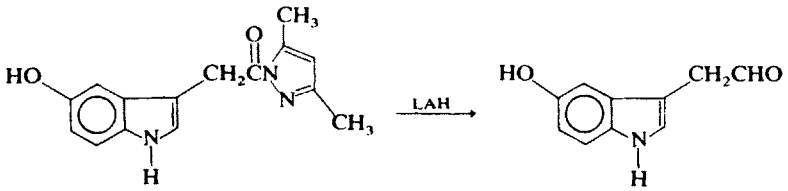
152 **153**



(46)

154; R = H
155; R = CH_3

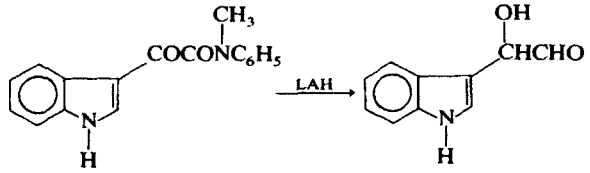
156; R = H
157; R = CH_3



(47)

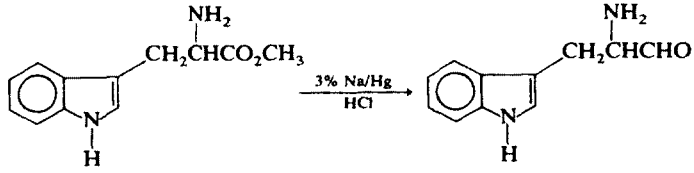
158 **159**

Careful reduction of indole-3-glyoxylylamide derivative **160** with a limited amount of LAH gave α-hydroxyindole-3-acetaldehyde (**161**)[191] (eq. 48). α-Aminoindole-3-propionaldehyde (tryptophanal, **163**, was prepared by sodium amalgam reduction of methyl tryptophanate (**162**)[192] (eq. 49).



(48)

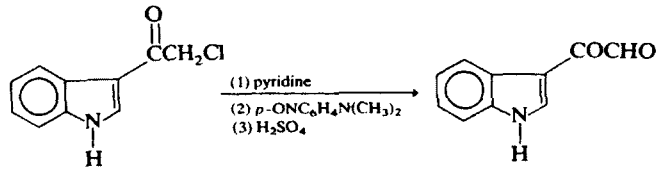
160 **161**



(49)

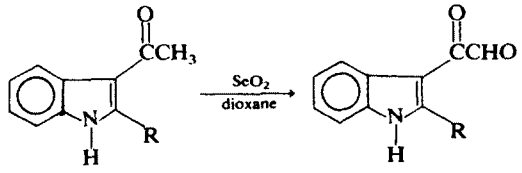
162 **163**

f. Oxidation of 3-Acetylindoles. Indole-3-glyoxaldehyde (**165**) was prepared by treating 3-chloroacetylindole (**164**) successively with pyridine, *p*-dimethylaminonitrosobenzene, and sulfuric acid[193] (eq. 50). 2-Substituted indole-3-glyoxaldehydes **168** and **169** were obtained upon selenium dioxide oxidation of the corresponding 3-acetyl derivatives **166** and **167**[194] (eq. 51).



(50)

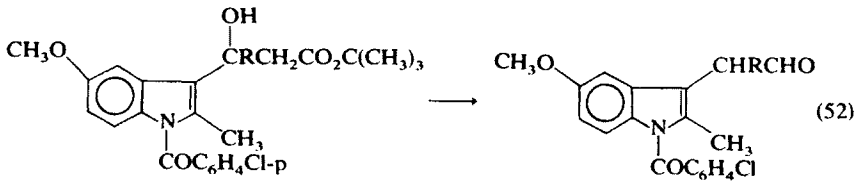
164 **165**



(51)

166; R = CH_3 **168**; R = CH_3
167; R = C_6H_5 **169**; R = C_6H_5

g. From 3-(3-Indolyl)-3-Hydroxypropionic Acid Esters. 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetaldehyde (**172**)[195] and its α-trifluoroacetyl derivative (**173**)[196] were prepared by heating the corresponding hydroxypropionic acid esters (**170** and **171**) with *p*-toluenesulfonic acid or with copper powder (eq. 52).

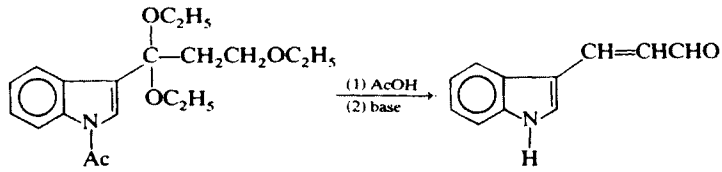


(52)

170; R = H
171; R = CF_3

172; R = H
173; R = CF_3

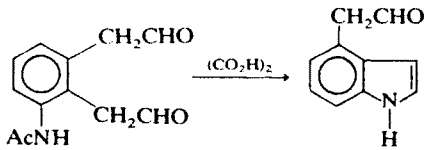
h. Miscellaneous Methods. 3-(3-indolyl)acrylaldehyde (**175**) was prepared by heating 1-acetyl-3-(1,1,3-triethoxypropyl)indole (**174**) in acetic acid–sodium acetate and basifying the product[197] (eq. 53).



(53)

174 **175**

There is one example in which an indoleacetaldehyde derivative (**177**) was obtained directly by cyclization of a nonindolic precursor (**176**). This cyclization was effected in 70% yield when oxalic acid was the catalyst[198] (eq. 54).



(54)

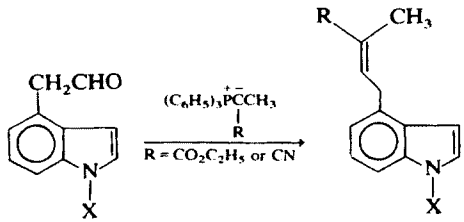
176 **177**

2. *Reactions and Functional Group Derivatives*

a. Conversion into Carboxylic Acid Derivatives. The oxime of indole-3-acetaldehyde underwent dehydration to indole-3-acetonitrile when heated with acetic anhydride or phosphorus oxychloride.[199] Another indole-3-acetaldehyde oxime was converted into a nitrile by aluminum chloride.[200] Silver oxide oxidized an indole-3-acetaldehyde to the corresponding indole-3-acetic acid.[201]

b. Condensation with Active Methylene Compounds. 4-indoleacetaldehydes blocked at position 1 with acetyl or sulfonyl groups

(**178** and **179**) underwent condensation with appropriate Wittig reagents to give compounds of *E*-stereochemistry (**180** and **181**) that were useful as ergot alkaloid intermediates[202,203] (eq. 55). Condensation of 1-acetylindole-3-acetaldehyde with malonic acid in the presence of ammonium acetate gave the corresponding α-amino acid derivative in very low yield.[204]

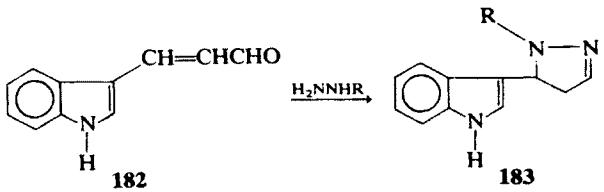


(55)

178; X = $COCH_3$
179; X = $SO_2C_7H_7$

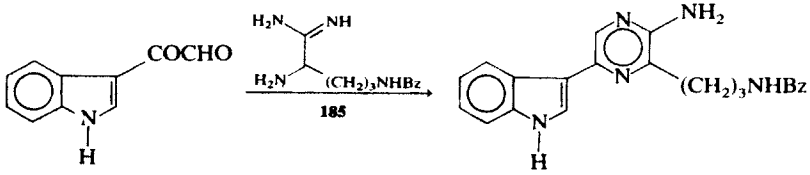
180; X = $COCH_3$; R = $CO_2C_2H_5$
181; X = $SO_2C_7H_7$; R = CN

c. Heterocycle Formation. Treatment of indole-3-acrylaldehyde (**182**) with a hydrazine gave the corresponding pyrrazoline **183**[205] (eq. 56). Condensation of 3-glyoxalylindole (**184**) with aminoacetamidine **185** yielded aminopyrimidine derivative **186**, a key intermediate in the total synthesis of *Cypridina* luciferin[206] (eq. 57).



182 **183**

(56)



184 **186**

(57)

d. Biochemical Transformations. Indole-3-acetaldehyde was converted into indole-3-carboxaldehyde in 50% yield by horseradish peroxidase at ph 3.7–4.5.[75] It was oxidized to indole-3-acetic acid by the oxidase from *Avena sativa*[207] and reduced to tryptophol by *Streptomyces cerevisiae* or *Z. priorianus*.[208] 5-Hydroxyindole-3-acetaldehyde was a

substrate in mammalian systems for 5-hydroxyindole-*O*-methyltransferase and it was reduced to 5-hydroxytryptophol in an NADPH-dependent reaction.[209]

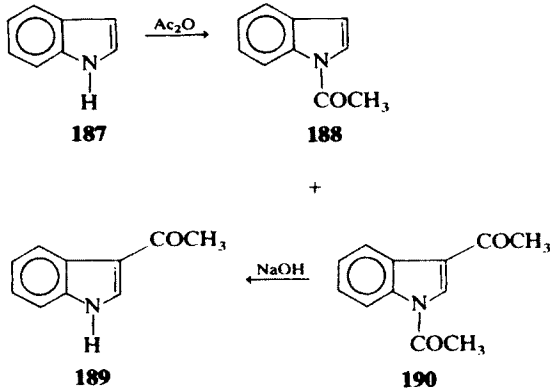
e. Functional Group Derivatives. A large number of the usual carbonyl-group derivatives have been prepared from indoleacetaldehydes. They include oximes,[193,199] phenylhydrazones,[193,194] semicarbazones,[189,191,193,198] imines,[204] and 2,4-dinitrophenylhydrazones.[190,192]

III. Indolyl Ketones

A. Carbonyl Groups Attached to Nucleus

1. *Preparation from Indoles*

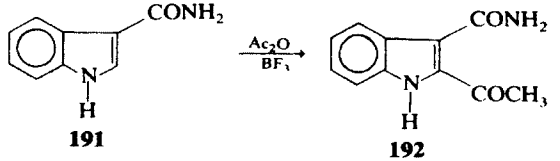
a. With Anhydrides. When indole (**187**) and acetic anhydride were heated at 180–200°, a mixture of 1-acetylindole (**188**) and 1,3-diacetylindole (**190**) was obtained. The steam volatility of 1-acetylindole allowed it to be removed from the mixture.[210] Partial hydrolysis of **190** then gave 3-acetylindole **189** (Scheme 10). Recently, more direct methods have been developed for **189**. The best of these appears to be treatment of indole with acetic anhydride in the presence of vinyl acetate (antioxidant). This method gave **189** in 66% yield.[211] Other methods for preparing **189** involve acetic anhydride and 60% perchloric acid (30% yield),[212] and acetic acid and silicon tetrachloride (21% yield).[213] Treatment of indole with acetic anhydride in the presence of magnesium perchlorate gave 2-acetylindole in 50% yield.[214]



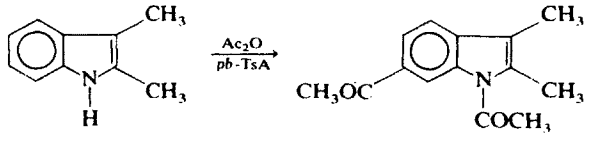
Scheme 10

The presence of substituents at the 2 or 3-position of indoles reduces their tendency to dimerize, allowing acylation in good yields. Thus the 3-acetyl derivatives were readily prepared from 2-methylindole, 2-phenylindole, and 1,2-dimethylindole.[215,216] Skatole gave 2-acetyl-3-methylindole on treatment with acetic anhydride and boron trifluoride etherate.[217]

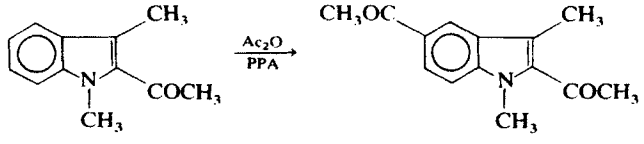
Indoles with electron-withdrawing substituents can be acylated by anhydrides. However, acylation in the benzene ring requires vigorous conditions. Indole-3-carboxamide (**191**) and acetic anhydride in the presence of boron trifluoride etherate gave the corresponding 2-acetyl derivative (**192**)[218] (eq. 58). Treatment of 2,3-dimethylindole (**193**) with acetic anhydride and toluenesulfonic acid gave the 1,6-diacetyl derivative **194**[215,219] (eq. 59). Substitution of the 6-position probably indicates that the 1-acetylation occurred first, by analogy to the conversion of **187** to **188**. 5-Acetylindole was acetylated at position 3 by acetic anhydride at 160–170°,[219,220] whereas acetic anhydride in hot polyphosphoric acid was used to acetylate the 5-position of 2-acetyl-1,3-dimethylindole[217] (eq. 60).



191 **192** (58)

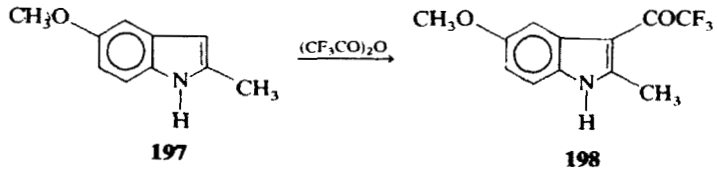


193 **194** (59)

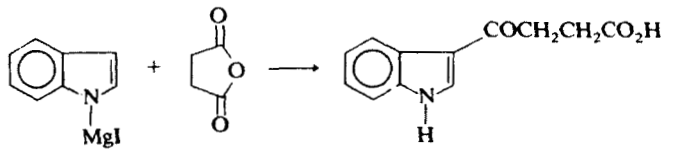


195 **196** (60)

Certain other anhydrides have been used successfully for the preparation of indolyl ketones. Thus trifluoroacetic anhydride converted indole into its 3-trifluoracetyl derivative in 63–95% yields.[221] 5-Methoxy-2-methylindole (**197**) similarly gave a trifluoroacetyl derivative **198**[222] (eq. 61). 2-Methylindolylmagnesium iodide **199** and succinic anhydride afforded 3-γ-ketobutyric acid derivative **200**[223] (eq. 62).



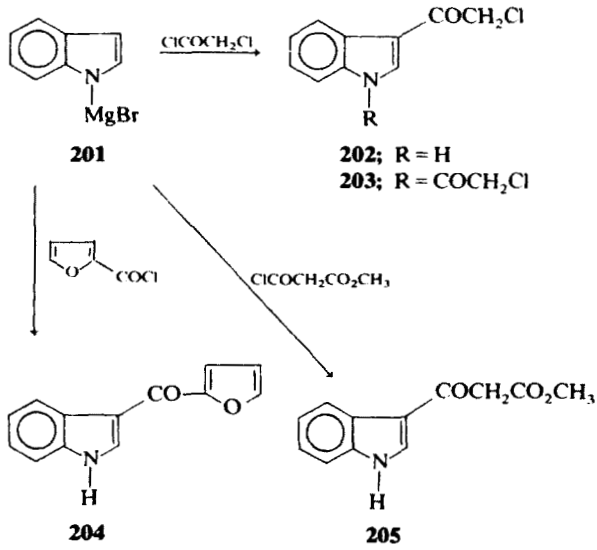
197 198 (61)



199 200 (62)

b. With Acid Chlorides. There are two important methods for preparing indolyl ketones from indoles and acid chlorides. One method involves acylation of indolylmagnesium compounds and usually gives 3-acylindoles. The other method involves Friedel–Crafts type acylation of the benzene rings of certain indoles or indolines.

Acylation of indolylmagnesium compounds has been widely used for preparing 3-acylindoles. An important example of this type of preparation is the synthesis of 3-(chloroacetyl)indole (**202**) from indolylmagnesium bromide (**201**) and chloroacetyl chloride.[224] Some 1,3-bis(chloroacetyl)indole (**203**) is also formed, but it can be hydrolyzed to



201 202; R = H 203; R = $COCH_2Cl$

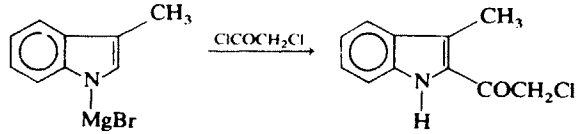
204 205

Scheme 11

202 by mild base.[225] Aryl or heterocyclic acid chlorides also may be used, as typified by the preparation of 3-furoylindole (**204**).[226] Because the acid chloride function is more reactive than the carboxylic acid ester, preferential reaction with one functional group of molecules containing both these groups has been obtained. Thus **201** and methyl 2-(chlorocarbonyl)-acetate afforded β-keto ester derivative **205**[227] (Scheme 11).

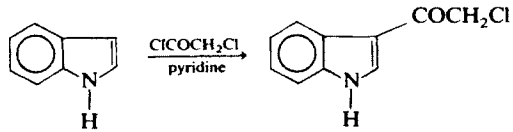
In addition to the acid chlorides just described, many other acid chlorides have been used to prepare 3-acyl or aroyl derivatives from indolylmagnesium compounds. These acid chlorides include butyryl,[228] dichloroacetyl,[229] trichloroacetyl,[229] ethoxyacetyl,[230] benzyloxyacetyl,[231] methylsuccinyl,[223] phenylacetyl (many examples with substituents on the phenyl group),[232,235] phenylpropionyl (with substituents on the phenyl group),[233] benzoyl,[234,235] thienoyl,[237] nicotinyl,[238] and 3-[4-(1-benzyloxycarbonylpiperidyl)] propionyl.[239]

One example was reported in which a 2-acylindole was formed. This example resulted from the reaction of skatolylmagnesium bromide (**206**) with chloroacetyl chloride to give **207**[224] (eq. 63).

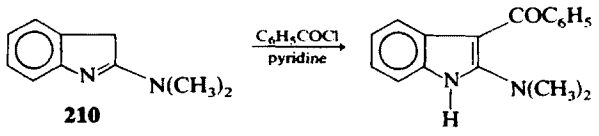


206 **207** (63)

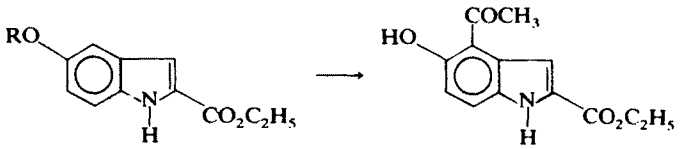
Indole and certain of its derivatives were acylated at position 3 under a variety of Friedel–Crafts conditions. Thus a reactive acid chloride such as chloroacetyl chloride acylated indole in pyridine solution[240] (eq. 64). 2-(Dimethylamino) indole (**210**) gave its 3-benzoyl derivative **211** with benzoyl chloride in pyridine[241] (eq. 65). The *N*-glucoside of indole was acylated at position 3 with acetyl chloride or nicotinyl chloride and aluminum chloride,[242] whereas acid chlorides and stannic chloride were used to prepare 3-acyl derivatives of 5-cyanoindole.[243] In ethyl 5-hydroxyindole-2-carboxylate (**212**) or its *O*-benzyl ether the electron density pattern is so changed from that of indole that the 4-acetyl derivative **214** is obtained under Friedel–Crafts conditions[244] (eq. 66).



208 **209** (64)



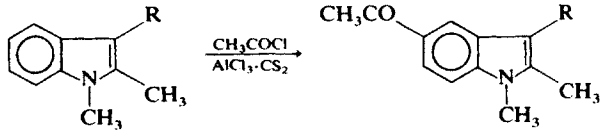
210 **211** (65)



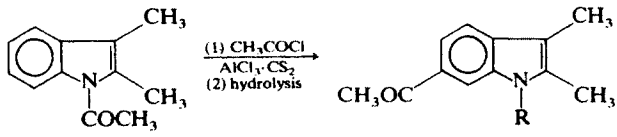
212; R = H
213; R = CH_3CO **214** (66)

Compound **214** also can be prepared by Fries rearrangement of ethyl 5-acetoxyindole-2-carboxylate (**213**).[244] In contrast to the formation of **214** is the preferred 6-acetylation of the 2-methyl homologue of **212**.[244]

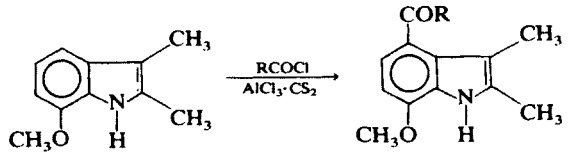
Indoles that are highly substituted in the pyrrole ring are difficult to acylate under ordinary conditions. However, under Friedel–Crafts conditions they can be acylated in the benzene ring. The position of acylation depends on the presence of substituents in the benzene ring and whether or not the indole nitrogen is acylated.[215] Thus 1,2-dimethylindole (**215**) and 1,2,3-trimethylindole (**216**) gave 5-acetyl derivatives (**217** and **218**) when they were treated with acetyl chloride and aluminum chloride (**215**) (eq. 67). However, 1-acetyl-2,3-dimethylindole (**219**) gave 6-acetyl derivative **220**, which was readily hydrolyzed to **221**[215,245] (eq. 68). 7-Methoxy-2,3-dimethylindole (**222**) gave 4-acetyl derivative **223** or 4-benzoyl derivative **224** under Friedel–Crafts conditions[215] (eq. 69).



215; R = H
216; R = CH_3 **217**; R = H
218; R = CH_3 (67)



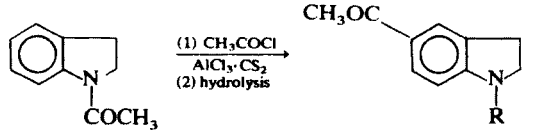
219 **220**; R = $COCH_3$
221; R = H (68)



(69)

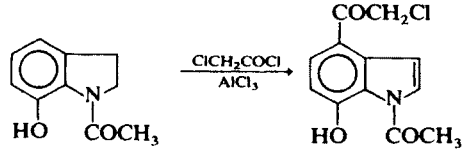
222 **223**; R = CH_3
224; R = C_6H_5

Friedel–Crafts acylation of *N*-acetylindolines usually gives the 1,5-diacyl derivatives, which can be hydrolyzed to the corresponding 5-acylindolines. Thus 1-acetylindoline (**225**) was converted into 5-acetylindoline (**227**) in good yield[246] (eq. 70). 5-(Chloroacetyl)indoline was prepared by a similar route.[246] Chloroacetylation of 1-acetyl-7-hydroxyindole (**228**) occurred at the 4-position to give **229**[62] (eq. 71). In this example the directive effect of the hydroxyl group evidently predominated over that of the acylamino group.



(70)

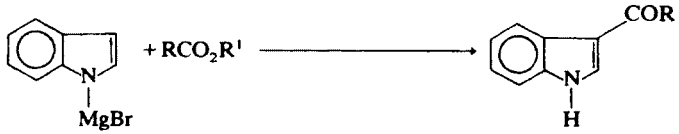
225 **226**; R = $COCH_3$
227; R = H



(71)

228 **229**

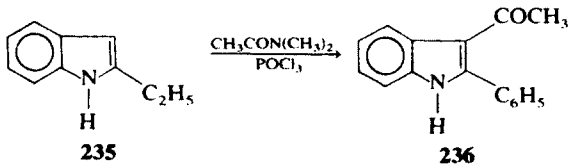
c. With Esters. Reactions of indolylmagnesium bromide **230** with certain esters have given indolyl ketones. For example, ethyl furoate (**231**) gave furyl ketone **233**. With β-keto ester **232** the product (**234**) resulted from preferential reaction with the ester function[228] (eq. 72). Treatment of **230** with dimethyl oxalate gave a mixture of 1,1′-, 3,3′-, and 1,3′-oxalyldiindoles.[228]



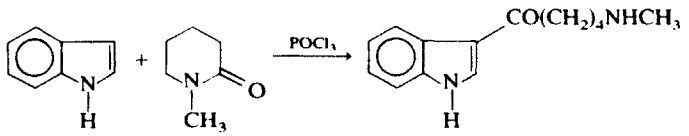
(72)

230 **231**; R = 2-furyl, $R^1 = C_2H_5$ **233**; R = 2-furyl
232; R = $CH_3COCH(C_2H_5)$, $R^1 = CH_3$ **234**; R = $CHCOCH_3(C_2H_5)$

d. WITH AMIDES. The Vilsmeier–Haack reaction involving indoles, phosphorus oxychloride, and *N,N*-dimethylcarboxamides has given a variety of indolyl ketones. Amides derived from many different carboxylic acids have been used successfully and the indoles have included those with substituents at the 1-, 2-, 5-, or even 3-position. Substitution is preferred at the 3-position unless it is occupied. In a typical experiment, treatment of 2-phenylindole (**235**) with phosphorus oxychloride and dimethylacetamide gave 3-acetyl derivative **236** in 76% yield[247] (eq. 73). Other *N,N*-dimethylamides have included those of the following carboxylic acids: *o*-fluorobenzoic,[248] *m*-methylbenzoic,[144] propionic, isobutyric, isovaleric, chloroacetic, benzoic, malonic (bisamide), 2-ethoxybutyric, and 2,2-dimethylpropionic.[249] Yields of the ketones obtained from these reactions varied from 17 to 98%. When *N*-methylpiperidinone (**238**) was used as the amide in the acylation of indole (**237**) it underwent ring opening, affording aminoketone **239**[250] (eq. 74).

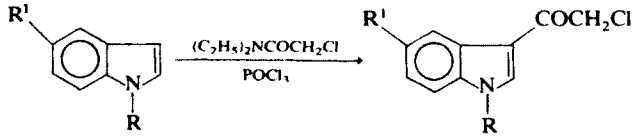


235 **236** (73)



237 **238** **239** (74)

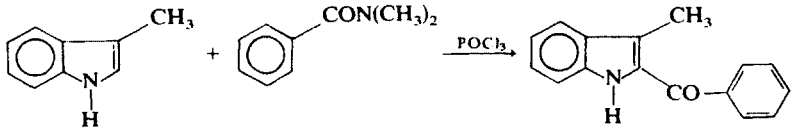
The synthesis of 3-(chloroacetyl)indoles from indolylmagnesium halides and chloroacetyl chloride was noted previously. Vilsmeier–Haack synthesis with (*N,N*-diethyl)chloroacetamide also is effective for these compounds. For example, indole (**240**), 1-methylindole (**241**), and 5-methoxyindole (**242**) all were converted into their 3-chloroacetyl derivatives in good yields[251–253] (eq. 75). The *N*-carbobenzyloxy derivative of 2-aminoindole was substituted at position 3 by (*N,N*-diethyl)chloroacetamide and numerous other chloroamides.[254,255]



240; R = R¹ = H
241; R = CH_3, R¹ = H
242; R = H, R¹ = CH_3O

243; R = R¹ = H
244; R = CH_3, R¹ = H
245; R = H, R¹ = CH_3O (75)

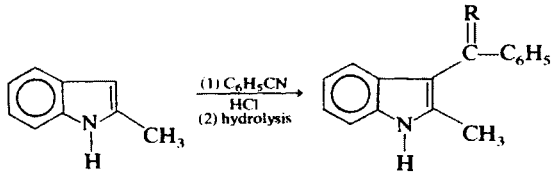
One example of 2-substitution of an indole by the Vilsmeier–Haack reaction has been reported.[255] In this example, skatole (**246**) was converted into its 2-benzoyl derivative **247** (eq. 76).



(76)

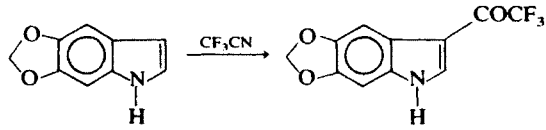
246 **247**

e. With Nitriles. One of the oldest methods for preparing 3-indolyl ketones is the Houben–Hoesch reaction, which involves treating the indole with HCl and a nitrile. The acidic conditions of this reaction limit its use to acid-stable indoles such as 2-methylindole **248**. Thus benzonitrile and **248** gave 3-benzoyl-2-methylindole (**250**) in 75% yield after hydrolysis of the imine intermediate **249**[256,257] (eq. 77). Phenylacetonitrile also acylated **248** in high yield.[256] Trifluoroacetonitrile was sufficiently reactive to acylate a variety of indoles under such mild conditions that indole polymers were not a serious problem. Thus 5,6-methylenedioxyindole (**251**) was readily converted into **252**[258] (eq. 78). Indoles also were effectively acylated with trichloroacetonitrile.[259]



(77)

248 **249**; R = NH
250; R = O

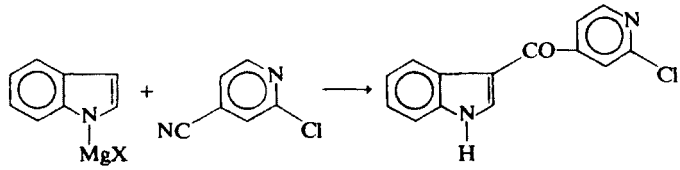


(78)

251 **252**

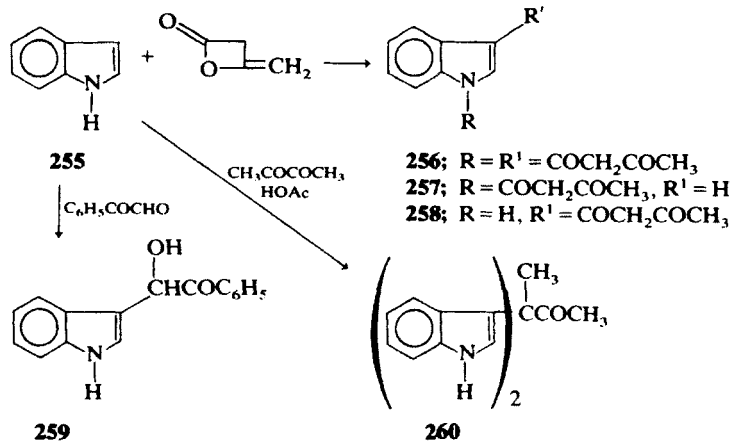
Indolylmagnesium compounds add to nitriles, forming imines that give ketones on hydrolysis, as illustrated by the conversion of indolylmagnesium bromide (**253**) into 3-(2-chloroisonicotinyl)indole (**254**)[250] (eq. 79).

f. With Diketene and Ketones. Indole (**255**) condensed with diketene in acetic anhydride to give 1,3-diacetoacetylindole (**256**). 1-Acetoacetylindole (**257**) was an intermediate in this reaction and it could be

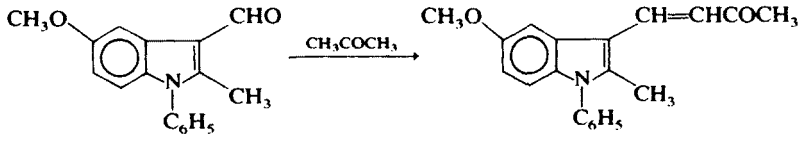


253 254 (79)

isolated under mild conditions. When acetic acid was the solvent, condensation of indole and diketene gave 3-acetoacetylindole (**258**)[259] (Scheme 12). Treatment of indole with phenylglyoxal afforded α-hydroxyketone **259** in 59% yield.[260] Other arylglyoxals gave similar products.[260] Acyldiindolylmethanes such as **260** were obtained when indole was heated with α-diketones such as diacetyl[261] (Scheme 12). Condensation of 5-methoxy-2-methyl-1-phenylindole-3-carboxaldehyde (**261**) with acetophenone and other aryl methyl ketones gave indolylvinyl methyl ketones such as **262**[262] (eq. 80). These ketones were claimed to have a variety of pharmacodynamic activities.[262]

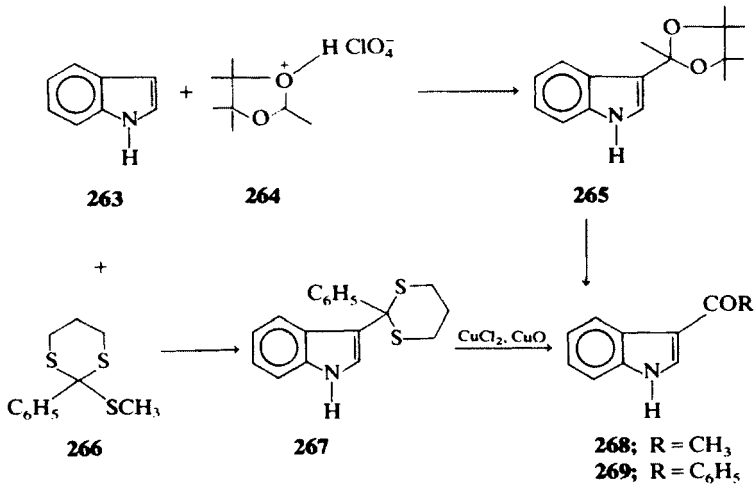


Scheme 12



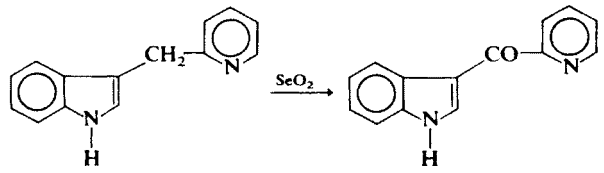
261 262 (80)

g. With Other Electrophilic Reagents. Treatment of indole (**263**) with the perchlorate salt of 2,4,4,5,5-pentamethyldioxolane (**264**) afforded intermediate **265**, which gave a 51% yield of 3-acetylindole (**268**) after acid hydrolysis[263] (Scheme 13). This procedure appears to be one of the better ones for **268**. 3-Benzoylindole (**269**) was prepared in 85–88% yields by treatment of indole (**263**) with 2-(methylthio)-2-phenyl-1,3-dithiane (**266**) followed by dethioketalization with cuprous chloride and cupric oxide in acetone[264] (Scheme 13). This procedure also is a superior one for 3-indolyl ketones.



Scheme 13

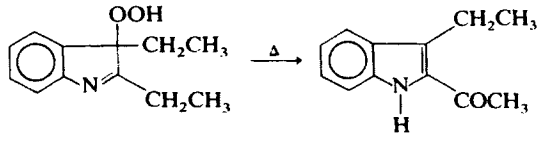
h. Oxidation of Methylene Groups. Selenium dioxide oxidation of 3-(2-pyridylmethyl)indole (**270**) gave the corresponding ketone **271** in low yield[265] (eq. 81).



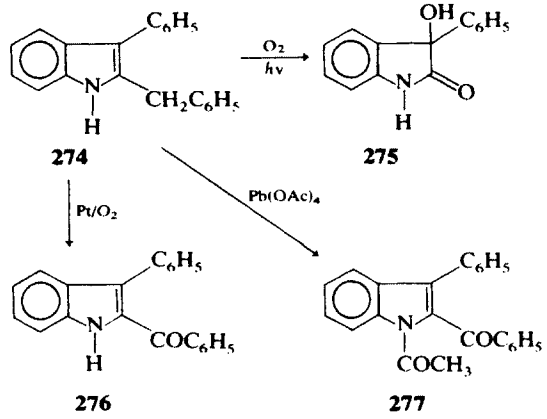
(81)

Autoxidation of certain 2,3-disubstituted indoles gave 2-acyl derivatives by way of hydroperoxyindolenine intermediates. Thus 2,3-diethylindole afforded hydroperoxide **272** in almost quantitative yield. When this hydroperoxide was heated on a steam bath it gave 52% of 2-acetyl-3-ethylindole (**273**)[266] (eq. 82). Autoxidation of 2-benzyl-3-phenylindole

(**274**) gave a 3-hydroxyoxindole (**275**), but when platinum catalyst was present the product was 2-benzoyl-3-phenylindole (**276**)[267] (Scheme 14). Lead tetraacetate oxidized **274** to 1-acetyl-2-benzoyl-3-phenylindole (**277**)[266] (Scheme 14).



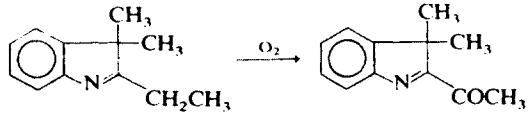
272 **273** (82)



274 **275** **276** **277**

Scheme 14

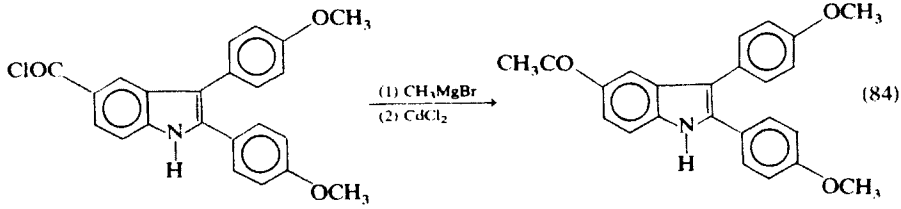
2-Alkyl-3,3-disubstituted indolenines also undergo autoxidation to give 2-acyl derivatives. For example, 2-ethyl-3,3-dimethylindolenine **278** was converted into **279** by this process[268] (eq. 83). The 3,3-spiropentane analogue of **278** was converted similarily into its 2-acetyl derivative.[269]



278 **279** (83)

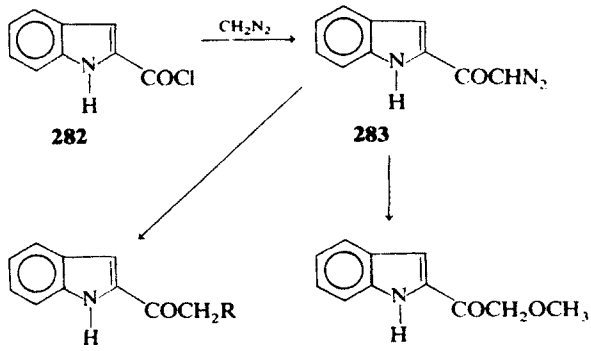
i. Transformation of Acid Chlorides. Two methods are known for the synthesis of indolyl methyl ketones from the corresponding indole carboxylic acid chlorides. In one method, exemplified by the conversion of **280** into **281**, the methylation was accomplished by methylmagnesium bromide followed by cadmium chloride[270] (eq. 84). The product **281** was

claimed to have antiinflammatory activity. The second method for methyl ketones was based on formation of a diazoketone with diazomethane, followed by catalytic hydrogenation. Thus indole-2-carbonyl chloride **282** was readily converted into diazoketone **283**. Hydrogenation of **283** in the presence of platinum gave 2-acetylindole (**285**) in 79% yield.[271] 2-Acetylindole also could be prepared by way of 2-(iodoacetyl)indole (**284**), but this intermediate was formed in only 8% yield when **283** was treated with cuprous iodide in acetonitrile[271] (Scheme 15). When diazoketone **283** was heated with copper in methanol the corresponding methoxymethyl ketone **286** was formed. 1-Trifluoroacetylindoline-2-carbonyl chloride (**287**) was converted into its 2-acetyl analogue **291** in 67% overall yield by a route involving diazoketone **288** and bromomethyl ketone **289**[272] (Scheme 16). Compound **291** is an intermediate in the synthesis of 1-amino-(*s*)-*z*-[(*s*)-1-hydroxyethyl]indoline (**290**), which is Corey's reagent for the asymmetric synthesis of amino acids.[272]



(84)

280 **281**

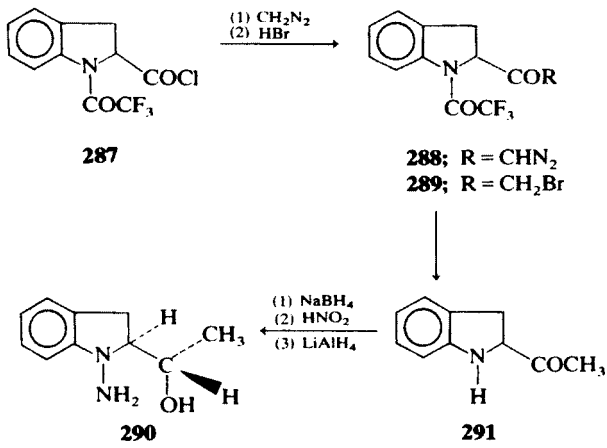


282 **283**

284; R = I
285; R = H

286

Scheme 15

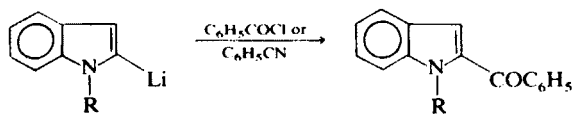


287 **288**; R = CHN_2
289; R = CH_2Br

290 **291**

Scheme 16

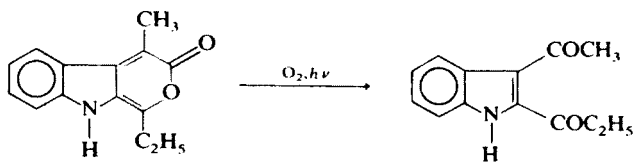
j. Miscellaneous Methods. Indole blocked at nitrogen by groups such as phenylsulfonyl or methoxymethyl could be lithiated at position 2. Treatment of the resulting lithium derivatives (e.g., **292** and **293**) with aroyl halides or nitriles gave 2-acylindoles such as **294** and **295** in good yields[273] (eq. 85). The benzenesulfonyl group was readily removed by alkaline hydrolysis and the methoxymethyl group could be removed by boron trifluoride.[273] Photooxygenation of pyrano[3,4-*b*]indol-3(9*H*)-ones gave 2,3-diacylindoles in good yields. For example, **296** was readily converted into 3-acetyl-2-propionylindole (**297**) by this method[274] (eq. 86).



(85)

292; R = $SO_2C_6H_5$
293; R = CH_2OCH_3

294; R = $SO_2C_6H_5$
295; R = CH_2OCH_3

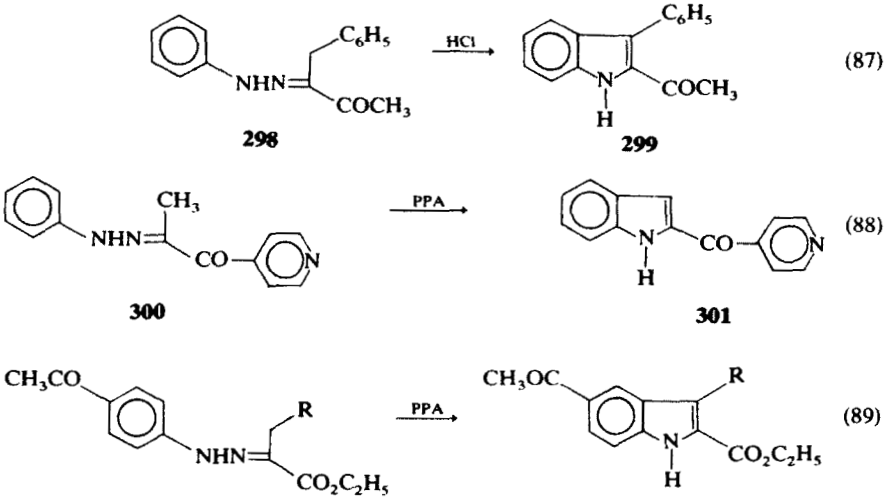


(86)

296 **297**

2. *Preparation from Indole Precursors Containing the Carbonyl Group*

a. FISCHER SYNTHESIS. Acid-catalyzed cyclizations of phenylhydrazones bearing a carbonyl group have given a variety of indolyl ketones. Thus 2-acetyl-3-phenylindole (**299**) was obtained in nearly quantitative yield when hydrazone **298** was heated with HCl[275] (eq. 87). 2-Indolyl 4-pyridyl ketone **301** was similarly prepared from hydrazone **300** and polyphosphoric acid[276] (eq. 88). Numerous other 2-acylindoles and 2-aroylindoles have been prepared from the monohydrazones of α-diketones.[277–279] However, the formation of 2-acetyl-3-alkylindoles from the corresponding hydrazones occurred in very low yields because of extensive resinification. 5-Acetylindole-2-carboxylic acid esters **304** and **305** were prepared conveniently from (4-acetylphenyl)hydrazones **302** and **303**[217,280] (eq. 89). An interesting method for the synthesis of 1-aminoalkyl-3-acylindoles (**307**) was provided by cyclization of the hydrazones obtained from **306** and acetylacetone or benzoylacetone[281] (eq. 90).



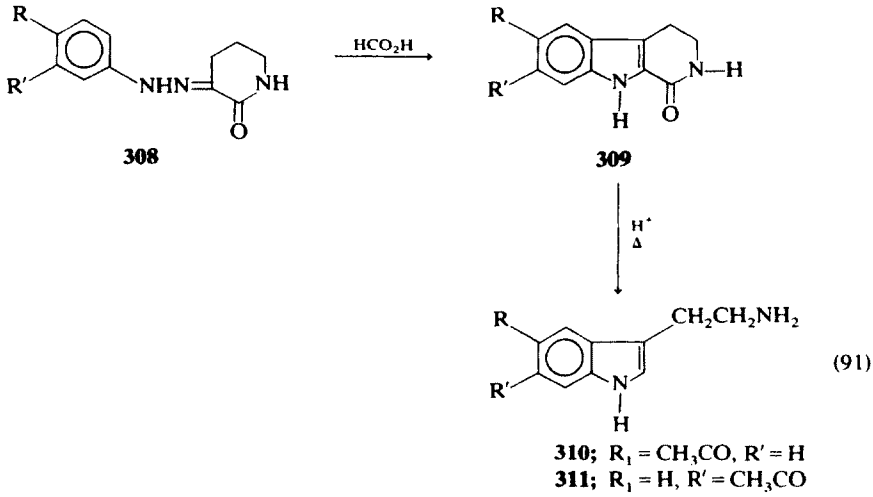
(87)

(88)

(89)

(90)

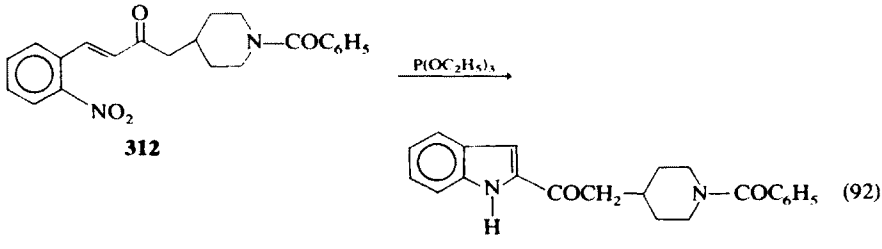
A useful synthesis for 5- and 6-acetyltryptamines (310 and 311) was based upon cyclization of the acetylphenylhydrazones of piperidinediones **308**, followed by hydrolysis and decarboxylation of the intermediate carbolines **309**[282] (eq. 91).



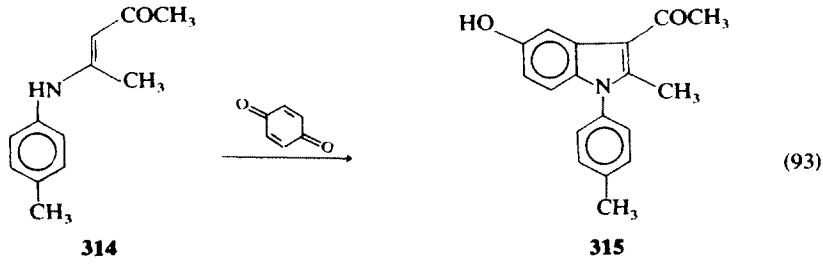
308 **309**

310; $R_1 = CH_3CO$, $R' = H$
311; $R_1 = H$, $R' = CH_3CO$ (91)

b. Other Methods. Reductive cyclization of *o*-nitrostyryl ketones such as **312** with trialkyl phosphites afforded the corresponding 2-acylindoles (**313**) in low yields[283,284] (eq. 92).



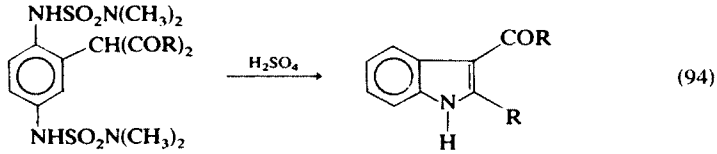
312 **313** (92)



314 **315** (93)

Nenitzescu condensation of benzoquinone with a variety of substituted enamine derivatives of acetylacetone, for example, **314**, gave the anticipated 3-acetyl-5-hydroxyindoles **315**[285] (Eq. 93).

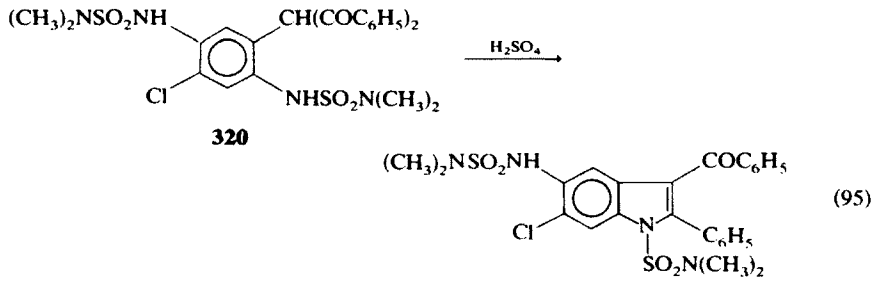
Treatment of bis-(dimethylsulfamoylamino)benzenes bearing diacetylmethyl or dibenzoylmethyl substituents with concentrated H_2SO_4 afforded 3-acetylindoles or 3-benzoylindoles. Thus **316** and **317** gave **318** and **319**, respectively[285] (eq. 94). However, in certain cases the sulfamoyl substituent was retained, as in the conversion of **320** into **321**[286] (eq. 95).



(94)

316; R = CH_3
317; R = C_6H_5

318; R = CH_3
319; R = C_6H_5

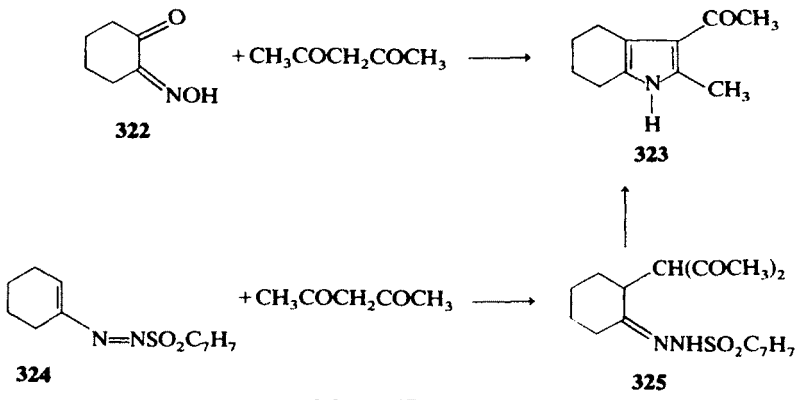


(95)

320

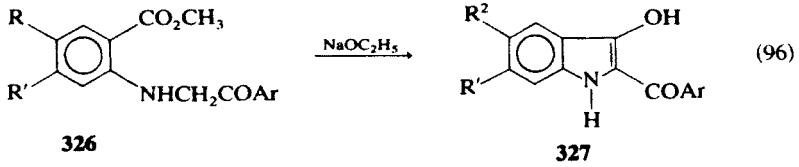
321

Condensation of 2-isonitrosocyclohexanone (**322**) with acetylacetone gave 3-acetyl-2-methyl-4,5,6,7-tetrahydroindole (**323**)[287] (Scheme 17). Compound **323** also was prepared by the condensation of *p*-toluenesulfonylazocyclohex-1-ene (**324**) with acetylacetone, followed by cyclization of the intermediate **325** in the presence of molecular sieves, and hydrolysis of the *p*-toluenesulfonyl group[288] (Scheme 17). Base-catalyzed cyclization of keto esters **326** gave a large number of 2-aroyl-3-hydroxyindoles **327**[280] (eq. 96). These compounds were alkylated on the 3-hydroxyl group with dialkylaminoethyl halides.[289] Thermal decomposition of phenylazides with appropriately substituted acrylic side chains (e.g., **328**) afforded 2-acylindoles (**329**) by way of nitrene insertion reactions[290] (eq. 97).



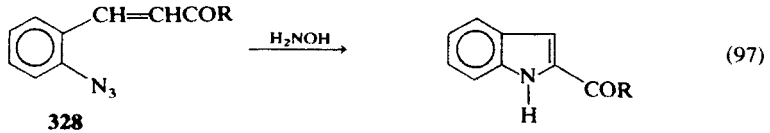
322 323 324 325

Scheme 17



(96)

326 327

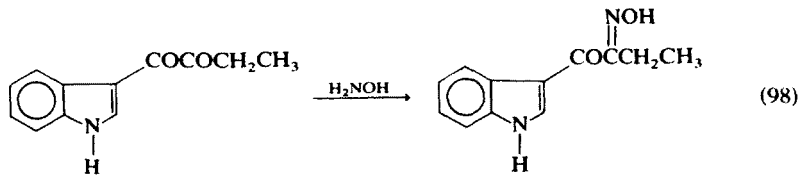


(97)

328 329

3. *Derivatives and Rections*

a. FUNCTIONAL GROUP DERIVATIVES. Indolyl ketones give most of the usual carbonyl group derivatives such as hydrazones and oximes.[291-293] However, these derivatives have not proved to be particularly important except as intermediates, for example, in Wolff–Kishner reductions (see below). Indoles with α-diketones in the side chain wherein one carbonyl

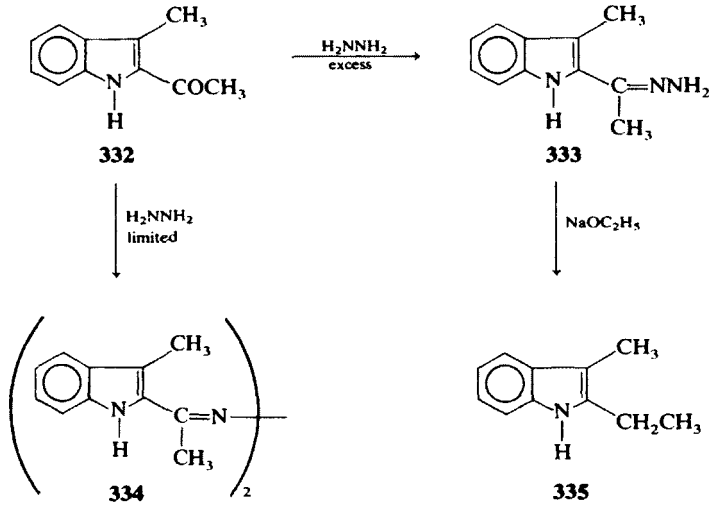


(98)

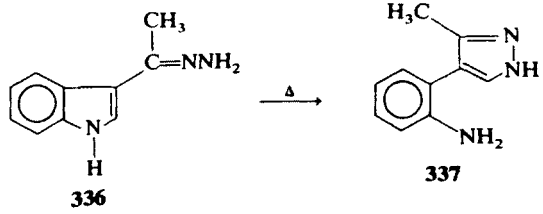
330 331

group is attached to indole position 3 form monoximes or monophenylhydrazones selectively at the other carbonyl group. For example, **330** gave oxime **331**[294] (eq. 98).

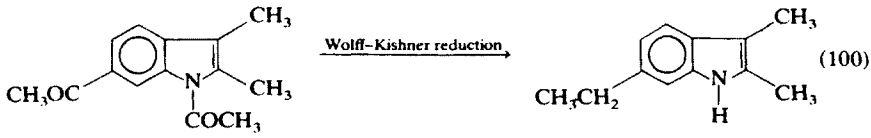
b. Reduction of the Carbonyl Group. The Wolff–Kishner reduction has been used for conversion of indolyl ketones into the corresponding alkyl derivatives. However, ketazine formation and even pyrazole formation occur under Wolff–Kishner conditions. Thus treatment of 2-acetyl-3-methylindole (**332**) with excess hydrazine gave hydrazone **333**, which was converted into 2-ethyl-3-methylindole (**335**) by sodium ethoxide.[291] When **332** was heated with an equivalent of hydrazine, the product was ketazine **334**[291] (Scheme 18). In another study, the hydrazone (**336**) of 3-acetylindole gave *o*-aminophenylpyrazole **337** on heating[295] (eq. 99). Wolff–Kishner reduction of 1,6-diacetyl-2,3-dimethylindole (**338**) gave 6-ethyl-2,3-dimethylindole (**339**)[219] (eq. 100).



Scheme 18

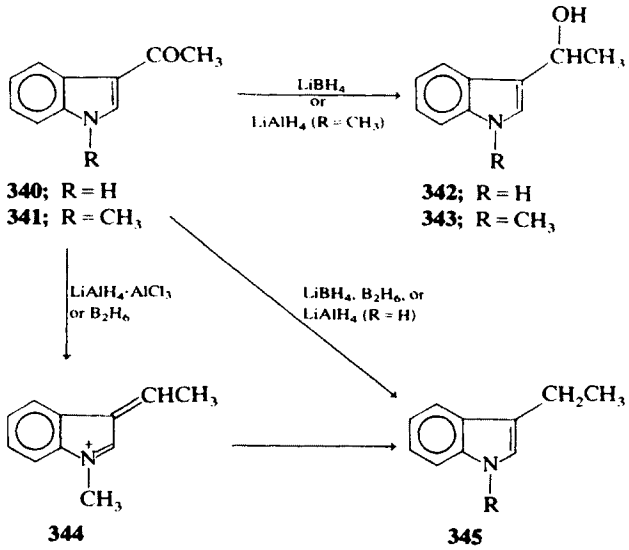


(99)



338 **339**

Reduction of 3-acetylindoles with alkali metal hydrides or with diborane proceeds in modes analogous to those of the corresponding 3-carboxaldehydes (Section II.A.3.c). Thus 3-acetylindole (**340**) gave 3-hydroxyethylindole (**342**) in poor yield when it was treated with lithium borohydride (LBH) in cold tetrahydrofuran,[296] whereas LBH in hot tetrahydrofuran, lithium aluminum hydride (LAH), or diborane reduced **340** to 3-ethylindole (**345**)[296] (Scheme 19). The 1-methyl homologue (**341**) was converted initially by LAH to hydroxyindole **343**, but this product was unstable and underwent polymerization.[297] A mixture of LAH and aluminum chloride reduced **340** to 3-ethyl-1-methylindole (**345**). Since LAH alone does not reduce indolyl ketones with 1-alkyl substituents beyond the 3-hydroxyalkyl stage, the role of aluminum chloride in the experiment just described was to promote decomposition of the intermediate aluminate complex to 3-ethylidineindoleninium ion **344**, which was then reduced to **345**.[297] Diborane also reduced **341** to **345**[156] (Scheme 19).



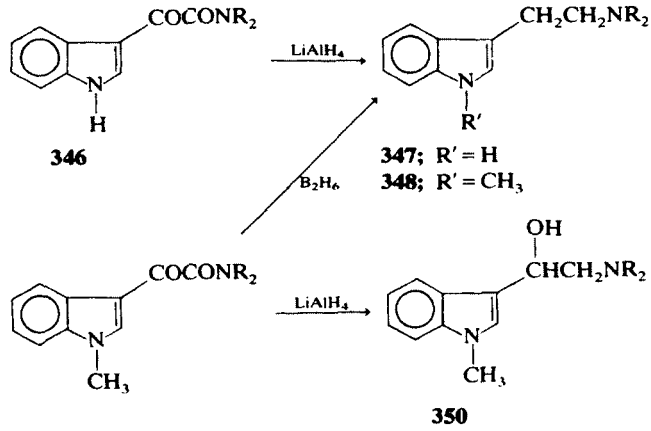
340; R = H
341; R = CH_3

342; R = H
343; R = CH_3

344 **345**

Scheme 19

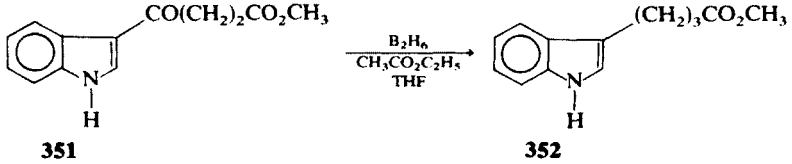
The reduction of indole-3-glyoxalylamides to tryptamines is an important synthetic method. When the indolic nitrogen is unsubstituted, this transformation can be effected in one step with LAH, as in **346** to **347**. However, the corresponding *N*-alkyl analogues such as **349** are reduced only to the β-hydroxytryptamines **350** with LAH.[298-300] When diborane is the reducing agent, even the *N*-alkyl analogues **349** are converted into tryptamines **348**[156] (Scheme 20).



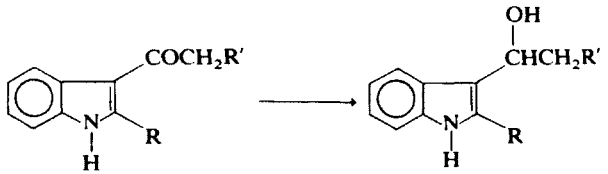
Scheme 20

Selective reduction of the ketonic carbonyl group of an indole ketoester (**351** to **352**) was obtained when ethyl acetate was added to the reduction of **351** by diborane in tetrahydrofuran[301] (eq. 101). There are two reported examples in which LAH reduction of 3-acylindoles unsubstituted on nitrogen (**353** and **354**) gave the corresponding 3-hydroxyethyl derivatives (**355** and **356**) in high yields[302,303] (eq. 102). Sodium borohydride reduction of α-epoxyketone **357** gave the corresponding α-hydroxyepoxide **358** (eq. 103). However, zinc in acetic acid converted **357** into β-phenylethyl indolyl ketone.[304]

c. Addition of Nucleophiles to the Carbonyl Group. Treatment of 3-indolyl ketones with Grignard reagents can lead to either 1,2-addition



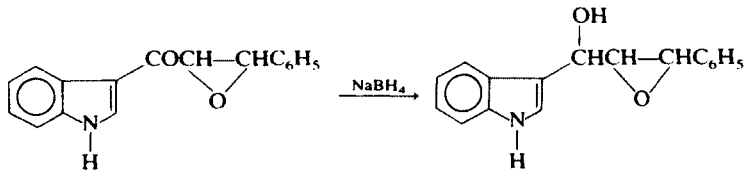
(101)



(102)

353; R = C_6H_5, R' = H
354; R = H, R' = $OCH_2C_6H_5$

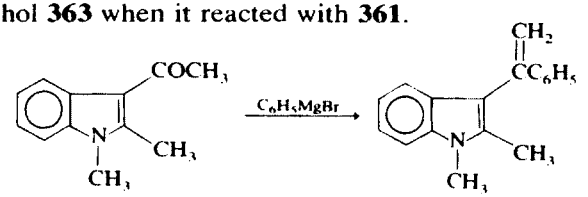
355; R = C_6H_5, R' = H
356; R = H, R' = $OCH_2C_6H_5$



(103)

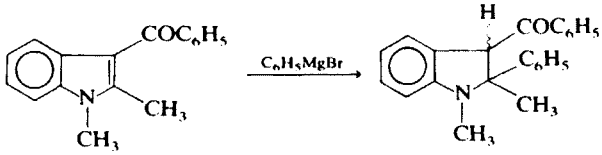
357 **358**

or 1,4-addition, depending on the particular ketone. Thus 3-acetyl-1,2-dimethylindole (**359**) gave methylene derivative **360** when treated with phenylmagnesium bromide, (eq. 104) whereas 3-benzoyl analogue **361** afforded 2-phenyl derivative **362**[305] (eq. 105). Even phenyllithium, which normally adds 1,2 to carbonyl groups, gave some **362** in addition to tertiary alcohol **363** when it reacted with **361**.



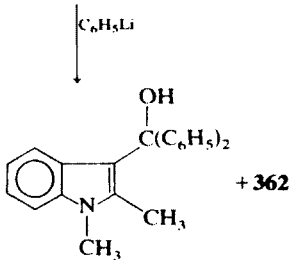
(104)

359 **360**



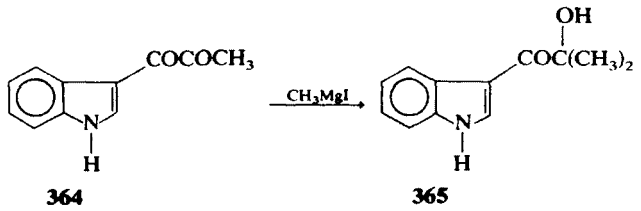
(105)

361 **362**



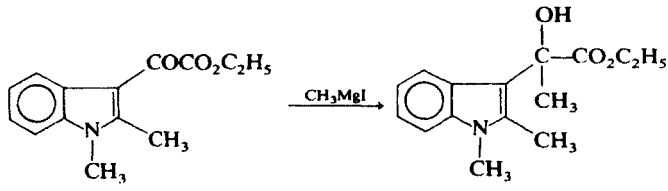
363

Since a carbonyl group at the 3-position of an indole is deactivated toward nucleophilic attack, the selective methylation of diketone **364** at the other carbonyl carbon to give **365** was anticipated when it was treated with methylmagnesium iodide[306] (eq. 106).

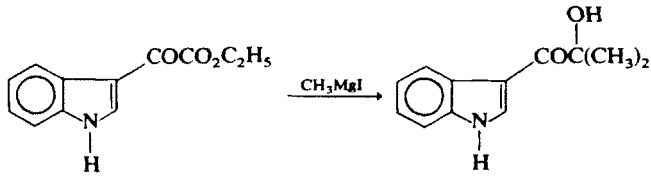


364 **365** (106)

Indole-3-glyoxylic esters substituted on nitrogen react preferentially at the ketonic carbonyl group when they are treated with Grignard reagents. For example, **366** and methylmagnesium iodide gave **367** (eq. 107). However, when the nitrogen was unsubstituted (as in **368**), the ketonic carbonyl became so deactivated by formation of an indolylmagnesium salt that methylation occurred preferentially at the ester carbonyl to give **369**[306] (eq. 108).



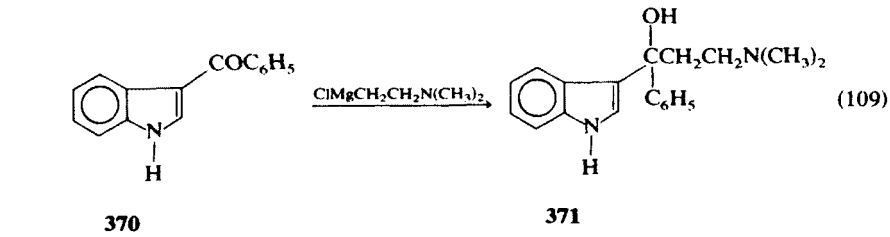
366 **367** (107)



368 **369** (108)

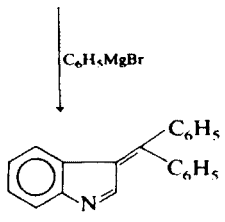
Grignard reactions with 3-benzoylindole (**370**) include the preparation of dimethylaminoethyl derivative **371**[235] and the formation of diphenylmethyleneindoline **372**[305] from the appropriate Grignard reagents (eq. 109).

Treatment of 3-trifluoroacetylindole derivative **373** with *t*-butyl chloroacetate and potassium *t*-butoxide gave the glycidic acid ester **374**[200] (eq. 110).

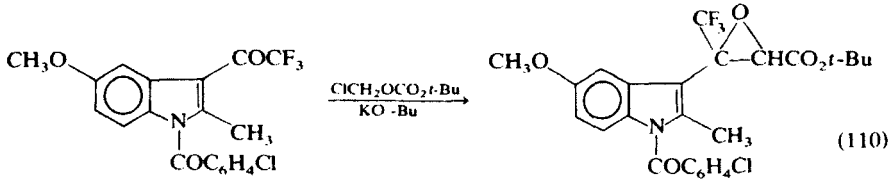


(109)

370 **371**



372



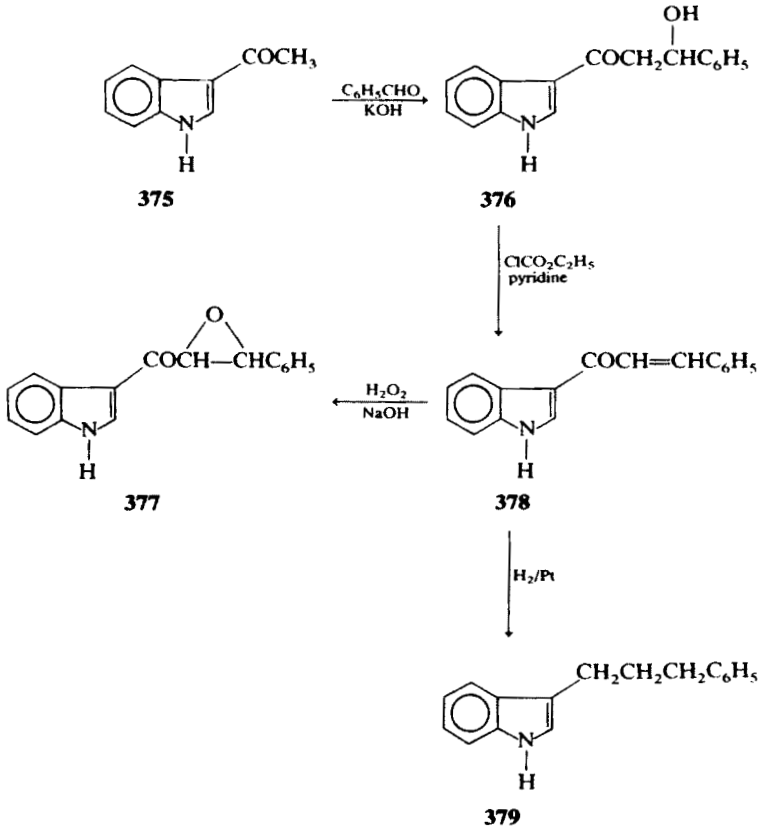
(110)

373 **374**

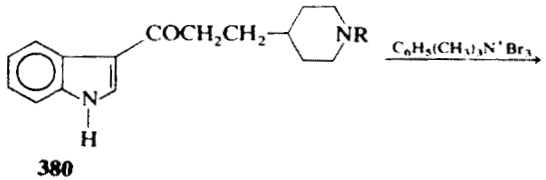
d. Condensation and Oxidation Adjacent to the Carbonyl Group. 3-Acetylindole (**375**) readily condensed with benzaldehyde in the presence of base to give β-hydroxyketone **376**, which was dehydrated to benzylidene **378**. This benzylidine was converted into epoxide **377** or hydrogenated to 3-(3-phenylpropyl)indole (**379**)[307] (Scheme 21). Many related α,β-unsaturated indolyl ketones and epoxyketones were prepared from **375** and aromatic aldehydes.[307]

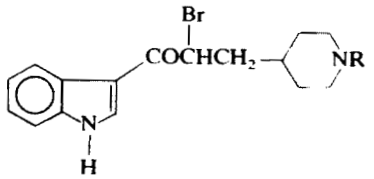
As discussed in Section II.A.1.f, selenium dioxide oxidation of 3-acetylindoles gave the corresponding glyoxalyl derivatives.

e. Halogenation Adjacent to the Carbonyl Group. Bromination of 3-acetylindole gave 3-(bromoacetyl)indole.[308] Phenyltrimethylammonium tribromide was used in the conversion of the substituted piperidylpropionylindole **380** to **381**[239] (eq. 111). The usual methods for preparing 3-(chloroacetyl)indoles involve indolylmagnesium compounds and chloroacetyl chloride or Vilsmeier–Haack reactions with *N,N*-dimethylchloroacetamide (Section III.A.1).



Scheme 21

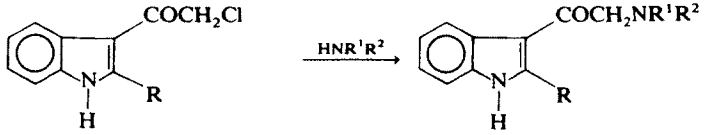




(111)

R = $CO_2CH_2C_6H_5$ **381**

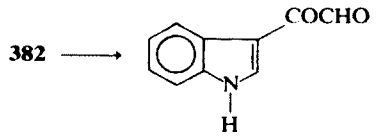
f. Nucleophilic Displacement at Carbon Adjacent to the Carbonyl. 3-(Chloroacetyl)indole (**382**) and its 2-methyl homologue **383** have been versatile intermediates for the preparation of other acetylindoles. Nucleophilic displacement of chlorine by ammonia or primary amines has given many 3-(aminoacetyl)indoles such as **385** and **386**[224,308-310] (eq. 112). The chlorine of **382** also was displaced by hydroxide ion and cyanide ion.[224,310] A number of secondary amines such as diethylamine, pyrrolidine, morpholine, piperidine, and 4-methylpiperazine were used in the conversion of 2-carbobenzyloxyamino-3-(chloroacetyl)indole (**384**) into its amide derivatives **387**[310] (eq. 112).



(112)

382; R = H
383; R = CH_3
384; R = $NHCO_2CH_2C_6H_5$

385; R = H
386; R = CH_3
387; R = $NHCO_2CH_2C_6H_5$



(113)

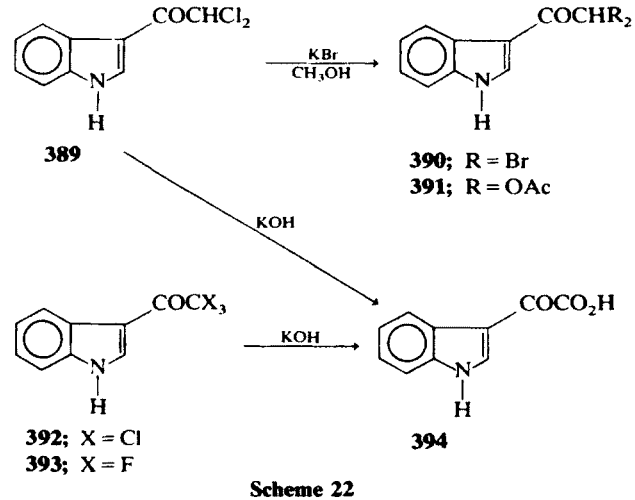
388

3-Glyoxalylindole (**388**) was prepared by treating **382** consecutively with pyridine, *p*-dimethylaminonitrosobenzene, and sulfuric acid[193] (eq. 113).

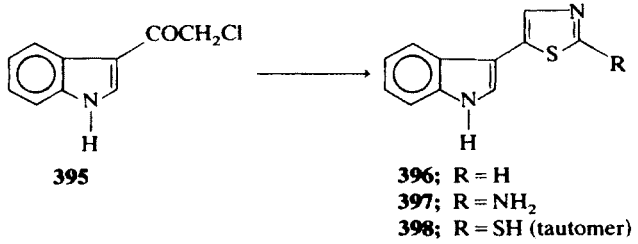
Many of the nucleophilic displacements described for **383** were also successful with the isomeric 2-(chloroacetyl)-3-methylindole.

3-(Dichloroacetyl)indole **389** was converted into the corresponding dibromo derivative **390** by potassium bromide in methanol and into the diacetoxy derivative **391** by sodium acetate[312] (Scheme 22). It gave indole-3-glyoxylic acid (**394**) on treatment with potassium hydroxide.[312] Compound **394** also was prepared by alkaline hydrolysis of 3-(trichloroacetyl)indole **392** and 3-(trifluoroacetyl)indole (**393**)[313,221] (Scheme 22).

g. Heterocycle Formation. 3-(Chloroacetyl)indole (**395**) gave 5-(3-indolyl)thiazole (**396**) when it was heated with phosphorus pentasulfide and formamide. 2-Substituted thiazole analogues **397** and **398** were formed when **395** was warmed with thiourea and ammonium dithiocarbamate, respectively[314] (eq. 114).

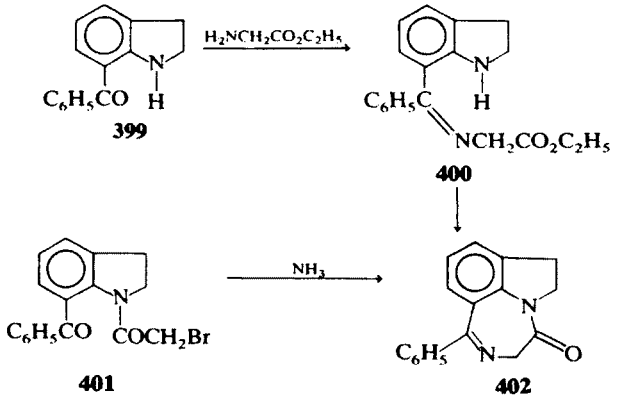


Scheme 22



(114)

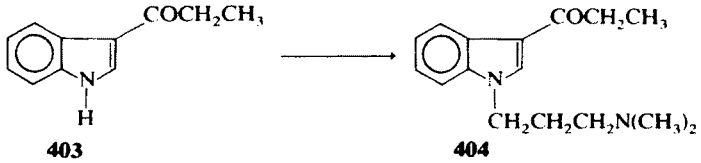
Pyrrolobenzodiazepine **402** was prepared by the condensation of 7-benzoylindoline (**399**) with ethyl glycinate[315] (eq. 115). This condensation apparently occurred by way of Schiff base **400**. An alternative preparation of **402** involved treatment of 7-benzoyl-1-(bromoacetyl)indoline (**401**) with ammonia[316] (eq. 116).



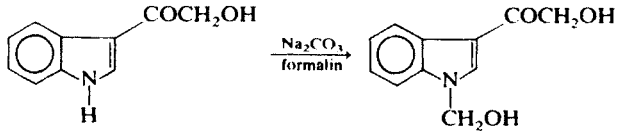
(115)

(116)

h. Alkylation of Nitrogen. Conjugation of the indole nitrogen with the 3-carbonyl group increases substantially the acidity of the N–H bond. Thus 3-acetylindole has a pK of 12.99 compared with a pK of 16.97 for indole. This relative acidity of 3-acylindoles allows the nitrogen to be alkylated with alkyl halides or sulfates in the presence of moderately strong bases. A frequently used combination is dimethyl sulfate and sodium hydroxide, for example, in the methylation of 3-propionylindole (**403**).[317] Sodium amide was used as the base in the alkylation of **403** with 3-(dimethylamino)propyl chloride to give **404** (eq. 117). Treatment of 3-acylindoles with sodium carbonate and formalin gave the corresponding 1-hydroxymethyl derivatives as illustrated by the conversion of 3-(hydroxyacetyl)indole (**405**) to **406**[318] (eq. 118).

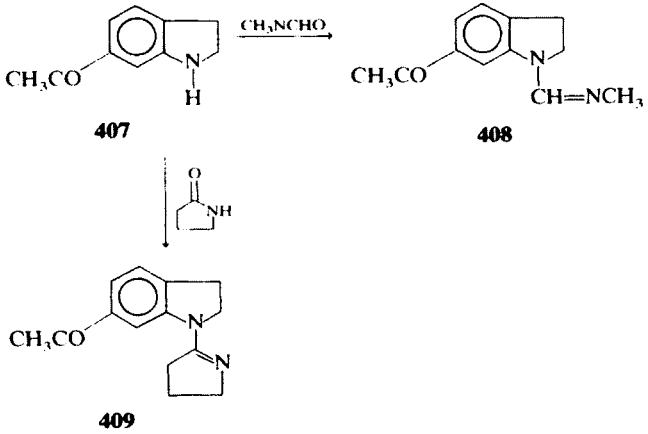


403 **404** (117)



405 **406** (118)

A series of 1-(iminomethyl)indolines was prepared by treating 3-acetylindolines with N-substituted amides. Thus **407** and N-methylacetamide gave **408**. The nitrogen could be in a ring, as exemplified by the synthesis of **409** from **407** and pyrrolidone[319] (Scheme 23).

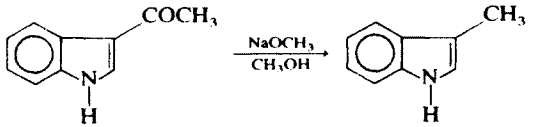


407 **408**

409

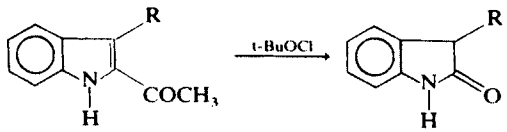
Scheme 23

i. CLEAVAGE OF THE ACYL GROUP. 3-Acylindoles are stable to dilute acid and alkali, but cleavage of the acyl group occurs in strong alkali at elevated temperature. Thus 3-acetylindole (**410**) gave skatole (**411**) when heated with sodium methoxide in methanol at 210–220°[320] (eq. 119). The formation of skatole can be interpreted as cleavage of the acetyl group (acetate is formed) followed by methylation of the resulting indolyl anion. When the cleavage of **410** was carried out in ethanol, the product was 3-ethylindole.[320] Similar results were reported for the cleavage of 3-acetyl-2-methylindole in methanol and ethanol.[320]



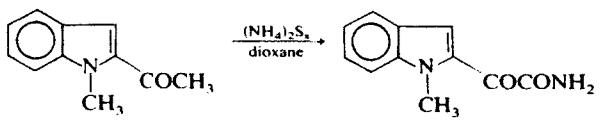
410 **411** (119)

Oxidation of 3-substituted 2-acetylindoles (**412**) with *t*-butyl hypochlorite gave the corresponding oxindoles (**413**)[321] (eq. 120).



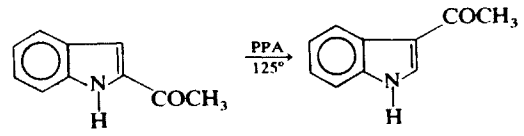
412 **413** (120)

j. MISCELLANEOUS REACTIONS. Application of the Willgerodt reaction to acetylindoles alkylated in nitrogen gave the corresponding glyoxalylamides.[322] For example, 2-acetyl-1-methylindole (**414**) was converted into **415** in 49% yield (eq. 121). 3-Acetylindoles substituted on nitrogen similarly gave the glyoxalylamides, but those unsubstituted on nitrogen did not give normal products.[322]

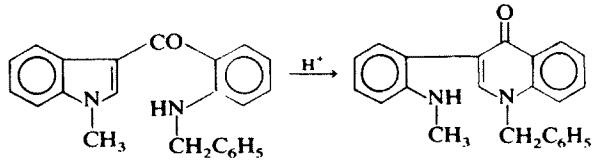


414 **415** (121)

The rearrangement of 2-acetylindole (**416**) to 3-acetylindole (**417**) was observed when **416** was heated at 125° in polyphosphoric acid[323] (eq. 122). Similar rearrangements in better yields were reported for a variety of 1-substituted 2-acetylindoles. They occurred with aluminum chloride, trifluoroacetic acid, or polyphosphoric acid catalysis.[324,325]



416 417 (122)



418 419 (123)

Treatment of 3-*o*-(benzylamino)benzoyl-1-methylindole (**418**) with acid resulted in rearrangement to quinolone **419**[248] (eq. 123).

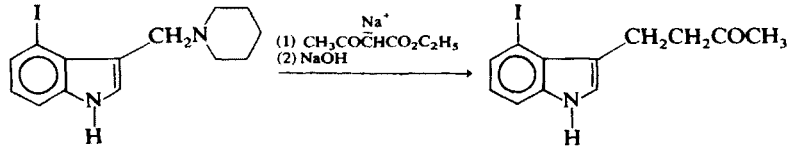
B. Carbonyl Groups in the Side Chain

1. *Preparation*

a. From Gramine-type Compounds. Treatment of 3-(dialkylaminomethyl)indoles such as **420** with the sodium salt of ethyl acetoacetate, followed by hydrolysis and decarboxylation, gave butanone derivatives such as **421**,[326,327] (eq. 124). In a related sequence, gramine methiodide (**422**) and 2-(methylsulfinyl)acetophenone afforded intermediate **423**, which was converted into **424** by aluminum amalgam reduction[328] (Scheme 24).

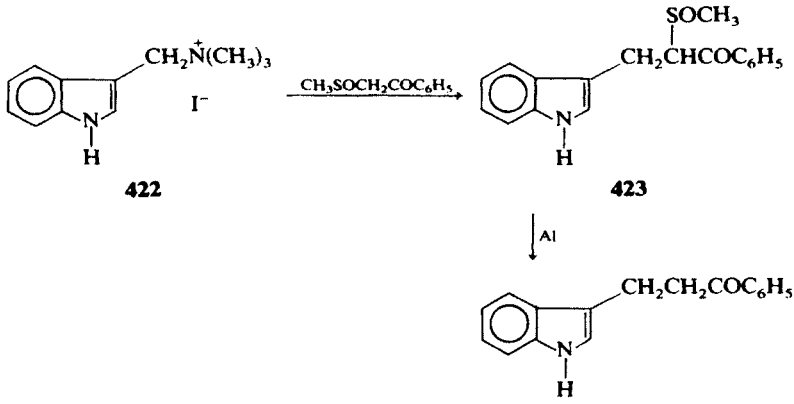
b. Michael-type Reactions. Condensation of methyl vinyl ketone with indole, 2-methylindole, skatole, or 2-phenylindole in the presence of acetic acid and acetic anhydride gave indolylbutanones in yields of 60–68%.[329,330] For example, 2-methylindole (**425**) and methyl vinyl ketone gave **426** (eq. 125).

c. With Diazo Compounds. When indole (**427**) was heated with diazoacetone in cyclohexane a moderate yield of 1-(3-indolyl)-2-propanone (**428**) was obtained (eq. 126). This product is probably formed by a carbene addition to indole.[331] Treatment of 1-acetylindole-4-acetaldehyde (**429**) with diazomethane gave 1-(1-acetyl-4-indolyl)-2-propanone, which was isolated as its semicarbazone **430**[332] (eq. 127).



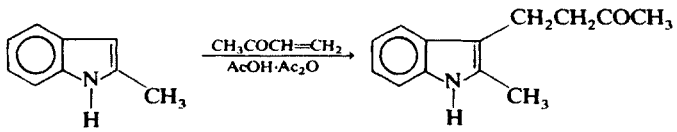
(124)

420 **421**



422 **423** **424**

Scheme 24



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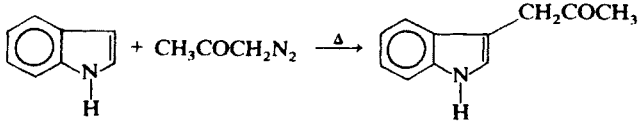
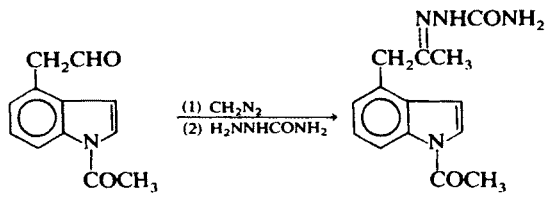
425 **426**



(126)

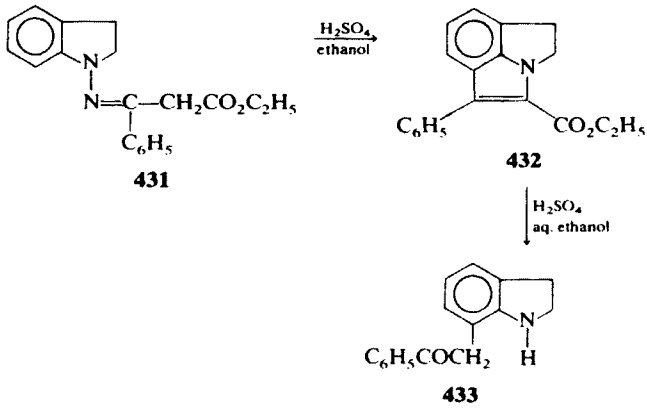
427 **428**



(127)

429 **430**

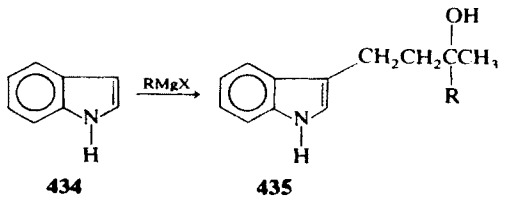
d. OTHER METHODS. An interesting rearrangement was obtained when indoline derivative **431** was treated with ethanolic sulfuric acid. This rearrangement corresponds to a variation of the Fischer indole synthesis and it gave tricyclic compound **432**. In contrast to ordinary indole-2-carboxylates, **432** was readily hydrolyzed by acid to cleave the indole system. The product was 7-phenacylindoline (**433**) which was isolated as its 1-acetyl derivative in overall yield of 75%[333] (Scheme 25).



Scheme 25

2. *Reactions*

Only a few reactions have been reported for the carbonyl groups of indolyl ketones with the carbonyl group in a side chain. However, it is anticipated that they would show normal carbonyl group reactivity. They should be more reactive to nucleophiles than the corresponding indolyl ketones in which the carbonyl group is attached to the 2- or 3-position. Among the carbonyl reactions reported are ketalization,[332] lithium aluminum hydride reduction to the corresponding alcohol,[331] and reductive amination.[334,335] Treatment with Grignard reagents produced the corresponding carbinols, as illustrated by the conversion of **434** into **435**[336] (eq. 128).



(128)

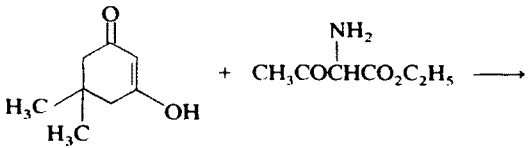
C. Carbonyl Group in the Six-Membered Ring

1. *Introduction*

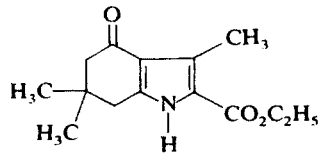
The 4-oxo-4,5,6,7-tetrahydroindoles have become prominent because one of them, molindone (**508**), is an established antipsychotic drug.[337] Following the discovery of this compound numerous analogues were prepared and tested. A variety of synthetic routes were developed for these analogues. 4-Oxo-4,5,6,7-tetrahydroindoles also are important because they can be dehydrogenated to give 4-hydroxyindoles, which are intermediates for the hallucinogens psilocin and psilocybin, the β-adrenergic blocking agent prindalol, and certain mitomycin analogues. The 6-oxooctahydroindole system is found in the structure of mesembrine and other alkaloids from *Sceletium* species. Some elegant syntheses of this system have been reported (Section III.C).

2. *Syntheses of 4-Oxo-4,5,6,7-tetrahydroindoles*

a. FROM 1,3-CYCLOHEXANEDIONES. The first preparation of a 4-oxo-4,5,6,7-tetrahydroindole (e.g., **438**) was reported in 1928.[338] It involved condensation of dimedone **436** with ethyl α-aminoacetoacetate **437**, which had been prepared from the corresponding α-oximinoketone (eq. 129). This process can be considered an example of the Knorr pyrrole synthesis. The α-aminoketone is usually not isolated in this synthesis. Rather, the α-oximinoketone is reduced by reagents such as zinc and acetic acid in the presence of the 1,3-cyclohexanedione. An example of this method is the synthesis of molindone precursor **439** form 1,3-cyclohexanedione **442** and oximinoketone **441**[339] (Scheme 26). Many other

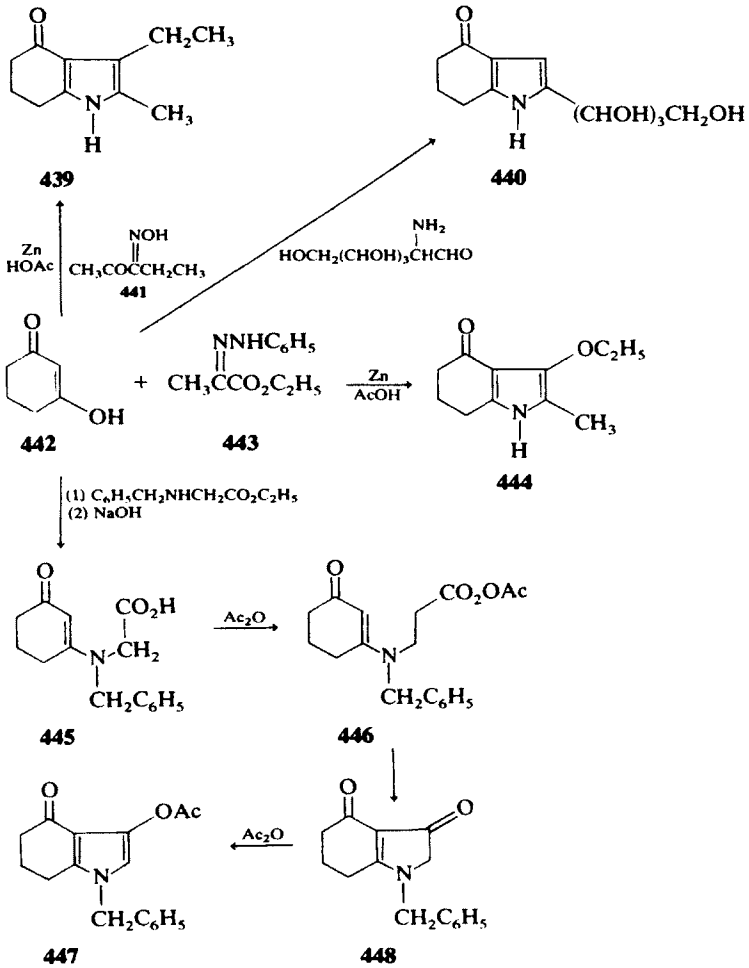


436 **437**



438 (129)

2,3-disubstituted compounds have been prepared by the Knorr synthesis.[340–344] Certain novel analogues, such as 2-arabino-4-oxo-4,5,6,7-tetrahydroindole (**440**) also have been prepared from **442**.[345,346] In this case 2-amino-2-deoxy-D-glucose was the α-aminoaldehyde.[346]

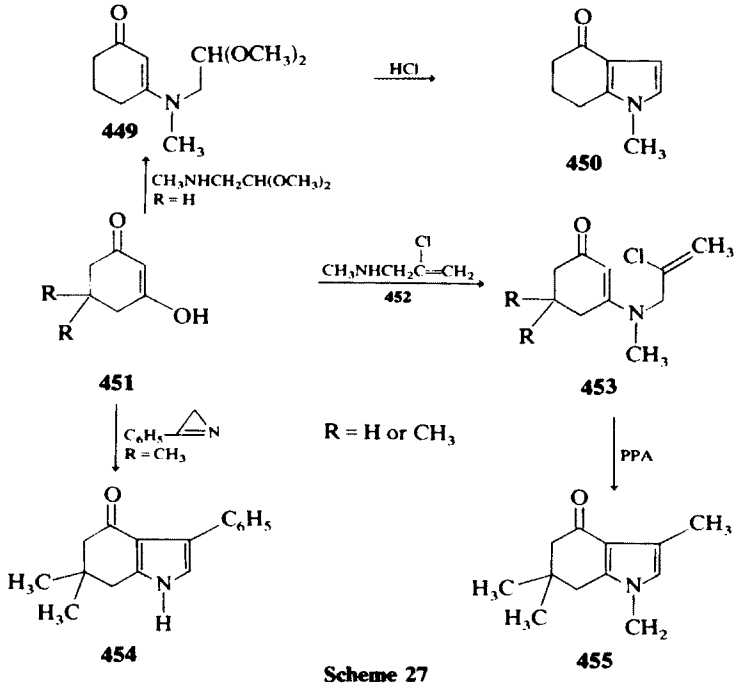


Scheme 26

A recent variant on the Knorr method involves the condensation of 1,3-cyclohexanedione (**442**) with the monoarylhydrazones of α-dicarbonyl compounds.[347,348] For example, **443**, the phenylhydrazone of ethyl pyruvate, and zinc–acetic acid gave 3-ethoxy-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (**444**)[347] (Scheme 26).

The intramolecular acylation of enamine-acids has been developed into a method for 3-acetoxy-4-oxo-4,5,6,7-tetrahydroindoles (e.g., **447**).[349] In this method, 1,3-cyclohexanedione (**442**) or its 5-methyl derivative is condensed with an α-aminoacetate derivative such as ethyl *N*-benzylglycinate. Following hydrolysis, the resulting free acid **445** is cyclized in the presence of acetic anhydride. This cyclization is thought to take place by way of the intermediate anhydride **446** and dione **448**[349] (Scheme 26).

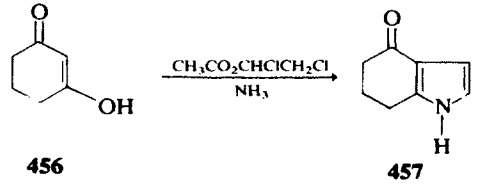
Condensation of 1,3-cyclohexanediones with amines bearing functional groups equivalent to ketones or aldehydes at the β-position, followed by acid-catalyzed cyclization, has provided two valuable synthetic methods. Thus **451** and 2-(methylamino)acetaldehyde dimethyl acetal gave the intermediate **449**, which cyclized on acidification to 1-methyl-4-oxo-4,5,6,7-tetrahydroindole (**450**) in 75% yield[350] (Scheme 27). In the second method, the addition of 2-(chloroallyl)enamines such as **452**, followed by treatment with polyphosphoric acid, gave 1,3-disubstituted products such as **455** in 30–48% yields[351] (Scheme 27).



Scheme 27

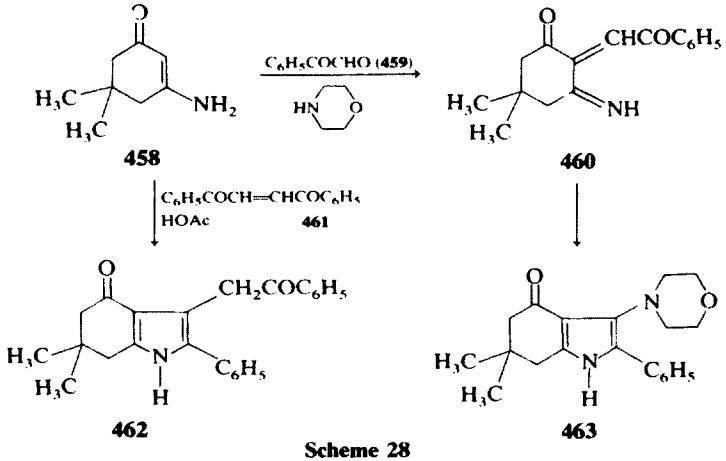
Two rather novel methods were investigated for the synthesis of 4-oxo-4,5,6,7-tetrahydroindoles. One method involved the formation of 3-phenyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindole (**454**) from dimedone (**451**) and 2-phenylazirine[352] (Scheme 27). The second method

was based on the Feist–Benary reaction. It featured the condensation of 1,3-cyclohexanedione (**456**) with 1,2-dichloroethyl acetate to give the parent 4-oxotetrahydroindole **457** in low yield[353] (eq. 130). Alternative preparations of **457** are described below.

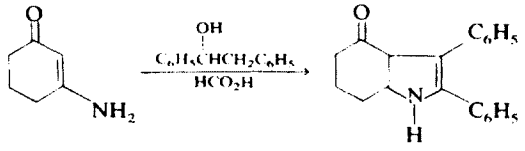


456 **457** (130)

b. From 3-Aminocyclohex-2-en-1-ones. The 3-amino derivative of dimedone (**458**) condensed with dicarbonyl compounds such as **459** and **461** to give 4-oxo-4,5,6,7-tetrahydroindoles **462** and **463**, respectively.[354,355] The latter example was thought to involve **460** as a key intermediate[355] (Scheme 28). 1,2-Diphenylethanol and 3-aminocyclohexenone **464** gave **465** when they were heated with a catalytic amount of formic acid[356] (eq. 131).

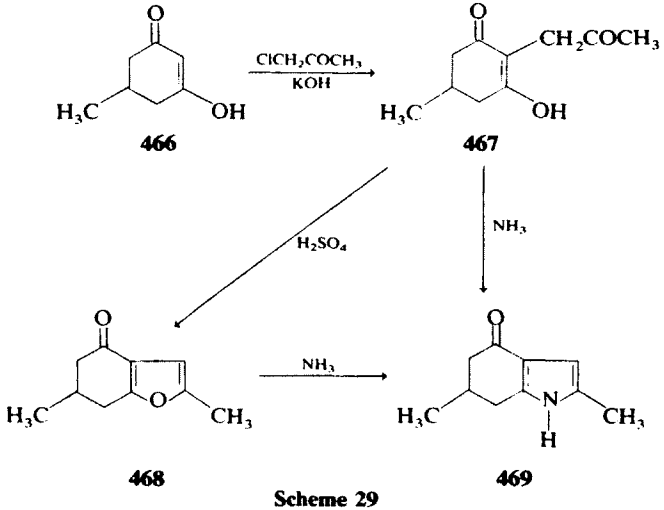


Scheme 28

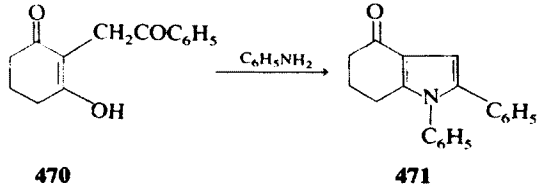


(131)

c. FROM 2-SUBSTITUTED 1,3-CYCLOHEXANEDIONES. This method is based on alkylation of the enolate of a 1,3-cyclohexanedione with an α-haloketone, followed by condensation of the resulting trione with ammonia or a primary amine. It is highly versatile because it can produce compounds with substituents at positions 1, 2, 3, or 6.[340,342,357-360] Thus the addition of chloroacetone to a solution of 5-methyl-1,3-cyclohexanedione (**466**) in methanolic KOH afforded the 2-acetonyl derivative **467**, which was converted into 2,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindole (**469**) upon heating with ammonia in a pressure vessel[357] (Scheme 29). Products with substituents on nitrogen were formed by condensation of the trione with a primary amine, as shown by the synthesis of 1,2-diphenyl derivative **471** from **470**[358] (eq. 132). Alternatively, the nitrogen of a 4-oxo-4,5,6,7-tetrahydroindole could be substituted by way of its alkali metal salts (Section III.C.3). Another useful method for 1-substituted compounds (e.g., **474**) was provided by alkylation of 1,3-cyclohexanedione enolate (**472**) with propargyl bromide, followed by condensation of the intermediate **473** with benzylamine in the presence of cuprous chloride[361] (Scheme 30). This method has not been widely exploited although it should give a variety of 4-oxo-4,5,6,7-tetrahydroindoles.



Scheme 29



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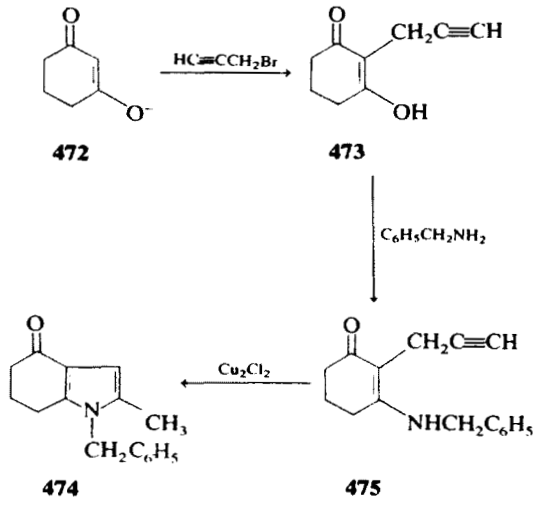
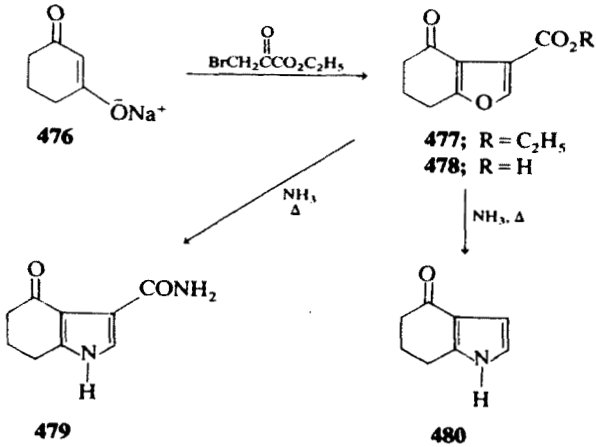


472 **473** **474** **475**

Scheme 30

d. FROM 4-OXO-4,5,6,7-TETRAHYDROBENZOFURANS. When this type of compound is heated with ammonia or a primary amine it undergoes ring opening and reclosure to the corresponding 4-oxotetrahydroindole. For example, **468** heated with ammonia in methanol gave **469** (Scheme 29). The 4-oxotetrahydrobenzofurans can be prepared in a variety of ways. One way is the ring closure of triones such as **467** in concentrated sulfuric acid[357] (Scheme 29). Another method involves the treatment of the sodium salt of 1,3-cyclohexanedione (**476**) with ethyl bromopyruvate.

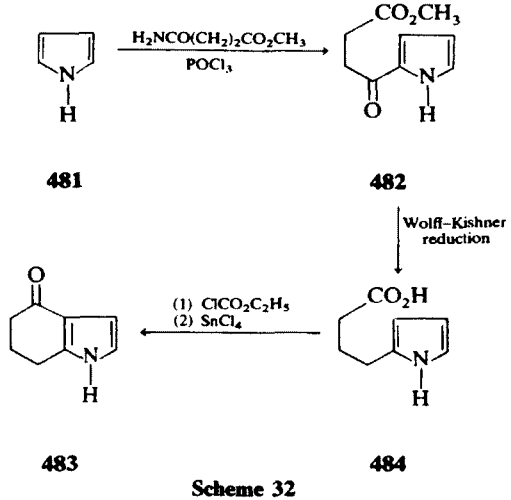


476 **477; R = C_2H_5** **478; R = H** **479** **480**

Scheme 31

The ethyl 4-oxotetrahydrobenzofuran-3-carboxylic acid **477** formed by this reaction was converted into 4-oxo-4,5,6,7-tetrahydroindole-3-carboxamide (**479**) upon heating with ammonia in methanol. If **477** is hydrolyzed to the carboxylic acid (**478**) before treatment with ammonia, the product is the unsubstituted 4-oxotetrahydroindole **480**[357] (Scheme 31).

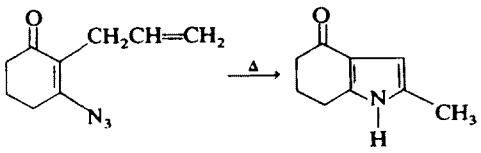
e. From 4-(2-Pyrrolyl)butyric Acids. This method is versatile in principle. However, only one example is known at present. In this example, 4-(2-pyrrolyl)butyric acid (**484**) was prepared from pyrrole (**481**) by a sequence involving acylation and Wolff–Kishner reduction (Scheme 32). The mixed anhydride of **484** was cyclized in the presence of zinc chloride or stannic chloride[362] (Scheme 32).



481 **482** **483** **484**

Scheme 32

f. Miscellaneous Methods. Thermal decomposition of 3-azido-2-allylcyclohex-2-en-1-one (**485**) gave a very low yield of 2-methyl-4-oxo-4,5,6,7-tetrahydroindole (**486**)[363] (eq. 133).

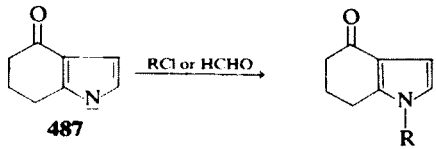


(133)

485 **486**

3. *Reactions of 4-Oxo-4,5,6,7-tetrahydroindoles*

a. SUBSTITUTION ON NITROGEN. Owing to conjugation of the carbonyl group with the pyrrole nitrogen in 4-oxo-4,5,6,7-tetrahydroindoles, the hydrogen on this nitrogen is relatively acidic.[360] It can be removed by strong bases and the resulting anion (**487**) is stable. This anion has been alkylated,[364,365] acylated,[360] and converted into benzyl, benzoyl, and benzenesulfonyl derivatives (**488–490**).[360] It also gave a hydroxymethyl derivative **491** when it was treated with formaldehyde.[366] These transformations are illustrated in eq. 134. Certain of the *N*-substituents have been useful in controlling the reactivity of the 4-oxotetrahydroindole molecule. Thus the benzyl derivative **488** allowed anion formation and reaction at the methylene group adjacent to the carbonyl.[367] Debenzylation was then accomplished by sodium-in-ammonia reduction.[360,367] The acetyl group was unstable even in hot methanol, but the benzoyl group (e.g., **489**) proved to be a useful substituent. It deactivated the pyrrole ring to the extent that electrophilic substitution occurred at the methylene group adjacent to the carbonyl (by way of the enol). It was removed by mild basic hydrolysis.[360] The benzenesulfonyl group of **490** similarly deactivated the pyrrole ring, but it was difficult to remove.[360]



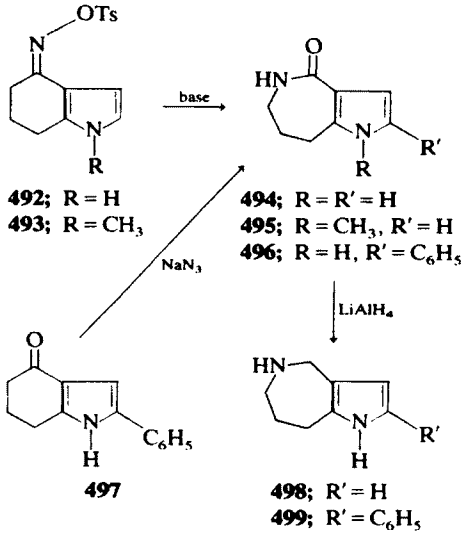
487

(134)

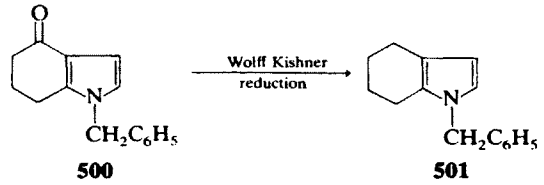
488; R = $CH_2C_6H_5$
489; R = COC_6H_5
490; R = $SO_2C_6H_5$
491; R = CH_2OH

b. REACTIONS OF THE CARBONYL GROUP. Conjugation of the carbonyl group with the pyrrole nitrogen renders it less reactive than normal carbonyls toward nucleophiles. Thus 4-oxo-4,5,6,7-tetrahydroindoles do not readily form bisulfite adducts or cyanohydrins,[360] However, they do give oximes. The oxime *p*-toluenesulfonates **492** and **493** of 4-oxo-4,5,6,7-tetrahydroindole and its 1-methyl homologue underwent Beckmann rearrangement to give tetrahydropyrrolo[3,2-*c*]azepin-4-ones **494** and **495**[368,369] (Scheme 33). Pyrroloazepin-4-ones also were produced by the action of sodium azide on 4-oxo-4,5,6,7-tetrahydroindoles, as illustrated by the conversion of **497** into **494**[370] (Scheme 33). These products were reduced by lithium aluminum hydride to the corresponding pyrroloazepines[368,370] (Scheme 33). 4-Oxo-4,5,6,7-tetrahydroindoles undergo

Wolff–Kishner reduction in the presence of excess hydrazine to yield the corresponding 4,5,6,7-tetrahydroindoles.[360,371] For example **500** was readily converted into **501** by this method (eq. 135). However, when **501** was treated with a limited amount of hydrazine the product was a ketazine.[360]

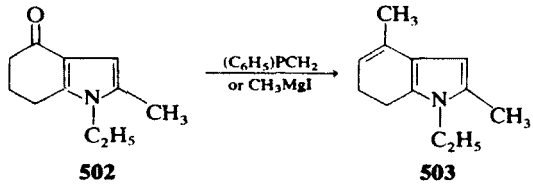


Scheme 33

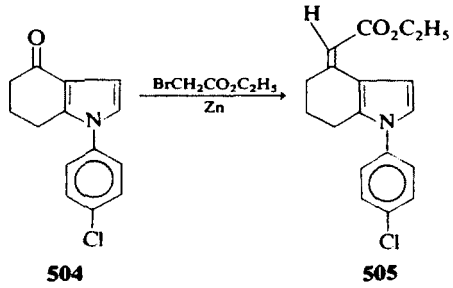


(135)

Because *N*-unsubstituted-4-oxo-4,5,6,7-tetrahydroindoles have an acidic hydrogen, it has not been possible to react their carbonyl groups with Grignard or Wittig reagents, even when excesses of such reagents have been used.[360] However, these reagents react readily with *N*-alkyl analogues, as shown by the conversion of **502** into the corresponding 4-methyl-6,7-dihydroindole derivative **503**[360] (eq. 136). The Reformatsky reaction was used to prepare a series of 1-aryl-4-carbethoxymethylene derivatives such as compound **505** (eq. 137). These derivatives were later converted into 3-indoleacetic acid derivatives, which showed significant antiinflammatory activity.[372]



(136)

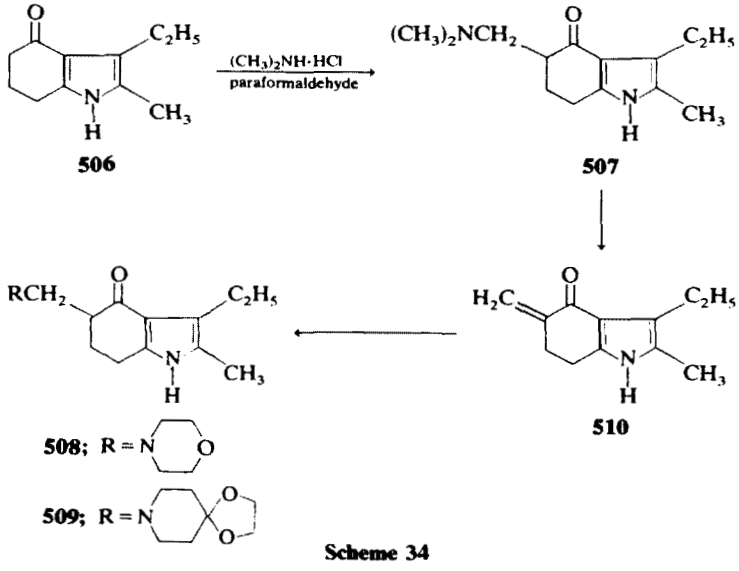


(137)

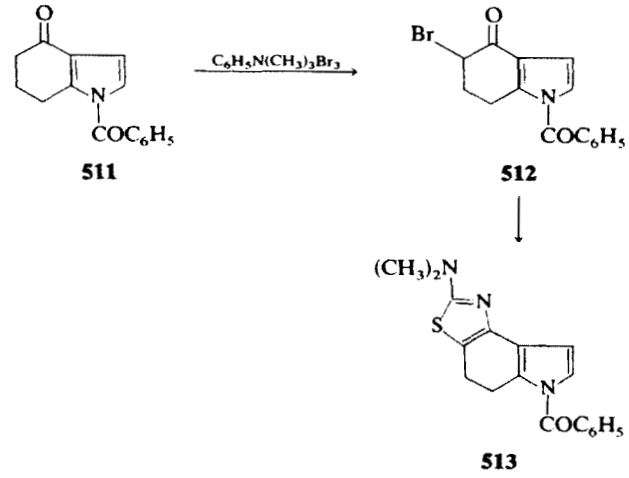
c. Reactions of the Methylene Group Adjacent to the Carbonyl. Mannich reactions of 4-oxo-4,5,6,7-tetrahydroindoles are sluggish and require forcing conditions, but they have been utilized very extensively owing to the important antipsychotic and sedative actions of certain of the products. The most important of these products is the 4-morpholinomethyl derivative (**508**) of 3-ethyl-3-methyl-4-oxo-4,5,6,7-tetrahydroindole (**506**). This compound, known as molindone (Moban®), has become important as an antipsychotic drug with antidepressant properties.[373,374] Molindone was not prepared directly from **506** because the Mannich reaction with morpholine was unfavorable. It had to be prepared by a route which included formation of the 5-(dimethylamino)-methyl derivative **507**, Hofmann elimination to the 5-methylene intermediate **510**, and Michael addition of morpholine[338,375] (Scheme 34). Numerous analogues of molindone have been made by this method or by direct Mannich reaction.[376,377] One analogue with interesting antiemetic properties is **509**[373,379] (Scheme 34).

Bromination of 4-oxo-4,5,6,7-tetrahydroindoles takes place in the pyrrole ring (Section III.C.3.d). However, if the nitrogen is substituted with a strong electron-withdrawing group like benzoyl or benzenesulfonyl, the bromine can be introduced on the methylene group adjacent to the carbonyl as in **511** to **512**.[360] Such bromoketones have been used to prepare aminothiazole derivatives, as illustrated by the condensation of **512** with dimethylthiourea to give **513**[360] (Scheme 35).

N-Substituted 4-oxo-4,5,6,7-tetrahydroindoles such as **514** give enolate anions when treated with base, although the N–H analogues do not.

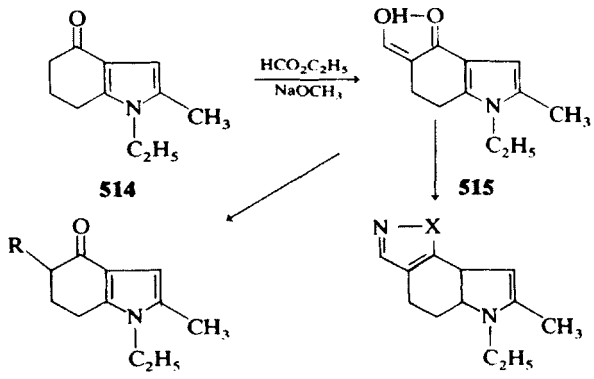


Scheme 34



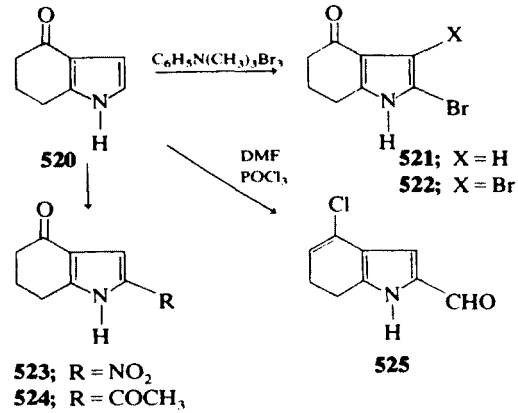
Scheme 35

These enolate anions react with ethyl formate to give the corresponding 5-hydroxymethylene derivatives (e.g., **515**). Such hydroxymethylene derivatives were useful for the introduction of other substituents into the 5-position, as illustrated by the preparation of 5-methyl and 5-cyano derivatives (**516** and **517**, respectively).[360] They also were used to prepare tricyclic products with isoxazole rings (**518**) or pyrazole rings (**519**)[360,367] (Scheme 36).



Scheme 36

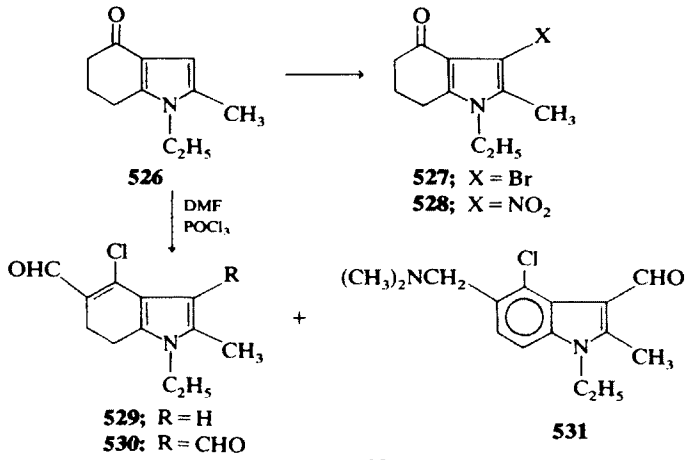
d. ELECTROPHILIC SUBSTITUTION. 4-Oxo-4,5,6,7-tetrahydroindole (**520**) has three possible sites for electrophilic substitution. Two of these are in the pyrrole ring and the third is afforded by enolization of the carbonyl group. Acid-catalyzed deuterium exchange rates were about equal for the two pyrrole ring hydrogens on carbon and these were somewhat faster than the exchange rate of the protons at the 5-position.[380] This result suggests that there should be minimal preference for the site of electrophilic substitution and that small steric or electronic effects in analogues of **520** might determine the site of substitution. These expectations were generally confirmed by a series of electrophilic substitutions.[380] Thus bromination, nitration, and acetylation of **520** all occurred preferentially at the 2-position, affording **521**, **523**, and **524**,



Scheme 37

respectively. With molecular bromine as the brominating agent, 2,3-dibromo derivative **522** was isolated. Vilsmeier–Haack formylation of **520** gave a low yield of **525**, a 2-formyl derivative in which the keto group was converted into a vinyl chloride. The *N*-benzyl analogue of **525** gave the corresponding product in better yield[380] (Scheme 37).

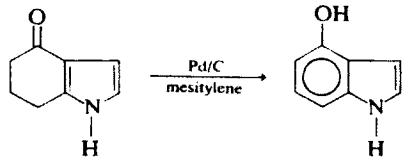
When the 2-position of a 4-oxo-4,5,6,7-tetrahydroindole is substituted with a methyl group, electrophilic substitution occurs preferentially at the 3-position. This preference is illustrated by the bromination and nitration of 1-ethyl-2-methyl derivative (**526** to **527** and **528**, respectively). Vilsmeier–Haack formylation of **526** appears to be an exception to this rule since with one equivalent of formylating complex the only product isolated (low yield) was the 4-chloro-5-formyl derivative **529**. Two equivalents of formylating complex converted **526** into a mixture of 3,5-diformyl derivative **530** and the interesting 5-dimethylaminomethyl-3-formylindole **531** (Scheme 38). Similar products were given by the 6-methyl homologue of **526**.[380]



Scheme 38

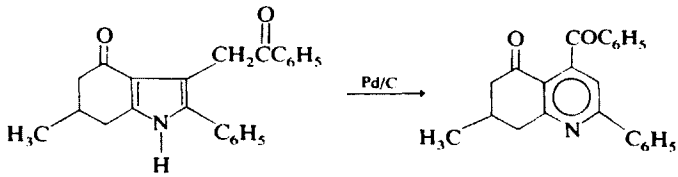
As mentioned in Section III.C.3.c, bromination of 4-oxo-4,5,6,7-tetrahydroindoles with electron-withdrawing groups on nitrogen occurred at the 5-position. A weak electron-withdrawing group such as bromine at the 2-position allowed subsequent bromination to take place at the 3-position, as in **521** to **522**, but the 2-acetyl substituent directed bromination to the 5-position and also to the acetyl methyl group. Bromination of 2-nitro derivative **523** occurred at the 5-position in tetrahydrofuran as solvent, but it took place at the 3-position in diemthylformamide.[380]

e. DEHYDROGENATION TO 4-HYDROXYINDOLES. Dehydrogenation of 4-oxo-4,5,6,7-tetrahydroindoles provides in some instances convenient routes to the corresponding 4-hydroxyindoles. Since certain other substituents can be introduced prior to dehydrogenation, a variety of 4-hydroxyindoles not readily obtained by other procedures are afforded by this method.[360] The usual method of dehydrogenation involves heating with palladium on charcoal in an aromatic hydrocarbon solvent such as cumene or mesitylene.[380] Thus 4-hydroxyindole (**533**) was prepared from **532** in good yield when mesitylene was used[381] (eq. 138). Various 4-oxo-4,5,6,7-tetrahydroindoles with alkyl substituents at the 1-, 2-, 3-, or 6-positions were similarly dehydrogenated to 4-hydroxyindoles,[360,382,383] However, a 5-methyl substituent drastically reduced the extent of dehydrogenation, possibly owing to steric hindrance to enolization. The presence of electronegative substituents such as acetyl or carboxylic acid at the 2- or 3-positions prevented dehydrogenation to 4-hydroxyindoles.[360,282] Attempted dehydrogenation of 5-methyl-3-phenacyl-2-phenyl-4-oxo-4,5,6,7-tetrahydroindole (**534**) gave a 5–oxo-4,5,6,7-tetrahydroquinoline (**535**) rather than a 4-hydroxyindole[354] (eq. 139).



(138)

532 **533**

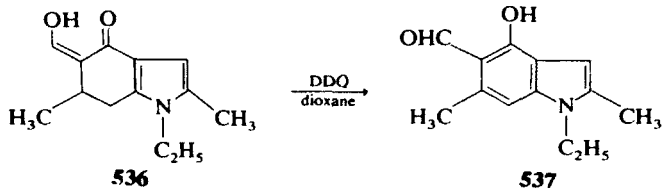


(139)

534 **535**

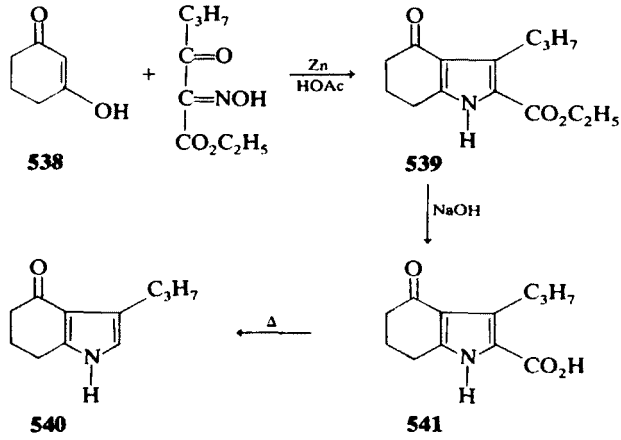
Dehydrogenation could also be effected by dichlorodicyanobenzoquinone (DDQ), but the product indoles were unstable to this quinone unless they contained an additional electron-withdrawing group. Thus 5-hydroxymethylene derivative **536** was converted into 4-hydroxyindole-5-carboxaldehyde **537** in 51% yield by this method[360] (eq. 140).

Many of the tetrahydroindoles and 6,7-dihydroindoles obtained from 4-oxo-4,5,6,7-tetrahydroindoles as described in Section III.C.3.c could also be dehydrogenated to indoles by catalytic or quinone methods.[360,372]



536 537 (140)

f. Decarboxylation of Carboxylic Acid Derivatives. The decarboxylation of 4-oxo-4,5,6,7-tetrahydroindole-2-carboxylic acids can be accomplished readily at higher temperatures.[338,382] This reaction is useful since it allows the preparation of a number of 3-alkyl-substituted 4-oxo-4,5,6,7-tetrahydroindoles. The route to these compounds originates with condensation of 1,3-cyclohexanedione and α-oximino-β-keto esters. Hydrolysis of the resulting 4-oxotetrahydroindole-2-carboxylic acid esters then gives the carboxylic acids. This route may be illustrated by the preparation of 3-propyl-4-oxo-4,5,6,7-tetrahydroindole **540** from 1,3-cyclohexanedione (**538**) as outlined in Scheme 39.[382]



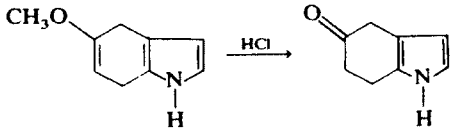
538 539 540 541

Scheme 39

4. *5-Oxo-4,5,6,7-tetrahydroindoles*

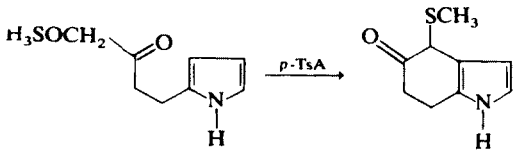
The parent compound of this type, **543** was prepared by acid hydrolysis at pH 3 of the enol ether **542** obtained from Birch reduction of 5-methoxyindole[383] (eq. 141). A similar route gave the 1-methyl homologue of **543**. These products were unstable and of limited value in

indole synthesis. Compound **543** did give a Wittig reaction with (carboxymethylene)triphenylphosphorane.[383] 4-Methylthio-2-phenyl-5-oxo-4,5,6,7-tetrahydroindole (**545**) was formed by the acid-catalyzed cyclization of pyrrolyl sulfoxide **544**[384] (eq. 142).



(141)

542 **543**

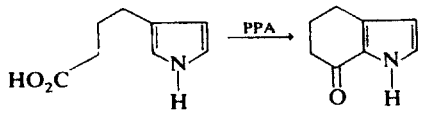


(142)

544 **545**

5. *7-Oxo-4,5,6,7-tetrahydroindoles*

Compounds in this family, including the parent **547**, were prepared by ring closure of 4-(3-pyrrolyl) butyric acid derivatives (e.g., **546**) in the presence of polyphosphoric acid[385] (eq. 143). Catalytic dehydrogenation of **547** gave 7-hydroxyindole.[385] 4-Phenyl-7-oxo-4,5,6,7-tetrahydroindole (**551**) was formed by condensation of pyrrolylmagnesium bromide (**548**) with 4-phenylbutyrolactone, followed by acid-catalyzed ring closure. Treatment of **551** with ethyl cyanoactate gave compound **550**[386] (Scheme 40).

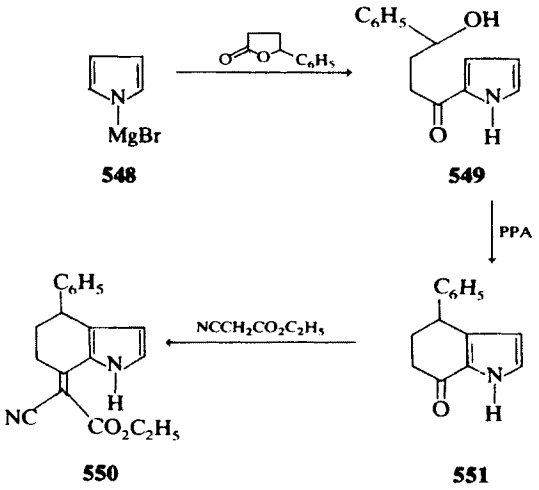


(143)

546 **547**

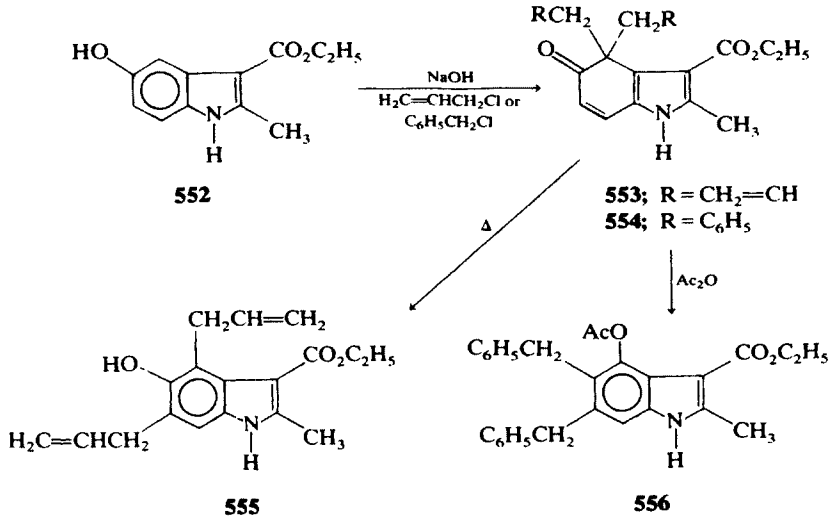
6. *5-Oxo-4,5-dihydroindoles*

This type of product is formed when alkali metal salts of 5-hydroxyindole-3-carboxylic acid esters are alkylated or acylated. Thus **552** gave 4,4-diallyl derivative **553** when it was treated with sodium hydroxide and allyl chloride.[387] Compound **553** underwent rearrangement to 4,6-diallyl-5-hydroxyindole **555** upon heating[387] (Scheme 41). The 4,4-dibenzyl



Scheme 40

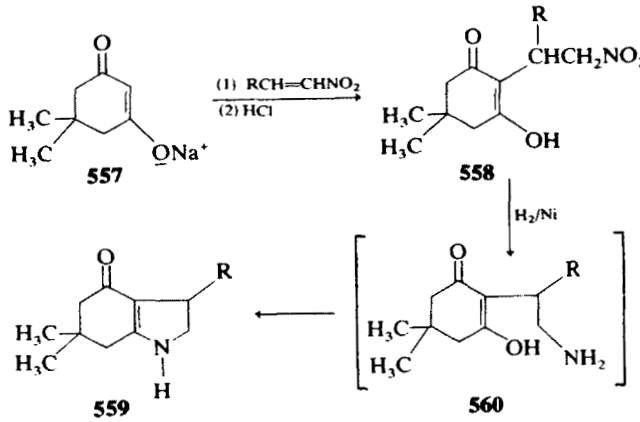
analogue **554** gave a different course of rearrangement when it was heated in acetic ahydride. In this case the product was 5,6-dibenzyl-4-acetoxyindole **556**[388] (Scheme 41). A variety of other 4,4-disubstituted 5-oxo-4,5,6,7-tetrahydroindoles have been prepared from **552**.[387,389]



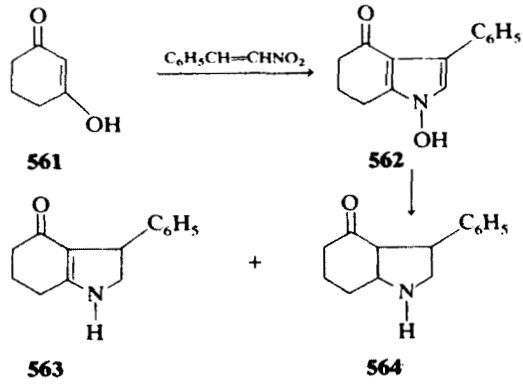
Scheme 41

7. *4-Oxo-2,3,4,5,6,7-hexahydroindoles*

A number of examples of this system are known. The main route for their preparation involves condensation of the enolate anion of a 1,3-cyclohexanedione (usually dimedone, **557**) with an alkyl derivative of nitroethylene. Catalytic reduction of the resulting 2-(2-nitroethyl)-1,3-cyclohexanedione **558** then gives the corresponding amino derivative **560**, which cyclizes to the hexahydroindole **559**[390–392] (Scheme 42). Derivatives of **559** have been prepared in which R is methyl, ethyl, and propyl.



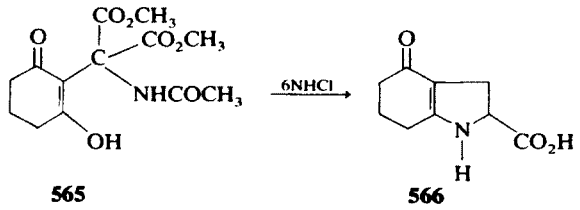
Scheme 42



Scheme 43

When 1,3-cyclohexanedione (**561**) was treated with β-nitrostyrene, the reaction took a different course and 1-hydroxy-4-oxo-3-phenyl-4,5,6,7-tetrahydroindole (**562**) was isolated. Catalytic reduction of **562** gave a mixture of the 4-oxohexahydroindole derivative **563** and 4-oxo-octahydroindole derivative **564**[393] (Scheme 43).

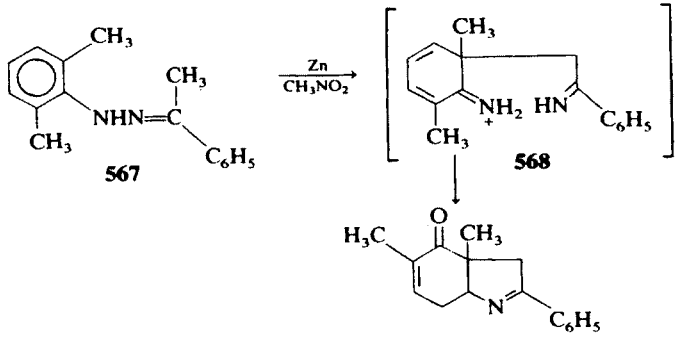
The 2-carboxylic acid derivative **566** of 4-oxo-2,3,4,5,6,7-hexahydroindole was prepared by a route involving hydrolysis of the amide and ester groups of **565** followed by ring closure and decarboxylation[394] (eq. 144).



565 566 (144)

8. *4-Oxo-3a,4,7,7a-tetrahydro-3H-indolenines*

A structure of this type (**569**) has been obtained by treatment of acetophenone 2,6-dimethylphenylhydrazone (**567**) with zinc chloride in nitromethane or nitrobenzene.[395,396] Cation **568** is thought to be an intermediate in this transformation[397] (Scheme 44).

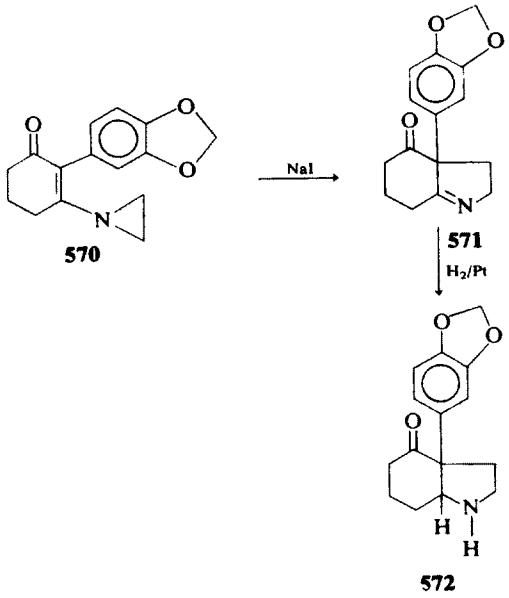


567 568 569

Scheme 44

9. *4-Oxo-3,3a,4,5,6,7-hexahydro-2H-indolenines*

Examples of this structural type have been obtained by iodide-catalyzed rearrangement of 2-substituted 3-ethyleneimine derivatives of 1,3-cyclohexanedione, as illustrated by the conversion of **570** into **571**.



Scheme 45

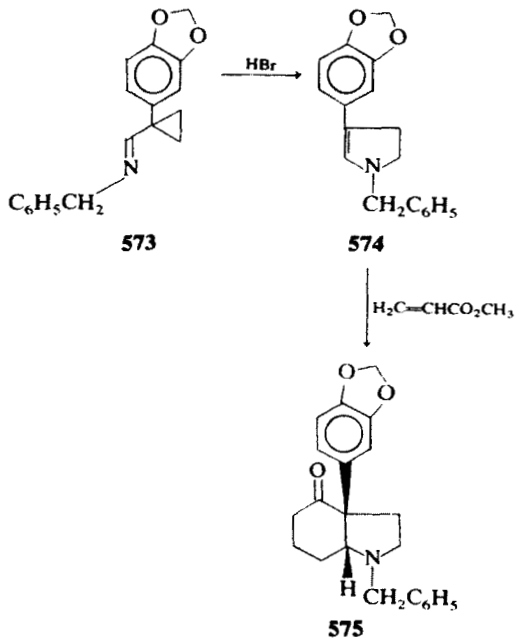
Catalytic reduction of **571** gave the corresponding octahydroindole derivative **572**[398] (Scheme 45). This derivative was an important intermediate in the synthesis of the alkaloid crinine.[399]

10. *4-Oxooctahydroindoles*

4-Oxooctahydroindoles have been synthesized by a variety of ingenious methods. One such method already was described for compound **572**. An interesting route to the alkaloid elivesine (dihydrocrinine) was based on the rearrangement of a cyclopropylimine **573** to a 2-pyrroline **574**, followed by annealation with methyl vinyl ketone to give the 4-oxotetrahydroindole **575**[400] (Scheme 46). Another route based on annealation involved the treatment of 2-methylenepyrrolidine **576** with acrylyl chloride and triethylamine to give **577**[401] (eq. 145). Photocyclization of compound **578** afforded 4-oxooctahydroindole **579** in 66% yield[402] (eq. 146).

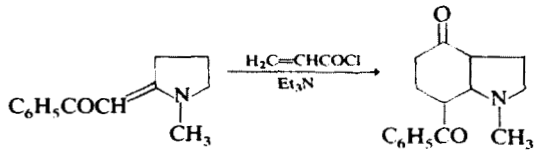
11. *6-Oxo-2,3,3a,4,5,6-hexahydroindoles and 6-Oxooctahydroindoles*

The 6-oxooctahydroindole nucleus is present in mesembrine (**581**) and related alkaloids. Δ^7-Mesembrenone (**588**) is the corresponding 6-oxo-2,3,3a,4,5,6-hexahydroindole. A number of total syntheses of these



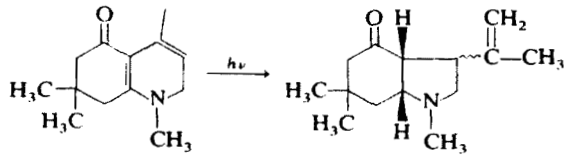
573 **574** **575**

Scheme 46



(145)

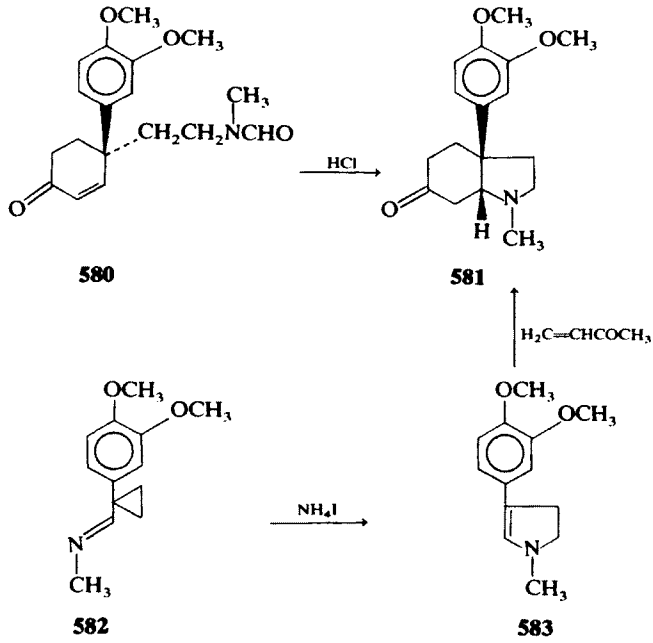
576 **577**



(146)

578 **579**

alkaloids and their analogues have been reported.[403–407] They provide much of the methodology for the construction of the ring systems just named. Thus the acid-catalyzed hydrolysis and ring closure of 4,4-disubstituted cyclohex-2-en-1-one **580** gave (+)-mesembrine (**581**) (Scheme 47). In a route closely related to the one described for the synthesis of elivesine (Section III.B.10), (+)-mesembrine (**581**) was synthesized by iodide-catalyzed rearrangement of cyclopropylimine **582**



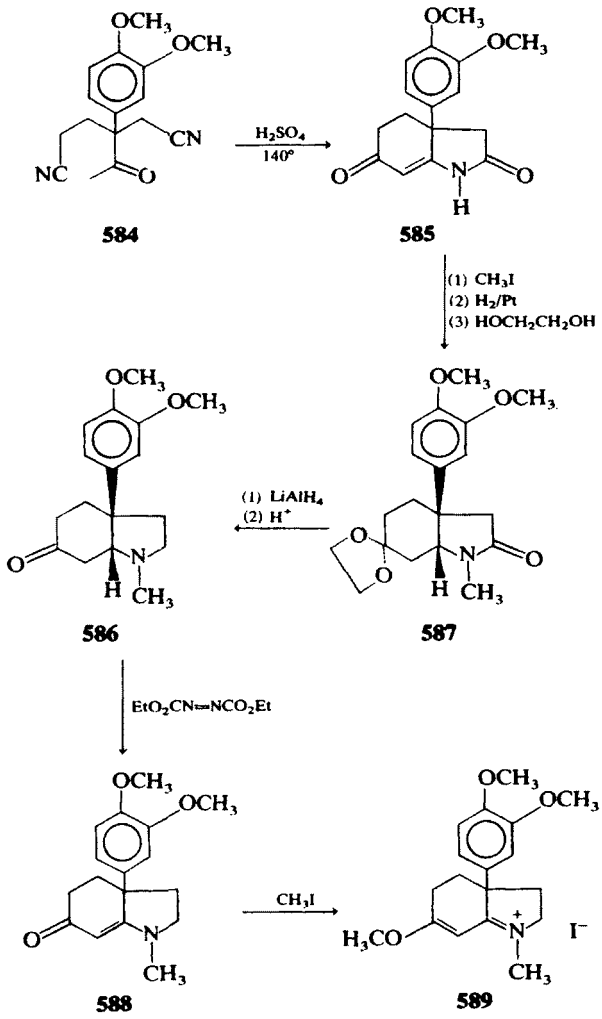
Scheme 47

to pyrroline **583**, followed by annealation with methyl vinyl ketone[404] (Scheme 47).

2-Oxo-Δ^7-mesembrenone (**585**) was prepared in 60% yield by the double ring closure of dicyanoketone **584**.[405] *N*-methylation of **585** followed by catalytic hydrogenation, selective ketalization of the 6-carbonyl group, lithium aluminum hydride reduction, and deketalization afforded (±)-mesembrine (**586**)[406,407] (Scheme 48). An unusual oxidation in which diethyl azodicarboxylate converted mesembrine (**586**) into Δ^7-mesembrenone **588** was reported.[408] Treatment of **588** with methyl iodide gave *O*-methylation to **589**, as anticipated for an enamino ketone[408] (Scheme 48).

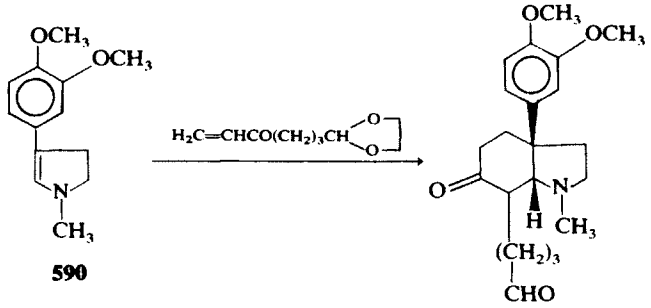
The annealation of pyrroline **590** with 4-(ethylenedioxy)butyl vinyl ketone gave a 6-oxooctahydroindole, which was converted into *Sceletium* alkaloid A_4 (**591**) upon hydrolysis of the ketal[409] (eq. 147).

Key steps in a synthesis of the alkaloid γ-lycorane (**594**) included the photochemical cyclization of 1-substituted 6-oxohexahydroindole **593** to give the tetracyclic derivative **595**, followed by lithium aluminum hydride reduction and catalytic hydrogenation. Compound **593** had been prepared by the treatment of 6-methoxy-2,3,4,5-tetrahydroindole **592** with



Scheme 48

3,4-methylenedioxybenzoyl chloride in aqueous alkali[410] (Scheme 49). Another synthesis of 1-substituted 6-oxo-2,3,3a,4,5,6-hexahydroindoles was based on intramolecular γ-alkylation of the anion derived from 3-substituted cyclohex-2-en-1-ones. Thus **596** gave 1-benzyl-6-oxohexahydroindole **597** when it was treated with lithium diisobutylamide[411] (eq. 148). 1-Substituted 6-oxooctahydroindole **599** was obtained by the acid-catalyzed cyclization of 4-(2-aminoethyl)-cyclohex-3-en-1-one derivative **598**[412] (eq. 149).



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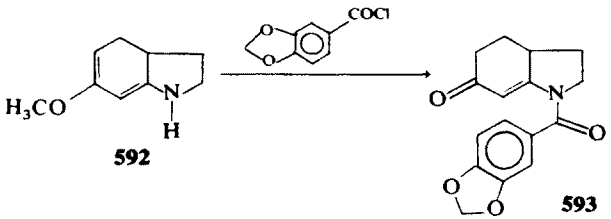
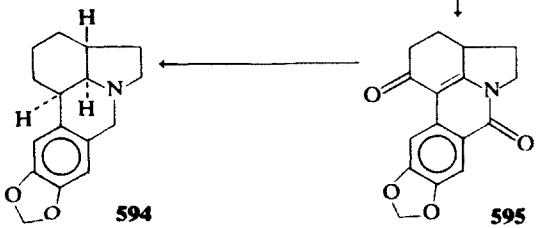
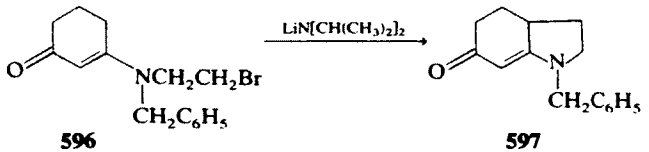




Scheme 49



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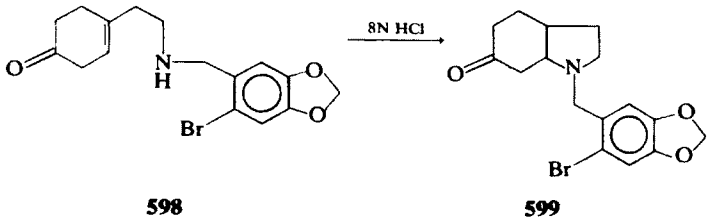


(149)

IV. Indolediones

A. Introduction

Indoles with two carbonyl groups in their six-membered rings are considered in this section. They include indole-4,5-diones, indole-4,7-diones, indole-5,6-diones, indole-6,7-diones, and 5,6-dihydroindole-4,7-diones. Most of these compounds exhibit characteristic quinone properties, and some have been termed indoloquinones. The indole-4,7-diones are the most numerous group of compounds in this section, since many of them were prepared as analogues of the mitomycin antibiotics.[413,414]

Perhaps the most important group is the 2,3-dihydroindole-5,6-diones, known as aminochromes. This group has been studied extensively and recently reviewed.[415,416] The aminochromes are formed by oxidation of catecholamines, including those which are important neurotransmitters. Specific aminochromes are often given trivial names based upon the catecholamine from which they are derived. For example, adrenochrome (**606**) is obtained from the oxidation of adrenalin (epinephrine). Aminochromes are represented best as a zwitterion with positive charge on the nitrogen and negative charge on the 6-oxygen.[417,418]

Aminochromes are thought to have considerable biological importance, since they are considered to be precursors to the melanin pigments.[419,420] Certain aminochromes have been suggested as minor or abnormal metabolites of catecholamines and two examples, **600** and **601**, were isolated from the urine of mentally retarded children,[421] Other physiological effects of aminochromes include stimulation of prostaglandin F2α formation[422] and stimulation of enzymes in the hexose monophosphate shunt.[423] Certain semicarbazone derivatives of aminochromes (e.g., **621**) show significant hemostatic activity.[424–426]

The 2,3-indolediones (isatins) are not treated in this section since they are the subject of a later chapter.

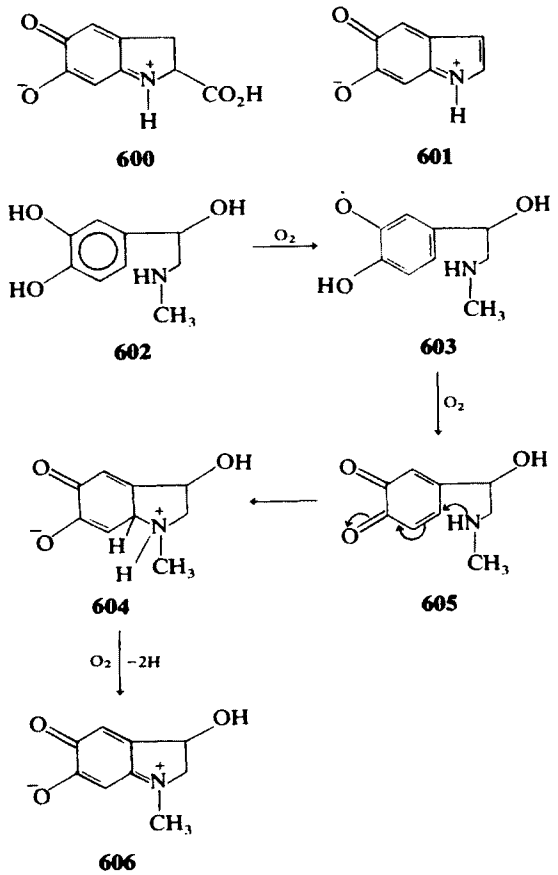
B. Aminochromes

1. *Formation*

a. Oxidation of Catecholamines by Oxygen. Catecholamines are rapidly oxidized by atmospheric oxygen in alkaline solutions.[427,428] At neutral pH the oxidation is slower. These reactions are complex and presumably involve free radicals.[429,430] They are not useful for preparing aminochromes.

Metal ions, especially Cu^{2+}, Fe^{2+}, and vanadium salts catalyze the oxidations of catecholamines in dilute solution.[431–433] Metal-containing proteins such as ceruloplasmin and ferritin also catalyze such oxidations.[431,434–436] Since adrenochromes are thought to represent minor or abnormal metabolites of catecholamines, efforts have been made to isolate enzyme systems capable of effecting these oxidations.[415,437] An enzyme system in rat brain that is capable of oxidizing dihydroxyphenylalanine (DOPA) to melanin-type pigments has been described.[437] It also has been found that xanthine oxidase converts epinephrine into adrenochrome.[438]

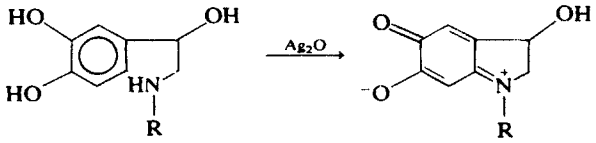
Although the mechanism of oxidation of catecholamines to aminochromes has not been established conclusively, it is thought to occur by the sequence illustrated for adrenochrome in Scheme 50. Thus a



Scheme 50

radical **603** is formed initially from epinephrine (adrenalin, **602**). This radical is further oxidized to *o*-benzoquinone **605**, which cyclizes and is further oxidized to adrenochrome (**606**).[415]

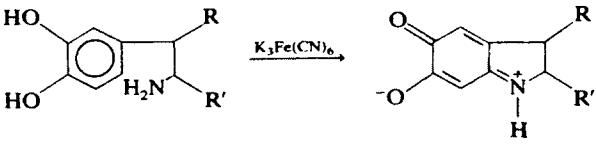
b. PREPARATIVE METHODS. The chemical oxidation of catecholamines to aminochromes has been accomplished on a preparative scale with silver oxide or potassium ferricyanide as the oxidizing agent. A method for the preparation of adrenochrome (**610**) involving silver oxide in methanol was introduced in 1942,[439] but traces of residual silver in the product resulted in instability (eq. 150). A pure, stable crystalline product was obtained by passing the reaction mixture through an anion exchange resin in the chloride form.[440] Pure, crystalline noradrenochrome was similarly prepared.[441] The use of formic acid as solvent also resulted in good yields. Thus D,L-epinephrine (**607**) readily gave D,L-adrenochrome (**610**) when treated with silver oxide in formic acid.[442,443] The *N*-ethyl and *N*-isopropyl homologues (**611** and **612**) of adrenochrome also have been prepared by the silver oxide method.[444] Examples of the use of potassium ferricyanide as oxidant include the conversion of 3,4-dihydroxyphenylalanine (DOPA, **613**) to dopachrome (**615**)[445] and the conversion of 3,4-dihydroxynorephedrine **614** to **616**[446] (eq. 151). Diphenyl selenoxide oxidized L-epinephrine to L-adrenochrome in 72% yield.[447]



(150)

607; R = CH_3
608; R = C_2H_5
609; R = C_3H_7

610; R = CH_3
611; R = C_2H_5
612; R = C_3H_7

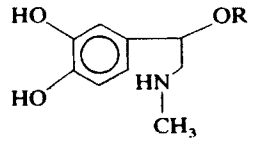


(151)

613; R = H, R' = CO_2H
614; R = OH, R' = CH_3

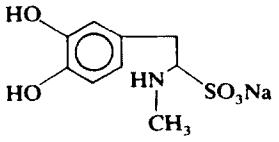
615; R = H, R' = CO_2H
616; R = OH, R' = CH_3

Aminochromes with other substituents have been synthesized by these methods. The methyl, ethyl, and isopropyl ethers (**618**) of adrenochrome were prepared from the corresponding adrenalin ethers **617**[444,448,449] (eq. 152). An *N*-hydroxyethyl ethyl derivative was also prepared from the



(152)

617; R = CH_3, C_2H_5, C_3H_7 **618**; R = CH_3, C_2H_5, C_3H_7



(153)

619 **620**

corresponding adrenalin analogue.[450] 2-Sulfonate derivatives were obtained by ferricyanide oxidation of the corresponding catecholamine sulfonic acids, for example, **619** to **620**[425,451] (eq. 153).

2. *Properties*

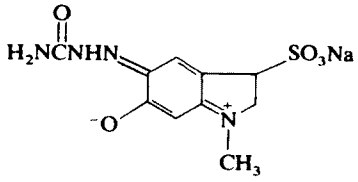
a. PHYSICAL. The aminochromes are deeply colored crystalline solids. These colors range from deep red for nonhalogenated compounds to violet-brown for haloaminochromes. Their slight solubility in polar solvents, insolubility in nonpolar solvents, and high decomposition temperatures (most do not melt) are consistent with zwitterionic structures.

Aminochromes show ultraviolet absorption maxima in the ranges 200–230 nm and also near 300 nm. Nonhalogenated compounds have visible absorption in the 470–490 nm region, whereas the corresponding iodo and bromo derivatives have maxima at 520–535 nm.[444,452] Bathochromic shifts are observed on going from methanol to water as solvent.[444] Aminochromes with a 3-hydroxyl group show infrared absorption between 3250 and 3420 cm^{-1}. The carbonyl region is complex, but an intense absorption at 1550–1600 cm^{-1} has been attributed to the ionized carbonyl group at the 6-position.[444,453,454] Paper chromatographic properties of the aminochromes have been reviewed.[415]

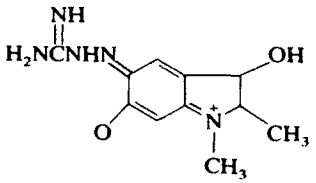
b. STABILITY. Pure, crystalline adrenochrome has been shown to be moderately stable at room temperature.[455] However, aminochromes without a 3-hydroxy or 3-alkoxy substituent rearrange readily, even in the solid state, to the corresponding 5,6-dihydroxyindoles.[456] Aminochromes are less stable in solution. Their decomposition is accelerated by factors such as the polarity of the solvent, pH, temperature, traces of metal ions, and dissolved oxygen. As in the crystalline state, those aminochromes with 3-oxygenation are more stable in solution than their 3-unsubstituted analogues.[456]

3. *Derivatives*

The semicarbazone derivatives of aminochromes have been extensively investigated because certain of these compounds show useful hemostatic (styptic) properties. Noteworthy in this respect are sodium epinochrome 3-sulfonate 5-semicarbazone (**621**)[424] and its 2-sulfonate isomer.[425] An aminoguanidine derivative (**622**) of the aminochrome obtained from 3,4-dihydroxy ephedrine also had styptic activity.[457] Many other monosemicarbazones of aminochromes have been reported.[426,446,448,450,458,459] The semicarbazone of adrenochrome was converted into the corresponding 7-bromo and 6-iodo derivatives by the usual methods.[460]

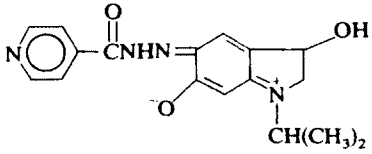


621

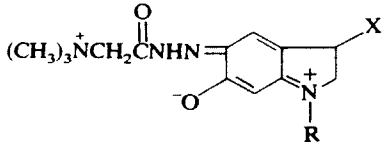


622

The isonicotinic acid hydrazone (**623**) of the aminochrome derived from isoproterenol was shown to inhibit hyaluronidase and control small capillary bleeding.[461] A study of the stability and solubility of adrenochrome hydrazone derivatives has been reported.[462] Girard T-reagent derivatives (**624**) of certain aminochromes were stated to have antipressor activities.[463]



623

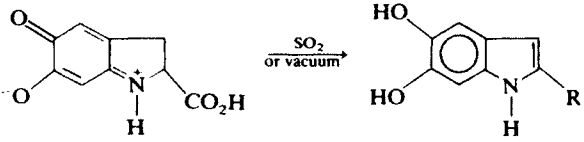


624; R = CH_3, X = OH
R = CH_3, X = H
R = $CH(CH_3)_2$, X = OH

Certain additives have been combined with adrenochrome monosemicarbazone in attempts to increase its water solubility. These additives include alkali metal salicylates,[464] aromatic or heterocyclic amides,[465,466] and sodium 4-aminonaphthalenesulfonate.[467]

4. *Reactions*

a. REARRANGEMENTS. In 1927 it was observed that dopachrome (**625**) underwent rearrangement and decarboxylation to 5,6-dihydroxyindole (**626**) when it was put under vacuum, whereas treatment with sulfur dioxide gave the corresponding 5,6-dihydroxyindole-2-carboxylic acid (**627**)[468] (eq. 154). Since that time, the rearrangements of aminochromes to 5,6-dihydroxyindole derivatives have been shown to be a general process.[469,470] These rearrangements occur in water of alcohol solutions and they are strongly catalyzed by metal ions (especially Zn^{2+}) and by bases.[452,471,472] The structure and hence the fluorescence properties of the rearrangement products depend on the aminochrome and the reaction conditions. Thus adrenochrome (**630**) rearranges in alkaline solution to 5,6-dihydroxyl-1-methylindoxyl (adrenolutin, **628**) a compound that shows intense yellow-green fluorescence[473] (Scheme 51). In contrast, compound **626** gave only weak blue fluorescence.[474]



(154)

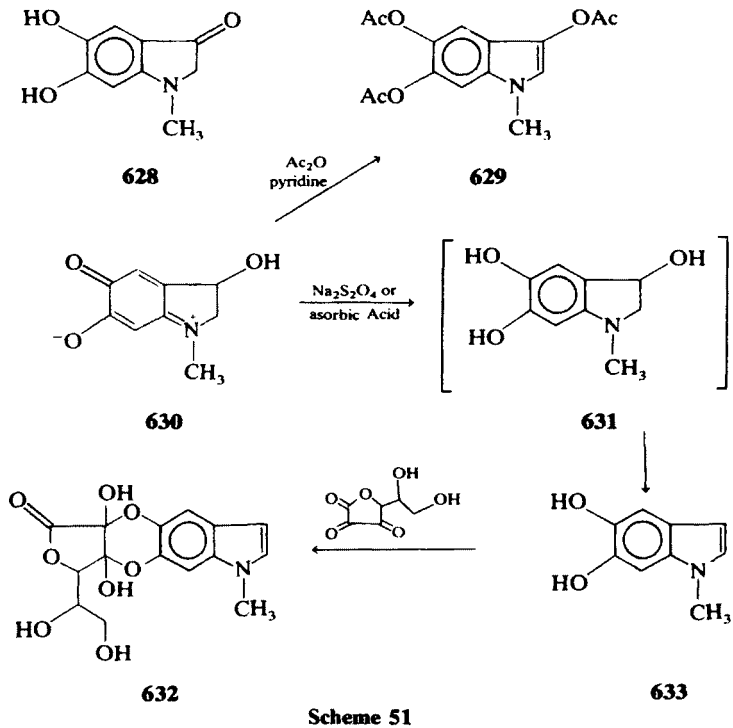
625

626; R = H
627; R = CO_2H

When adrenochrome (**630**) was treated with acetic anhydride in pyridine rearrangement with acetylation occurred to give **629**.[418] This type of reaction is general for aminochromes with and without oxygenation at the 3-position.[444,445,456,475,476] Noradrenolutin could not be prepared directly from noradrenochrome, but it was obtained by careful hydrolysis of 3,5,6-triacetoxyindole, which had been obtained previously from 7-iodonoradrenochrome.[477]

The rearrangement of an aminochrome to the corresponding 5,6-dihydroxyindole is equivalent to an intramolecular redox reaction. This kind of process is not surprising, since it is known that certain quinones (chloranil) readily oxidize the 2,3-bond of indolines. The actual mechanism of rearrangement has not been conclusively established; however, base-catalyzed removal of a proton from the 3-position, followed by a series of prototropic shifts has been postulated.[415] The slower rearrangement rates of 3-substituted aminochromes is consistent with this idea.

b. REDUCTIONS. Since aminochromes have an orthoquinone function



Scheme 51

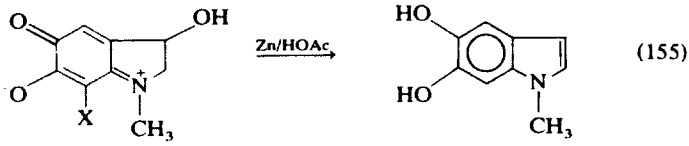
they are readily reduced to colorless products by a variety of reducing agents.[478,479] However, complex mixtures of products are sometimes obtained, depending on the reagents and conditions, and the reactions are not always reversible. Reduction of adrenochrome (**630**) by sodium hydrosulfite gave a mixture of 5,6-dihydroxy-1-methylindole (**633**) and the bisulfite addition product of adrenochrome.[480,481] The formation of **633** evidently procedes by way of intermediate **631**, which is dehydrated irreversibly. Similar reactions are given by various analogues and homologues of adrenochrome, including the 3-methoxy derivatives which lose methanol upon reduction.[482]

Alkali metal borohydrides rapidly reduce aminochromes to the corresponding 5,6-dihydroxyindoles, which are usually obtained in good yields.[482,483] Deiodination was not a problem when 7-iodoaminochromes were reduced by borohydrides.[444]

Ascorbic acid reduces adrenochrome **630** to a mixture containing **633** and its dehydroascorbic acid adduct **632**[484] (Scheme 51). This adduct is the main product in water, but if an ether phase is also present the **633** is extracted before the adduct forms. The two-phase procedure affords a

convenient preparative method for **633**.[485] Homologues of adrenochrome react with ascorbic acid in a similar mode.[415] Iodoaminochromes undergo partial deiodination under the same conditions.[415]

Aminochromes are readily reduced by zinc in dilute acetic acid to the corresponding 5,6-dihydroxyindoles.[480,482] Under these conditions the iodine of 7-iodoaminochromes is almost completely eliminated as in **634** to **636**.[444] In contrast, only partial debromination was observed with the 7-bromo analogue **635**[415] (eq. 155).



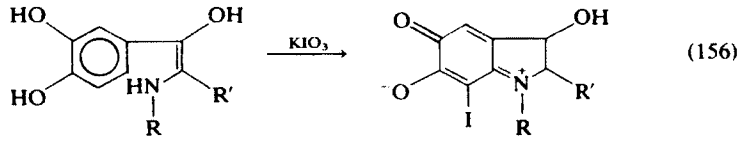
(155)

634; X = I
635; X = Br

636

A variety of thiols have been used to reduce aminochromes. Hydrogen sulfide converted aminochromes to the corresponding 5,6-dihydroxyindole in good yields.[415,486] Haloaminochromes did not undergo dehalogenation under these conditions.[415]

c. HALOGENATION. Potassium iodate or hydriodic acid converted catecholamines into iodinated aminochromes. Examples of such transformations included epinephrine (**637**) to 7-iodoadrenochrome (**640**),[487] isoproterenol (**638**) to 3-hydroxy-7-iodo-1-isopropylaminochrome (**641**),[445] and dihydroxyephedrine (**639**) to 7-iodo-2-methyladrenochrome (**642**)[458] (eq. 156). The position of iodination in iodoaminochromes was not known with certainty for many years. However, it was finally established to be the 7-position by analysis of the nuclear magnetic resonance spectra of their reduction products (7-iodo-5,6-dihydroxyindoles),[476] and by unambiguous synthesis of one of these products.[488]



(156)

637; R = CH_3, R′ = H
638; R = $CH(CH_3)_2$, R′ = H
639; R = R′ = CH_3

640; R = CH_3, R′ = H
641; R = $CH(CH_3)_2$, R′ = H
642; R = R′ = CH_3

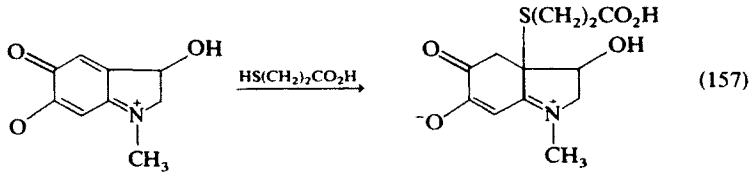
Formation of 7-iodoaminochromes is thought to occur by a two-stage process, which involves initial oxidation of the catecholamine to the simple adrenochrome, followed by iodination. In one of the supporting

experiments for this process it was found that adrenalin was converted into adrenochrome by potassium iodate at pH 2.9. Increasing the pH of this mixture to 7.2 resulted in formation of 7-iodoaminochrome.[489] The rate of iodination of adrenochrome by iodine in aqueous potassium iodide was directly proportional to the concentrations of iodine, adrenochrome, and iodide. It was independent of pH, but subject to general base catalysis.[490] A proposed mechanism involved iodine and adrenochrome as the reactive species, with the reaction proceeding by way of quinoid species. Removal of the 7-proton was thought to be the rate-determining step.[490] In another study, a mechanism involving acetyl hypoiodite as an iodinating species at very low iodide ion concentration was proposed for the iodination of adrenochrome in acetic acid–sodium acetate buffer solution.[491]

7-Bromoadrenochrome was obtained by treating adrenochrome with bromine in acetic acid.[442] It was directly obtained from adrenalin under the same conditions.[418]

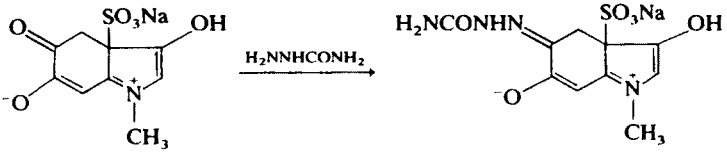
d. Addition of Thiols. Aminochromes react with primary thiols to form thioethers. At pH 3–4, 4-(thio-substituted) 5,6-dihydroxyindoles or indolines are formed. However, at pH 5–6 the main products are 3a-thio-substituted-3a,4-dihydroaminochromes. These products are formed reversibly and they are gradually replaced by irreversible indolic products.[492] In one example, the product (**644**) obtained from adrenochrome (**643**) and 3-mercaptopropionic acid was isolated as its *p*-nitrophenylhydrazone before it could decompose[493] (eq. 157). The difference in the position of substitution at pH 3–4 and at pH 5–6 was explained on the grounds that at lower pH the 6-oxygen of the adrenochrome is protonated and the thiol is un-ionized, whereas at higher pH the 6-oxygen is negatively charged and the thiol is partly ionized.[492] Secondary and tertiary thiols did not add to aminochromes. It was postulated that the observed addition of *N*-acetylcysteine and *N*-acetylpenicillamine to adrenochrome might be related to the biochemical process by which melanoproteins are formed.[495]

e. Other Reactions. Aminochromes readily form addition products



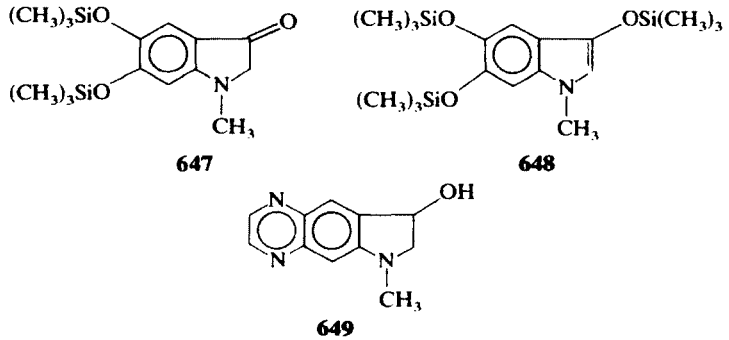
643 644 (157)

with sodium bisulfite. The crystalline adduct from adrenochrome is thought to have the sulfur substituted at position 3a on the basis of spectroscopic evidence.[496,497] Bisulfite addition is reversible and the aminochromes can be regenerated in alkaline solution.[497] Because the bisulfite adducts (e.g., **645**) have a free carbonyl group they can be converted into derivatives such as the semicarbazone **646**[497] (eq. 158).



645 646 (158)

Adrenochrome reacted with three different silylating agents to give trimethylsilyl derivatives (**647** and **648**) of adrenolution and 5,6-dihydroxy-1-methylindole.[498]



647 648

649

A mixture of adrenochrome and ethylenediamine in air forms in low yield the highly fluorescent pyrrolo[4,5-g]quinoxaline (**649**).[499,500]

C. Other Indolediones

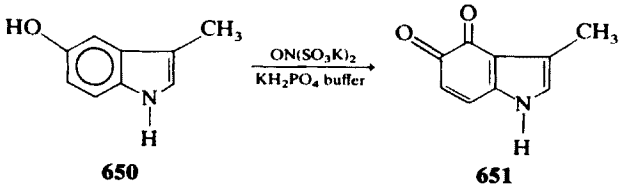
1. *Introduction*

The indole-4,5-diones, indole-4,7-diones, and indole-6,7-diones differ in properties from the aminochromes. Most of the simpler indolediones have definite melting points and good solubility in polar and nonpolar organic solvents.[501] In contrast, the aminochromes decompose before melting and are poorly soluble due to their zwitterionic nature. Indole-4,5-diones tend to be red and indole-4,7-diones are purple.[501] The

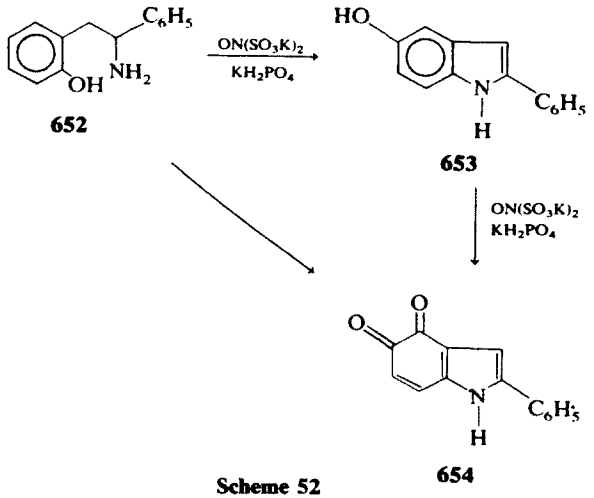
nonhalogenated aminochromes are deep red.[418] Although the other indolediones have been studied much less than the aminochromes, many indole-4,7-dione derivatives have been synthesized as analogues of the mitomycin antibiotics.[413,414]

2. *Preparation*

Potassium nitrosodisulfonate (Fremy's salt) oxidation of hydroxyindoles or aminoindoles has been the most important method used to date for the preparation of indoloquinones. This method is mild and usually highly effective unless the indole contains strong electron-withdrawing groups.[501] 5-Hydroxyindoles are converted into the corresponding indole-4,5-diones by this method, as illustrated by the formation of **651** in 94% yield from **650**[502] (eq. 159). 2-Phenylindole-4,5-dione (**654**) could be prepared from the corresponding 5-hydroxyindole **653** or its phenolic precursor **652** by Fremy's salt oxidation[502,503] (Scheme 52). Other oxidizing agents can convert 5-hydroxyindoles into quinones. For example, compound **655** was converted into 4,5-dione **656** by nitric acid (eq. 160).

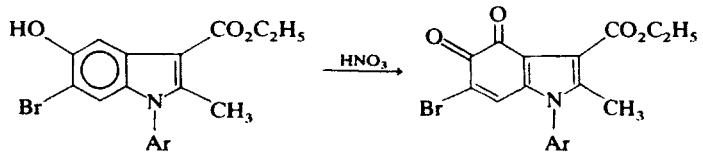


650 **651** (159)



652 **653** **654**

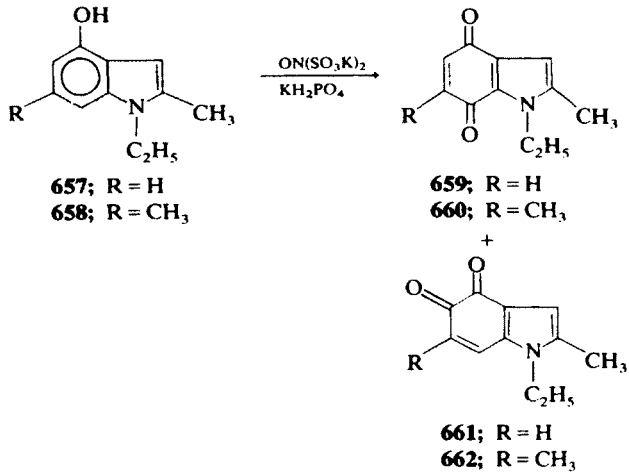
Scheme 52



655 **656** (160)

However, the corresponding 1-methylindole gave a 4,6-dinitro derivative.[504]

When 4-hydroxyindoles are treated with Fremy's salt the products are indole-4,7-diones or mixtures of these compounds with the isomeric indole-4,5-diones. Such isomers are readily differentiated since the 4,7-diones tend to be red and the 4,5-diones tend to be blue.[501] In one example, Fremy's salt oxidation of 1-ethyl-4-hydroxy-2-methylindole (**657**) gave 68% of the 4,7-dione **659** and 12% of the 4,5-dione **661**[501] (Scheme 53). However, with the corresponding 6-methyl homologue **658** the yield of each dione (**660** and **662**) was only 5%.[505] Only the 4,7-dione **664** was isolated from the reaction of Fremy's salt with 4-hydroxy-2,3-diphenylindole (**663**)[506,507] (eq. 161).

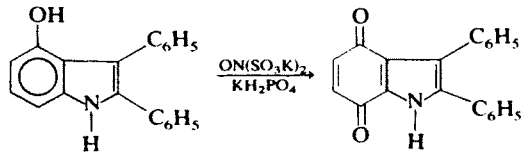


657; R = H
658; R = CH_3

659; R = H
660; R = CH_3

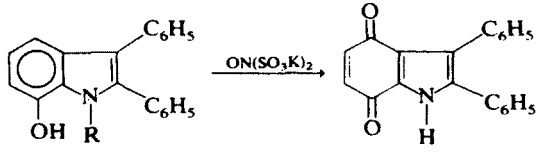
661; R = H
662; R = CH_3

Scheme 53



663 **664** (161)

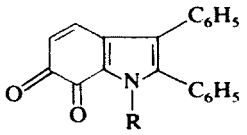
7-Hydroxyindoles give 4,7-diones and/or 6,7-diones when they are treated with Fremy's salt. Thus 2,3-diphenyl-7-hydroxyindole (**665**) gave a mixture of 4,7-dione **667** and 6,7-dione **668**. However, the 1-methyl homologue **666** gave only the 6,7-dione **669**[508] (Scheme 54).



665; R = H
666; R = CH_3

667

+

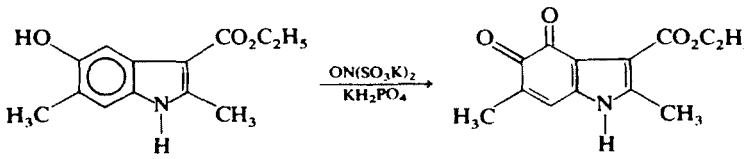


668; R = H
669; R = CH_3

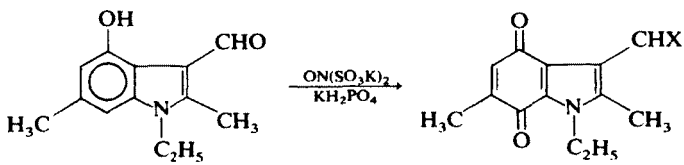
Scheme 54

The presence of a 3-carbethoxy substituent did not adversely affect the conversion of **670** to quinone **671**[509] (eq. 162). In contrast, the 3-formyl group of **672** caused a very sluggish conversion to quinone **673**, and oxime **674** was also formed[505] (eq. 163).

Fremy's salt oxidations of certain 4-aminoindoles also afford indole-4,7-diones. These oxidations were particularly useful in the synthesis of mitomycin analogues, wherein 4-aminoindole-3-carboxaldehydes such as



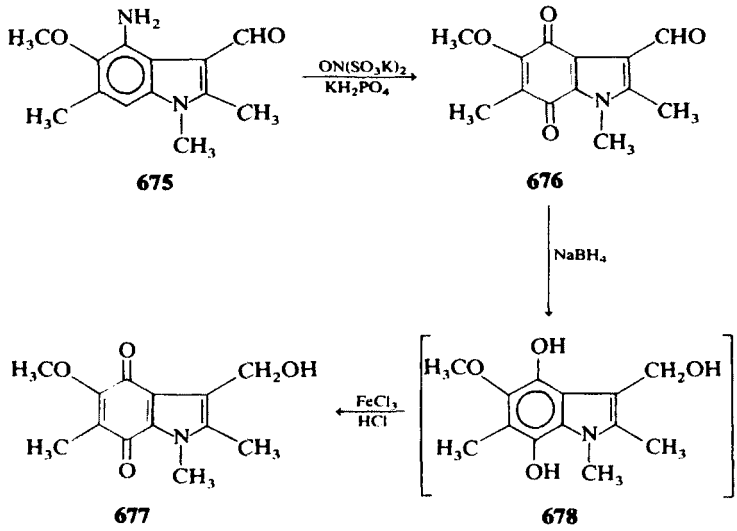
670 **671** (162)



672

673; X = O
674; X = NOH

(163)

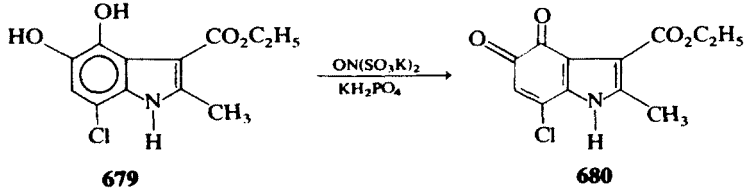


Scheme 55

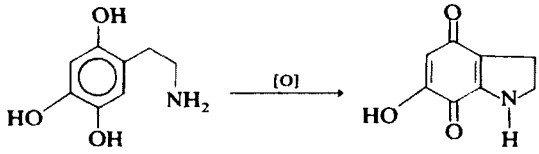
675 were converted to the desired indole-4,7-dione-3-carboxaldehydes **676** in good yields[510] (Scheme 55).

Oxidation of 4,7-dihydroxyindoles to the corresponding indole-4,7-diones is facile, since it represents a hydroquinone-to-quinone type of transformation. Thus 4,7-dihydroxy-3-hydroxymethylindole derivative **678** (obtained by $NaBH_4$ reduction of **676**) was oxidized to the corresponding indole-4,7-dione **677** by ferric chloride[510] (Scheme 55). It should be noted that the quinone system of **677** stabilizes the 3-hydroxymethyl substituent, which would otherwise undergo diindolylmethane formation.[413] 7-Chloro-4,5-dihydroxyindole derivative **679** was oxidized to the corresponding indole-4,5-dione **680** by Fremy's salt[509] (eq. 164). 6-Hydroxydopamine (**681**) was oxidized by air to 6-hydroxyindoline-4,7-dione (**682**) at pH 7.4, but not at pH 3 (eq. 165). It was suggested that covalent binding with quinones such as **682** might be responsible for the destruction of adrenergic neurons.[512,513]

4,7-Dimethoxyindoles have been oxidized and cleaved to 4,7-diones. Thus compounds **683** and **684** readily gave the indoloquinones **685** and

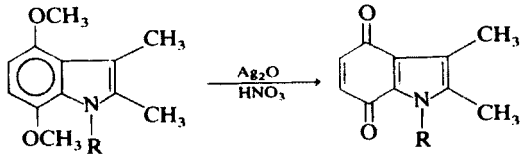


(164)



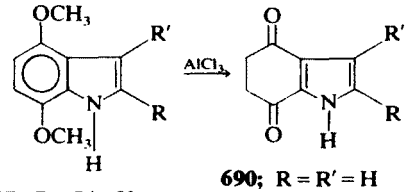
681 **682** (165)

686 when they were treated with silver oxide in nitric acid[514] (eq. 166). The nonoxidative cleavage of 4,7-dimethoxyindoles by aluminum chloride provided some surprising results. In certain examples, including 4,7-dimethoxyindole (**687**),[515] its 2-methyl analogue (**688**),[516] 2,3-dimethyl analogue (**689**),[517] and certain 2-aryl analogues,[518] the products were not 4,7-dihydroxyindoles, but rather the tautomeric 5,6-dihydro-indole-4,7-diones (**690–692**) (eq. 167). With 3-acyl or aroyl-4,7-dimethoxyindoles such as **693** and **694** the cleavage products were stable as the 4,7-dihydroxyindoles **695** and **696**[519] (eq. 168). 2-Phenyl-4,7-dimethoxyindole (**697**) gave 4,7-dihydroxy-2-phenylindole (**698**) on cleavage with anhydrous aluminum chloride, but it gave the 4,7-dione **699** with anhydrous hydrogen chloride. Dihydroxyindole **698** was converted into dione **699** on sublimation at 165–175°[516] (Scheme 56). Structural features of the 5,6-dihydro-4,7-dione tautomers were readily discerned in their infrared absorption and nuclear magnetic resonance spectra.[516,517]



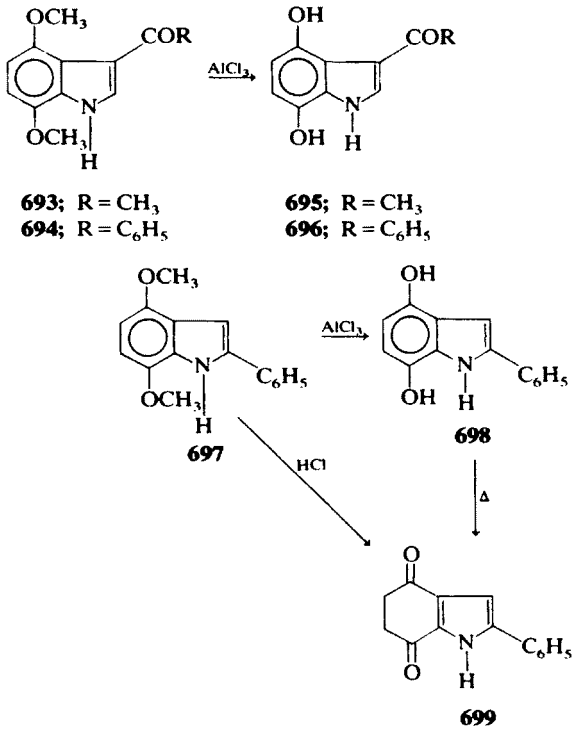
683; R = H
684; R = CH_3

685; R = H
686; R = CH_3 (166)



687; R = R' = H
688; R = CH_3, R' = H
689; R = R' = CH_3

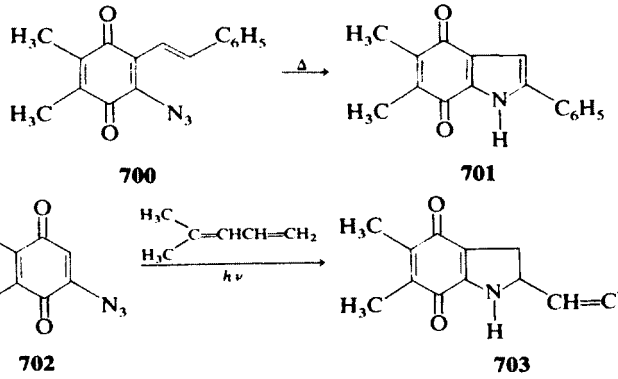
690; R = R' = H
691; R = CH_3, R' = H
692; R = R' = CH_3 (167)



(168)

Scheme 56

A new method for the synthesis of indole-4,7-diones (**701**) was based on thermal decomposition of 2-azido-3-vinyl-1,4-benzoquinones such as **700**[520] (eq. 169). In a variant on this method, 2-vinylindoline-4,7-diones (e.g., **703**) were formed by photocyclization of 2-azido-1,4-benzoquinones such as **702** and substituted butadienes[521] (eq. 170).

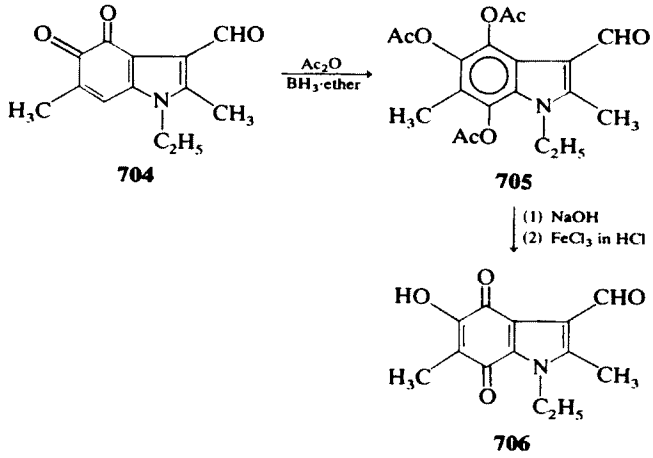


(169)

(170)

3. *Reactions*

Indoloquinones undergo many of the same reactions as do related naphthoquinones. They are readily reduced to the hydroquinones by sodium hydrosulfite[521] or converted into hydroquinone acetates by zinc in acetic anhydride.[501] Indole-4,5-diones are converted by acetic anhydride and boron trifluoride etherate (Thiele reaction) into the corresponding triacetoxyindoles, which afford 5-hydroxyindole-4,7-diones upon hydrolysis and ferric chloride oxidation. The conversion of **704** to **706** by way of **705** was an example of this process[413] (Scheme 57). A similar conversion of **704** to the related 5-hydroxyindole-4,7-dione was accomplished on a small scale by prolonged treatment in 0.1*N* HCl.[509]



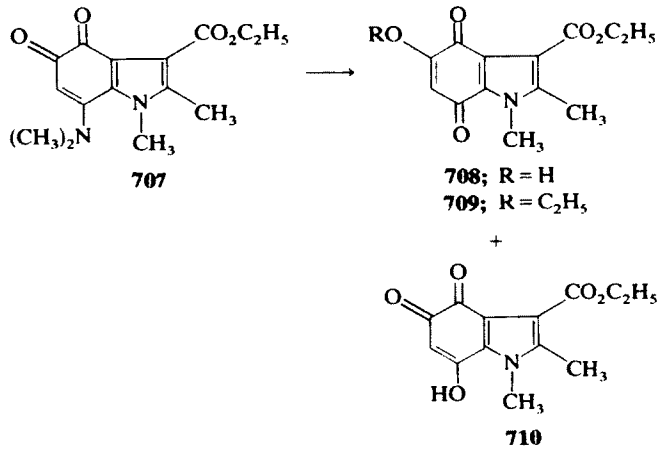
704 **705** **706**

Scheme 57

Acid hydrolysis of 7-(dimethylamino)indole-4,5-dione **707** gave a separable mixture of the 5-hydroxy-4,7-dione **708** and the 7-hydroxy-4,5-dione **710**[522] (Scheme 58). Treatment of **707** with hydrogen chloride in ethanol gave only 5-ethoxy-4,7-dione **709** in 84% yield[523] (Scheme 58).

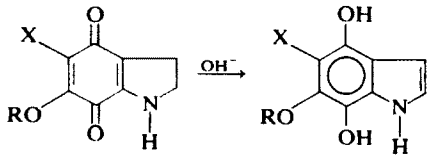
6-Hydroxyindoline-4,7-dione (**711**) was stable to rearrangement in alkaline solution, in contrast to the lability of related aminochromes.[522] However, the corresponding 6-methoxy analogue **712** and the 5-bromo-6-methoxy analogue **713** underwent base-catalyzed rearrangement to 4,7-dihydroxyindoles **714** and **715**[512,524] (eq. 171).

A series of transformations on indole-4,7-dione-3-carboxaldehyde **718** revealed the typical quinone behavior of this modecule (Scheme 59). Thus bromination gave 5,6-dibromo derivative **716**. This derivative was



707 → **708**; R = H; **709**; R = C_2H_5 + **710**

Scheme 58



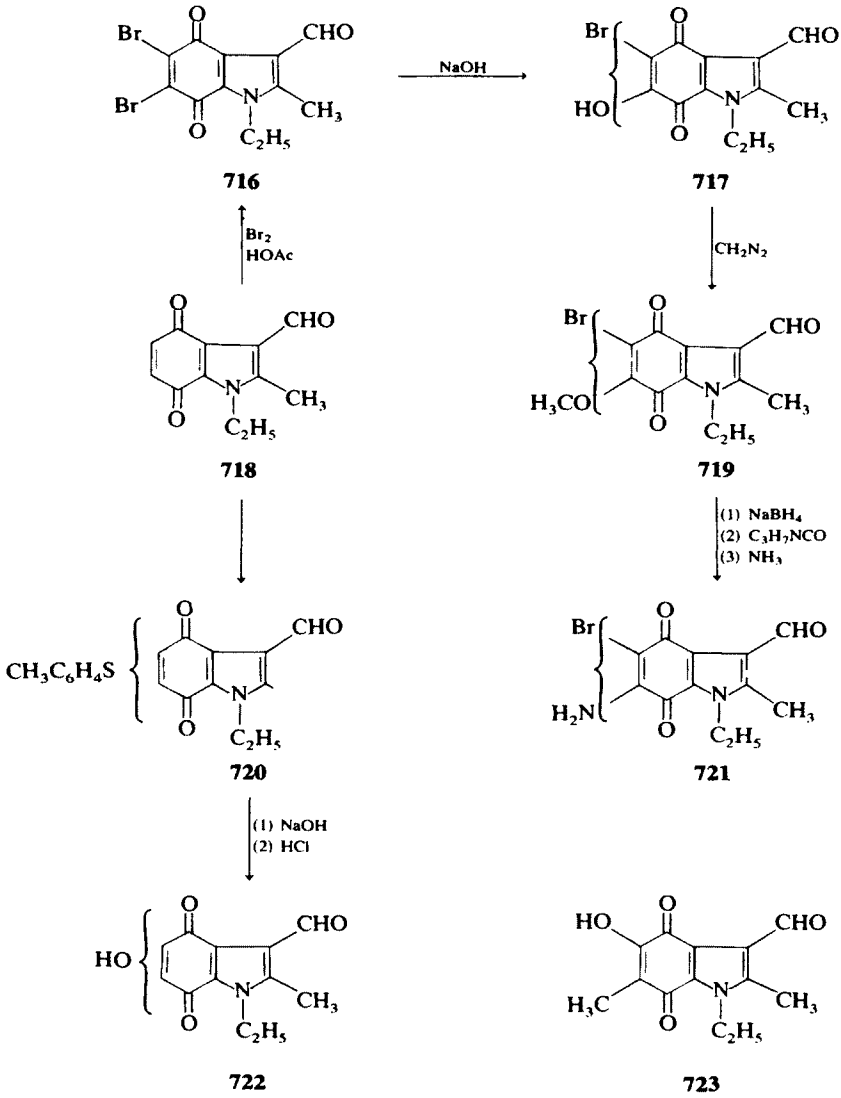
(171)

711; R = X = H
712; R = CH_3, X = H
713; R = CH_3, X = Br
714; R = CH_3, X = H
715; R = CH_3, X = Br

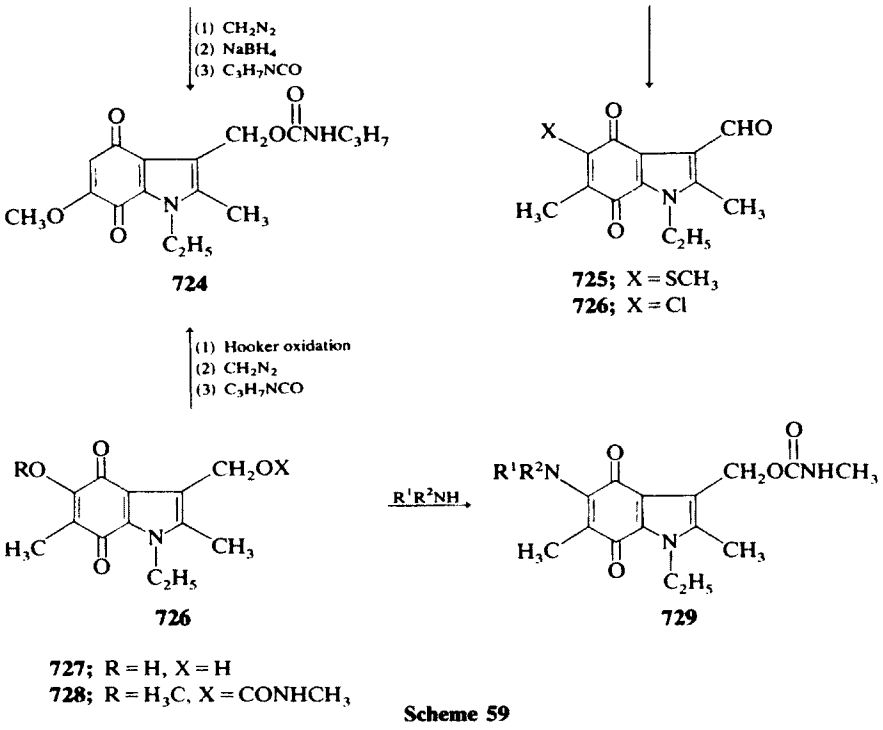
converted by NaOH into a mixture of isomeric bromohydroxyindole-4,7-diones **717**. After methylation of the **717** isomers with diazomethane, the resulting bromomethoxy isomers **719** were separated by partition chromatography. Conversion of either isomer to the corresponding 3-hydroxymethyl carbamate, followed by treatment with ammonia, resulted in displacement of the methoxy group, with aminobromoindole-4,7-dione carbamates **721** as the products.[501] Addition of *p*-toluenethiol to **718** gave a mixture of isomeric mono-*p*-toluenethio derivatives **720**, which was separated by fractional crystallization. Treatment of either isomer with sodium hydroxide gave the corresponding hydroxyindole-4,7-dione **722**. The 6-hydroxy isomer **722** was converted into **724**, which was prepared unambiguously by a route involving Hooker oxidation of **727**[501] (Scheme 59).

Certain transformations of **723** were also useful in the preparation of mitomycin analogues. For example, the corresponding 5-methylthio derivative **725** was obtained by treating **723** with methyl mercaptan in acid solution, and the 5-chloro derivative **726** was afforded by the reaction of $POCl_3$ with **723**. In both cases the yields were low.[525]

Another type of reaction important to the mitomycin analogues was displacement of the 5-methoxy group of indoloquinone carbamate **728** with ammonia and various primary and secondary amines. The resulting 5-aminoindoloquinones **729** could be readily detected and separated because of their purple color. When R^1R^2N was ethyleneimino, the best activity against Gram(+) bacteria was obtained.[414,525]



Scheme 59 (*Concluded overleaf*)



Scheme 59

V. Tables of Indole Aldehydes and Ketones

The compounds in each table are listed in order of the type of substituents present in addition to the carbonyl function. Thus indoles with no substituents other than carbonyl are first, followed in order by those with alkyl, alkenyl, aryl, halogen, nitrogen, sulfur, and oxygen substituents. Within each group, the compounds with the least number of substituents are given first.

Indole aldehydes and ketones bearing the substituents described in Chapters IV to VIII are included in these tables. However, those with carboxylic acid and related substituents are to be found in tables in Chapter XI, Part Four. This especially refers to the numerous glyoxalylamides. Oxindoles which bear aldehyde or other keto groups are in Chapter X, Part Four. One exception to the rules just mentioned is the indolediones, including aminochromes. Since this is a rather unique group of indole derivatives, it seems appropriate to include all of them in one set of tables. Consequently, the indolediones bearing carboxylic acid and related substituents are found in tables in this chapter.

Throughout each table, the functional group derivatives are listed immediately under the parent carbonyl compound. For example, indole-2-carboxaldehyde is followed by its thiosemicarbazone and 2,4-dinitrophenylhydrazone (2,4-DNP) derivatives, their melting points, and literature references. No separate tables of derivatives are given.

Methods of synthesis are noted for compounds in the tables and, where available, yields are given. These yields pertain only to the reaction specified, which might be the last one in a sequence of steps. Consequently, when attempting to evaluate relative efficiencies for the preparations of these compounds from available starting materials, a person should consult the indicated reference for previous steps. In some cases the immediate precursor can be found with its preparation and yield in another table in this chapter.

TABLE I. INDOLE-2-CARBOXALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
None	Redn. of 2-COCl	—	140–141	60, 61, 538
2,4-DNP		—	315–320	60
Thiosemicarbazone		—	231	545, 546
1-CH_3	Formylation of 2-Li	—	83–85	33
Formylhydrazone		—	226	92
Acetylhydrazone		—	201–202	92
Propionylhydrazone		—	175–176	92
3-CH_3	Redn. of 2-COCl	—	139–140	6, 61, 53
	SeO_2 oxidn. of CH_3	22	139	55
	Photooxidn. of CH_3	17	139–140	57
2,4-DNP		—	306–309	6
4-CH_3	Oxidn. of 2-CH_2OH	—	—	52
5-CH_3	Redn. of 2-CO_2H	90	175–176	526
2,4-DNP		—	285	526
2-CH_3, 4-NO_2phenylhydrazone		—	251–252	
7-CH_3	Redn. of 2-CO_2H	45	190	526
2,4-DNP		—	265	526
5-C_2H_5	Oxidn, of 2-CH_2OH	—	—	52
3,5-$(CH_3)_2$	Redn. of 2-CO_2H	90	140	526
2,4-DNP	Photooxidn. of 2-CH_3	18	186–189	57
2,4-DNP		—	315	526
3,7-$(CH_3)_2$	Redn. of 2-CO_2H	80	138	526
2,4-DNP		—	276	526
4,5-$(CH_3)_2$	Oxidn. of 2-CH_2OH	—	—	52
1,3-$(CH_3)_2$	Oxidn. of 2-CH_3	35	86	58
2,4-DNP		—	253	58
3-$CH_2C_6H_5$	Redn. of 2-$COSC_6H_5$	—	115–115.5	62
3-C_6H_5	Rearrgt. of benzodiazepine	—	—	51

TABLE I. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
	Photooxidn. of 2-CH_3	40	194–197	57
3-C_6H_5, 5-CH_3	Photooxidn. of 2-CH_3	41	204–206	57
5-Br	Oxidn. of 2-CH_2OH	—	—	48, 52
7-Br	Oxidn. of 2-CH_2OH	—	—	48
5-Br, 3-CH_3	Redn. of 2-CO_2H	—	181–182.5	38
4-Cl	Oxidn. of 2-CH_2OH	—	—	48
6-Cl	Oxidn. of 2-CH_2OH	—	—	48
5-Cl, 3-CH_3	Photooxidn. of 2-CH_3	17	230d	57
5-Cl, 4-CH_3	Oxidn. of 2-CH_2OH	—	—	52
4-Cl, 1-$CH_2C_6H_5$	Oxidn. of 2-CH_2OH	—	93–96	33
5-Cl, 3-C_6H_5	Photooxidn. of 2-CH_3	47	240–242	57
6-Cl, 3-C_6H_5	Rearrgt. of benzodiazepine	—	235–240	50
Dimethyl acetal		—	134–137	50
6-Cl, 3-C_6H_5, 1-CH_3	Rearrgt. of benzodiazepine	—	156–159	50
5-Cl, 3-C_6H_5, 1-CH_3	Stevens rearrgt.	—	—	64
5-NO_2	Photooxidn. of 2-CH_3	10	246–247	57
4-NO_2, 3-CH_3	Photooxidn. of 2-CH_3	2	225d	56, 57
5-NO_2, 3-CH_3	Photooxidn. of 2-CH_3	43	290d	56, 57
6-NO_2, 3-CH_3	Photooxidn. of 2-CH_3	30	254–256	56, 57
7-NO_2, 3-CH_3	Photooxidn. of 2-CH_3	48	158–160	56, 57
5-NO_2, 1,3-$(CH_3)_2$	Photooxidn. of 2-CH_3	41	220–222	57
5-NO_2, 3-C_6H_5	Photooxidn. of 2-CH_3	51	273–274	57
6-NO_2, 3-C_6H_5	Photooxidn. of 2-CH_3	33	250–252	57
7-NO_2, 3-C_6H_5	Photooxidn. of 2-CH_3	55	168–170	57
1-CH_3, 3-$(CH_3)_2NCH_2$·HCl	Formylation of 2-Li	—	238–239	33
1-$C_6H_5CH_2N(CH_3)CH_2$-CH_2·HCl	Formylation of 2-Li	—	170–175	33
1-$(C_2H_5)_2NCH_2CH_2$·HCl	Formylation of 2-Li	—	156–158	33
4-$(CH_3)_2CHNHCH_2CH$-$(OH)CH_2O$	Oxidn. of 2-CH_2OH	—	—	50
1-CH_3, 3-NO		—	—	
Oxime		—	173	547
1-CH_3O	Redn. of 2-CO_2H	—	—	59
5-CH_3O	Oxidn. of 2-CH_2OH	—	136–137	51, 52
5-CH_3O, 6-CH_3	Oxidn. of 2-CH_2OH	—	172–173	51
5-C_2H_5O, 4-CH_3	Oxidn. of 2-CH_2OH	—	—	52
5-$C_6H_5CH_2O$	Oxidn. of 2-CH_2OH	—	178–179	51
5-$C_6H_5CH_2O$, 6-CH_3	Oxidn. of 2-CH_2OH	—	172–175	51
5-CH_3O, 3-CH_3	Redn. of 2-CO_2H	—	213–215	60, 71
2,4-DNP		—	275	60
1-CH_2OCH_3	*N*-Methylformanilide on 2-Li	46	Oil	273
3-CH_2CH_2OCOCH	Oxidn. of 2-CH_2OH	—	Oil	538
2,4-DNP		—	266–269	538
3-CHO	Oxidn. of 2-CH_2OH	—	—	49

TABLE II. INDOLINE-2-CARBOXALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-CH_3CO, 3-OH	Redn. of 2-CO_2CH_3	—		537
Semicarbazone			220	
3-Oxo	Oxidn. of 2-CH_3	—	170–173	70, 527

TABLE III. INDOLE-3-CARBOXALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
None	Vilsmeier–Haack formylation	94	194–196	4, 6, 29, 540
	Reimer–Tiemann	31		329
	Heating anil of ethyl 3-formylindole-2-carboxylate	78		6, 541, 542
	$(C_6H_5)_3PBr_2$ + DMF	—		31
	Ethyl formate and indolylmagnesium halides	41		36, 37, 38
	Hexamethylene-tetramine	60		528
	Sommelet redn. on gramine	—		68
	DMF + CH_3COBr	89		30
	DMF + C_6H_5COCl	85		30
Oxime			197–198	36, 68
Thiosemicarbazone			230–232	80, 81, 529, 546
Subst. thiosemicarbazone				
CH_3			218–219	91
C_2H_5			223–224	91
C_3H_7			209–211	91
CH_2=$CHCH_2$			215–216	91
C_4H_9			177–178	91
C_6H_{11}			170–172	91
C_6H_5			209–210	91
o-$CH_3C_6H_4$			209–210	91
m-$CH_3C_6H_4$			188–189	91
p-$CH_3C_6H_4$			202–203	91
o-$CH_3OC_6H_4$			190–191	91
o-$C_6H_5OC_6H_4$			211–213	91
p-$C_2H_5OC_6H_4$			205–206	91
p-$(CH_3)_2CHC_6H_4$			259–260	91
Subst. imines				
CH_3			119–120	93
C_6H_5			126–127	94
HCl			240–246	94

TABLE III. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Hydrazones				
CH_3			96	90
CH_3, CH_3			103	90
CH_2CH_2Cl, CH_2CH_2Cl·HCl			151–153	89
COC_6H_5			234–235	91
$COC_6H_4OH(o)$			261–263	91
$COC_6H_4OH(p)$			278–280	91
$COC_6H_4NH_2(p)$			259–260	91
Nicotinyl			255–257	91
Isonicotinyl			230–232	91
$COC_6H_4NO_2(p)$			255–257	91
Amidino·HCl			232–234	91
Alkyl				
1-CH_3	Alkylation of indole-3-CHO	70	68–70	104, 105, 107
Thiosemicarbazone			219	529
Méthoxime		90	78–80	157
2-CH_3	Gattermann	85	198–199	35, 256
	Alkyl *formate* and Grignard	Low		36, 38, 544
	Reimer–Tiemann	—		543
	CO and indolyl K	45	201.5–202.5	67
	DMF + CH_3COBr	88	202–203	80
Semicarbazone			224	543
Picrate			181	36, 543
Methylimine			151–152.5	93
5-CH_3	Alkyl formate and Grignard	—	151	548
	Vilsmeier–Haack	92	148–149	131
2-$C(CH_3)_3$	Vilsmeier–Haack	80	224	11
1,2-$(CH_3)_2$	Methylation of 2-CH_3	—	131–132	104, 530, 155, 549
Oxime			171	530
Phenylhydrazone			154	530
2,5,7-$(CH_3)_3$	Vilsmeier–Haack	—	230	
2,5,7-triisopentyl	Formamide, heat	—	136	32
6-CH_3, 2-isopentenyl	Vilsmeier–Haack	53	175–177	12
Aryl				
2-C_6H_5	Hexamethylene-tetramine	99	250–255	528
	DMF + CH_3COBr	96	250–255	30
	Photooxidn. of 3-CH_3	35	253–255	57
2-C_6H_5, 4,5,6,7-tetrahydro	Vilsmeier–Haack	—	217–218	23
Oxime			210–211	23

TABLE III. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-$CH_2C_6H_5$		—		84
Isonicotinylhydrazone		95	229–230	84
2-C_6H_5, 1-CH_3	Vilsmeier–Haack	94	124–126	551, 29, 550
	Methylation with $(CH_3)_2SO_4$	95	125–126	552
			168–169	97
2-C_6H_5, 1-C_2H_5	Vilsmeier–Haack	—		
Hydroxyethylimino			149–150	97
2-C_6H_5, 1-C_3H_7	Vilsmeier–Haack			
Hydroxyethylimino			122–124	97
2-C_6H_5, 1-C_4H_9	Vilsmeier–Haack	—		
Hydroxyethylimino			91–94	97
2-C_6H_5, 5-CH_3	Vilsmeier–Haack	91	272	553
Semicarbazone	Photooxidn. of 2-CH_3	38	269–271	57
Thiosemicarbazone			257	553
2-(4-ClC_6H_4), 1-CH_3				149
2-C_6H_5, 7-CH_3	Vilsmeier–Haack	91.5	230	553
2,4-DNP			245	554
1,2-$(C_6H_5)_2$	Vilsmeier–Haack	—	—	142
2-α-Naphthyl	Vilsmeier–Haack	—	250	563
Oxime			180	563
2-β-Naphthyl	Vilsmeier–Haack	—	255	563
Oxime			182	563
2-*p*-Biphenyl	Vilsmeier–Haack	—	314	563
Oxime			235	563
Heteroaromatic				
2-(2-Thienyl)	Vilsmeier–Haack	90	238–239	7
Oxime			183.5	7
2-(2-Piperidyl)	Vilsmeier–Haack	21	216–217.5	7
Oxime			160–161.5	7
Halogen				
5-Br	Vilsmeier–Haack	100	211	558–560
	Bromination of ald.	low		163
4-(1-Adamantyl)-thiosemicarbazone				83
6-Br	Bromination of ald.	low	203–204	163
	Vilsmeier–Haack			163
5-Br, 7-CH_3	Vilsmeier–Haack	—	200	561
Semicarbazone			226	561
Thiosemicarbazone			224	561
5-Br, 1-CH_3	Br_2, HOAc	92	137–138	164
6-Br, 1-CH_3	Br_2, HOAc	88	150–151	164
	Vilsmeier–Haack	35	138	559
	Vilsmeier–Haack on oxindole	—	—	28
5,6-Br_2	Br_2, Fe	5	295–297	163

TABLE III. (*Continued*)

Substituent	Method of synthesis	Yield (%)	mp (°C)	Ref.
5,6-Br_2, 1-CH_3	Decarbox. of indolyl-3-pyruvic acid deriv.	23	209–211	164
2-*p*-Br-C_6H_4	Vilsmeier–Haack	—	270	562
Oxime			235	562
2-Cl	Vilsmeier–Haack on oxindole	58	232–235	27
Thiosemicarbazone			205–210d	82
N-Methylthiosemicarbazone			208–210d	82
Guanylhydrazone HCl			252–254d	82
2-Cl, 1-CH_3	Vilsmeier–Haack on oxindole	—	—	28
Thiosemicarbazone			225–227d	82
N-Methylthiosemicarbazone			215–218d	82
Guanylhydrazone			256–258d	82
2-Cl, 2-CH_3	Vilsmeier–Haack on oxindole	—	—	88
Oxime		—	—	88
4-Cl	Vilsmeier–Haack	—	175–176	10, 563
	Decarbethoxylation	—	164	53
5-Cl	Vilsmeier–Haack	—	213.5–214	558, 563
6-Cl	Vilsmeier–Haack	—	202–203	563
7-Cl	Vilsmeier–Haack	—	179	563
2,4-Cl_2	Vilsmeier–Haack on oxindole	—	—	25
2,4,7-Cl_3	Vilsmeier–Haack on oxindole	—	—	25
2-Cl, 1-CH_3	Vilsmeier–Haack on oxindole	—	—	26
2,4-DNP		—	305	26
5-Cl, 7-CH_3	Vilsmeier–Haack	80	213	561
Semicarbazone		—	229	561
Thiosemicarbazone		—	238	561
2-(C_6H_4-4-Cl)	Vilsmeier–Haack	—	261	562
Oxime		—	228	562
4-F	Vilsmeier–Haack	73	190–191	169
5-F	Vilsmeier–Haack	—	160–162	564
6-F		76	178-179	565
2,4-DNP		—	315–318	565
2-(C_6H_4-4-I)	Vilsmeier-Haack	—	277	562
Oxime		—	205	—
2-Cl, 1-C_6H_5	Vilsmeier-Haack on oxindole	75	164–166	27, 28
Thiosemicarbazone		—	233–235d	82
N-Methylthiosemicarbazone			213–215d	82

TABLE III. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Guanylhydrazone		—	236–239d	82
2-Cl, 1-COC_6H_5	Vilsmeier–Haack on oxindole	—	—	82
Thiosemicarbazone		—	218–220d	82
N-Methylthiosemicarbazone		—	218–220d	82
Guanylhydrazone		—	233–235d	82
2-Cl, 1-(COC_6H_4-2-Cl)	Vilsmeier–Haack on oxindole	—	139–141	82
Thiosemicarbazone		—	202–203	82
N-Methylthiosemicarbazone		—	212–214	82
2-Cl, 1-(COC_6H_4-3-Cl)	Vilsmeier–Haack on oxindole	—	156–158	82
Thiosemicarbazone		—	203–204	82
N-Methylthiosemicarbazone		—	218–220d	82
Guanylhydrazone		—	225–230d	82
2-Cl, 1-(COC_6H_4-4-Cl)	Vilsmeier–Haack on oxindole	—	—	82
Thiosemicarbazone		—	219–220d	82
N-Methylthiosemicarbazone		—	200d	82
Guanylhydrazone		—	240–245d	82
2-Cl, 1-(COC_6H_4-4-CH_3)	Vilsmeier–Haack on oxindole	—	120–121	82
Thiosemicarbazone		—	224–225d	82
N-Methylthiosemicarbazone		—	217–218d	82
Guanylhydrazone		—	245–250d	82
2-Cl, 1-COC_4H_9	Vilsmeier–Haack on oxindole	—	58–60	82
Thiosemicarbazone		—	182–183	82
N-Methylthiosemicarbazone		—	181	82
5-Cl, 2-C_6H_5	Photooxidn. of 3-CH_3	26	295–297	57
2-Cl, 5-OCH_3	Vilsmeier–Haack on oxindole	77	252–255	27
Nitro				
4-NO_2	Vilsmeier–Haack	90	191–192	566
	From glyoxalylamide	40	189–191	69
Semicarbazone		—	>320	566
Thiosemicarbazone		—	>320	566
5-NO_2	Vilsmeier–Haack	97.5	302–303	566
	Nitration	—	312–314	158–159
Semicarbazone		—	320	566
Thiosemicarbazone		—	280–281	566
6-NO_2	Vilsmeier–Haack	97.5	301–302	566
	Nitration	28	301.5–302	158–159
Semicarbazone		—	255–256	566
Thiosemicarbazone		—	260–261	566
7-NO_2	Vilsmeier–Haack	85	210	9

TABLE III. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Thiosemicarbazone		—	266–267	9
4-NO_2, 1-CH_3	Nitration	Low	233–234.5	161
5-NO_2, 1-CH_3	Nitration	15	198–200	160
6-NO_2, 1-CH_3	Nitration	8	203–205	160–161
6-NO_2, 2-CH_3	Nitration	—	>260d	161
5-NO_2, 1,2-$(CH_3)_2$	Vilsmeier–Haack	—	206–208	161
	Nitration	—	—	161
6-NO_2, 1,2-$(CH_3)_2$	Nitration	low	246–248	161
5-NO_2, 2-C_6H_5	Photooxidn. of 3-CH_3	18	330d	57
6-NO_2, 2-C_6H_5	Photooxidn. of 3-CH_3	42	320d	57
7-NO_2, 2-C_6H_5	Photooxidn. of 3-CH_3	21	278–280	57
2-C_6H_4-NO_2-4	Vilsmeier–Haack	—	244	252
Other nitrogen substituents				
4-CN	Vilsmeier–Haack	88	224–226	567
5-CN	AcCl, $SnCl_4$	66	254–255	243
2-$N(CH_3)_2$	Vilsmeier–Haack	74	280d	241
2-NHC_6H_5	Aniline on 2-Cl	59	168-172	27
Anil		—	192–195	27
Phenylhydrazone		—	198	27
5-$NHCOCH_3$	Vilsmeier–Haack	—	231–234	568
5-$NHCO_2CH_2C_6H_5$	Vilsmeier–Haack	—	237.5–239	568
2-$NHCO_2C_6H_5$	Vilsmeier–Haack	—	172–173	254
2-$NHCO_2C_6H_5$, 5-Cl	Vilsmeier–Haack	—	225–227	254
2-$NHCO_2C_6H_5$, 1-$CH_2C_6H_5$	Vilsmeier–Haack	—	145–146	254
2-$NHCO_2C_2H_5$	Vilsmeier–Haack	—	179–180	254
1-$N(CH_3)_2$	Mannich	—	Oil	113
Methiodide		—	194	113
5-$CH_2N(CH_3)_2$, 4-Cl, 1-C_2H_5	Vilsmeier–Haack	28	95–96	47
5-$CH_2N(CH_3)_2$, 4-Cl, 1-C_2H_5 2,6-$(CH_3)_2$	Vilsmeier–Haack	31	108–110	47
2-N=CHN$(CH_3)_2$	Vilsmeier–Haack	—	—	14
Hydroxy				
5-OH, 2-CH_3	Gattermann	—	275	34
2,4-DNP		—	291	34
4-OH, 1-C_2H_5, 2-CH_3	Acetate hydrolysis	—	169–170	501
4-OH, 1-C_2H_5, 2,6-$(CH_3)_2$	Acetate hydrolysis	—	178–180	505
4-OH, 1-C_2H_5, 2,5,6-$(CH_3)_3$	Acetate hydrolysis	—	162–163.5	505
4-OH, 1-CH_3, 2,5-$(CH_3)_2$	Cleavage of ether	—	183–186	413
2-*p*-HO-C_6H_4	Vilsmeier–Haack	—	210	562
5-OH, 1,2-$(CH_3)_2$	Vilsmeier–Haack	—	—	526
5-OH, 2-CH_3, 1-C_6H_5	Vilsmeier–Haack	—	—	526
5-OH, 2-CH_3, 1-$CH_2C_6H_5$	Vilsmeier–Haack	—	—	526
Alkoxy and aralkoxy				
2-OCH_3	Diazomethane methylation	Low	252–253	112

TABLE III. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Oxime		—	181–182	107
2-OCH_3, 1-CH_3	CH_3I and KO*t*-Bu	—	138–139	107
2-OCH_3, 1-$COCH_3$	Acetic anhydride	—	161–163	107
5-OCH_3	Reimer–Tiemann	73	178	44
	Vilsmeier–Haack	94	181–182	131, 459
6-OCH_3	Reimer–Tiemann	—	185	45, 555
	Vilsmeier–Haack	83	185	345, 131
7-OCH_3	Reimer–Tiemann	Low	159–160	44
	Vilsmeier–Haack	—	163–165	557
2,4-DNP		—	343–345	557
4-$OCH_2C_6H_5$	Vilsmeier–Haack	91	168	569
5-$OCH_2C_6H_5$	Vilsmeier–Haack	85	241–242	569
6-$OCH_2C_6H_5$	Vilsmeier–Haack	90	215–216	53, 569
7-$OCH_2C_6H_5$	Vilsmeier–Haack	93.5	159	569
5,7-$(OCH_3)_2$	Vilsmeier–Haack	60	149–150	17
5,6-$(OCH_2C_6H_5)_2$	Vilsmeier–Haack	79	195	569
4,5,6-$(OCH_3)_3$	Vilsmeier–Haack	62	170	16
4-$OCH_2C_6H_5$, 1-CH_3	Vilsmeier–Haack	—	120	571
5-$OCH_2C_6H_5$, 1-CH_3	Methylation with CH_3I	—	128–129	106
5-OCH_3, 6-$OCH_2C_6H_5$	Vilsmeier–Haack	79	207	18
5-OCH_3, 2-CH_3, 1-$CH_2C_6H_5$	Vilsmeier–Haack	50	110.5	573
Oxime		—	166	573
p-Nitrophenylhydrazone		—	230	573
5-OCH_3, 2-CH_3, 1-($CH_2C_6H_4$-4-Cl)	Vilsmeier–Haack	—	139	135
5-OCH_3, 2-CH_3, 1-(COC_6H_4-4-Cl)	Vilsmeier–Haack	—	165	135
2-OCH_3, 1-CH_3	Methylation with CH_2N_2	23	183	112
5-OCH_3, 2-CH_3	Vilsmeier–Haack	—	—	21
5-OCH_3, 6-CH_3	Vilsmeier–Haack	—	192–195	574
5-OCH_3, 1,2-$(CH_3)_2$	Vilsmeier–Haack	—	—	21
5-OCH_3, 2,6-$(CH_3)_2$	Vilsmeier–Haack	—	227–228.5	574
5-OCH_3, 1-C_2H_5, 6-CH_3	Vilsmeier–Haack	—	92–94	574
5-OCH_3, 2-CH_3, 1-C_6H_5	Vilsmeier-Haack	—	—	21
5-OCH_3, 1,2,6-$(CH_3)_3$	Vilsmeier-Haack	—	174–178	574
5-OCH_3, 1-C_2H_5, 2,6-$(CH_3)_2$	Vilsmeier-Haack	—	134–136	574
5-OCH_3, 1-C_3H_7, 2,6-$(CH_3)_2$	Vilsmeier-Haack	—	117.5–119.5	574
5-OCH_3, 1-$CH(CH_3)_2$, 2,6-$(CH_3)_2$	Vilsmeier-Haack	—	172–174	574
5-OCH_3, 1-C_4H_9, 2,6-$(CH_3)_2$	Vilsmeier-Haack	—	96–97	574
5-OCH_3, 1,2-$(C_2H_5)_2$	Vilsmeier-Haack	—	95.5–97	574
5-OCH_3, 1,6-$(C_2H_5)_2$	Vilsmeier-Haack	—	109–110	574
5-OCH_3, 2-CH_3, 1-$CH_2C_6H_5$	Vilsmeier-Haack	—	—	21
1-OCH_3, 2-C_6H_5	Vilsmeier-Haack	—	—	13

TABLE III. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-OC_2H_5, 2-C_6H_5	Vilsmeier–Haack	—	—	13
5-OCH_3, 1-$CH_2CH_2OSO_2CH_3$, 2,6-$(CH_3)_2$	Vilsmeier–Haack	—	187.5–189	574
5-OCH_3, 2-CH_2OCOCH_3, 6-CH_3	Acetylation	—	122.5–123.5	574
5-OCH_3, 4-NO_2, 1-C_2H_5, 6-CH_3	Nitration	—	150–152	574
5-OCH_3, 4-NO_2, 1-C_2H_5, 2,6-$(CH_3)_2$	Nitration	—	155–157	574
5-OCH_3, 4-NO_2, 2,6-$(CH_3)_2$	Nitration	—	280	574
5-OCH_3, 4-NO_2, 1,2,6-$(CH_3)_3$	Nitration	—	183–187	574
5-OCH_3, 4-NO_2, 1-C_3H_7, 2,6-$(CH_3)_2$	Nitration	—	136–138	574
5-OCH_3, 4-NO_2, 1-$CH(CH_3)_2$, 2,6-$(CH_3)_2$	Nitration	—	—	574
5-OCH_3, 4-NO_2, 1-C_4H_9, 2,6-$(CH_3)_2$	Nitration	—	127–128	574
5-OCH_3, 4-NO_2, 1,2-$(C_2H_5)_2$, 6-CH_3	Nitration	—	151–154	574
5-OCH_3, 4-NO_2, 1,6-$(C_2H_5)_2$, 2-CH_3	Nitration	—	181–182.5	574
5-OCH_3, 4-NO_2, 1-$CH_2CH_2OSO_2CH_3$, 2,6-$(CH_3)_2$	Nitration	—	181.5–183	574
5-OCH_3, 4-NO_2, 1-CH_2CH_2F, 2,6-$(CH_3)_2$	KF on mesylate	—	175–178	574
5-OCH_3, 4-NO_2, 1-$CH_2CH_2OCOCH_3$, 2,6-$(CH_3)_2$	NaOAc on mesylate	—	179–180	574
5-OCH_3, 4-NH_2, 2,6-$(CH_3)_2$	Fe/HOAc	—	—	574
5-OCH_3, 4-NH_2, 1-$CH(CH_3)_2$, 2,6-$(CH_3)_2$	Fe/HOAc	—	Oil	574
5-OCH_3, 4-NH_2, 1,2-$(CH_3)_2$, 6-C_2H_5	Fe/HOAc	—	110.5–112.5	574
5-OCH_3, 4-NH_2, 1-CH_2CH_2F, 2,6-$(CH_3)_2$	Fe/HOAc	—	139–141	574
5-OCH_3, 4-NH_2, 1-$CH_2CH_2OCOCH_3$, 2,6-$(CH_3)_2$	Fe/HOAc	—	178–180	574
5-OCH_3, 4-NH_2, 1-$CH_2CH_2OSO_2CH_3$, 2,6-$(CH_3)_2$	Fe/HOAc	—	133–135	574
5-OCH_3, 4-NH_2, 1-$CH_2CH_2N_3$, 2,6-$(CH_3)_2$	NaN_3 on mesylate	—	123–124	574
5-OCH_3, 4-NH_2, 1-$CH_2CH_2SCH_3$, 2,6-$(CH_3)_2$	CH_3SNa on mesylate	—	128.5–130	574
5-OCH_3, 4-NH_2, 1-CH_2CH_2OH, 2,6-$(CH_3)_2$		—	157–159	574
5-CH_3O, 2-Cl	Vilsmeier–Haack	—	—	25

TABLE III. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Acetoxy				
4-$OCOCH_3$, 1-C_2H_5	Vilsmeier–Haack	—	169–170	501
4-$OCOCH_3$, 1-C_2H_5, 6-CH_3	Vilsmeier–Haack	—	168–171	505
4-$OCOCH_3$, 1-C_2H_5, 5,6-$(CH_3)_2$	Vilsmeier–Haack	—	165–168	505
4,5,7-$(OCOCH_3)_3$1-C_2H_5 2,6-$(CH_3)_2$	Thiele acetoxylation of quinone	—	194.5	574
4,7-$(OCOCH_3)_2$, 1-C_2H_5, 2-CH_3	Vilsmeier–Haack	—	124–126	501
5-$OCOCH_3$, 1,2-$(CH_3)_2$	Vilsmeier–Haack	—	—	526
5-$OCOCH_3$, 2-CH_3, 1-C_6H_5	Vilsmeier–Haack	—	—	526
5-$OCOCH_3$, 2-CH_3, 1-$CH_2C_6H_5$	Vilsmeier–Haack	—	—	526
Other				
1-$COCH_3$	Acetic anhydride	90, 98	159–162	62, 197
1-COC_6H_5	Benzoyl chloride	68	85–86	596
1-(4-$ClC_6H_4CH_2$)	Vilsmeier–Haack	—	—	135
1-(4-ClC_6H_4CO)	Vilsmeier–Haack	—	—	135
1-$SO_2C_6H_4CH_3$	$CH_3C_6H_4SO_2Cl$-pyridine	—	148–150	109
1-$CO_2C(CH_3)_3$	Acyl fluoride	93	124–125	110
	Acyl azide	95	—	111
1-$COCH_2C_6H_5$	Acyl chloride	63	—	108
1-$COCH_2CH_2C_6H_5$	Acyl chloride	55	—	108

TABLE IV. INDOLES WITH CARBOXALDEHYDE GROUPS ON THE SIX-MEMBERED RING

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
4-CHO	Oxidn. of alcohol	70	142–144	53, 54, 531
	Redn. of nitrile	70	—	531
Semicarbazone		—	222	53
5-CHO	Oxidn. of alcohol	—	99–101	54, 575
	Redn. of nitrile	90–98	—	532
6-CHO	Oxidn. of alcohol	—	127–129	54, 575
	Redn. of nitrile	90–98	—	532
7-CHO	Oxidn. of alcohol	—	87–89	54
6-CHO, 1-CH_3	Dehydrogenation of indoline	64	82–83	22
	Redn. of nitrile	—	79–81	532

TABLE IV. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Semicarbazone		—	214–215	22
5-CHO, 3-CH_3	Redn. of nitrile	90–98	85–86	532
6-CHO, 4-CH_3	Redn. of nitrile	90–98	104–105	532
5-CHO, 2, 3-$(CH_3)_2$	McFayden–Stevens	—	137–139	64
2, 4-DNP		—	290	64
6-CHO, 2, 3-$(CH_3)_2$	McFayden–Stevens	—	95–96	64
2, 4-DNP		—	>340	64
7-CHO, 2, 3-$(CH_3)_2$	McFayden–Stevens	—	126–127	64
Semicarbazone		—	220–222	64
4-CHO, 2, 3-$(C_6H_5)_2$	McFayden–Stevens	—	204–205	64
2, 4-DNP		—	310–312	64
5-CHO, 2, 3-$(C_6H_5)_2$	McFayden–Stevens	—	208–210	64
Semicarbazone		—	332–335	64
6-CHO, 2, 3-$(C_6H_5)_2$	McFayden–Stevens	—	187–188	64
2, 4-DNP		—	304–307	64
7-CHO, 2, 3-$(C_6H_5)_2$	McFayden–Stevens	—	138–139	64
Semicarbazone		—	209–210	64
7-CHO, 4, 6-$(OCH_3)_2$	Vilsmeier–Haack	56	201–202	15
5-CHO, 4-Cl, 6, 7-H_2, 2-CH_3	Vilsmeier–Haack	Low	122–124	360
5-CHO, 4-Cl, 6, 7-H_2, 1-C_2H_5, 2-CH_3	Vilsmeier–Haack	—	100–107	360
5-CHO, 4-Cl, 6, 7-H_2 1-$SO_2C_6H_5$	Vilsmeier–Haack	45	150–154	360
3,5-$(CHO)_2$, 4-Cl, 6, 7-H_2, 2-CH_3	Vilsmeier–Haack	—	dec>180	360
3,5-$(CHO)_2$, 4-Cl, 6, 7-H_2, 1-C_2H_5, 2-CH_3	Vilsmeier–Haack	28	124–134	360
3, 5-$(CHO)_2$, 4-OCH_3, 6, 7-H_2, 1-C_2H_5, 2-CH_3	Methanolysis of 4-Cl	45	110–120	360
3, 5-$(CHO)_2$, 4-Cl, 1-C_2H_5, 2-CH_3	DDQ on 6,7-dihydro	70	160	360
3, 5-$(CHO)_2$, 4-OCH_3, 1-C_2H_5, 2-CH_3	DDQ on 6,7-dihydro	25	187–190	360
5-CHO, 4-OH, 1-C_2H_5, 2,6-$(CH_3)_2$	DDQ on 6,7-dihydro	51	129–130.5	501
3,7-$(CHO)_2$, 4-OCH_3	Vilsmeier–Haack	—	242–248	15
3,7-$(CHO)_2$, 2-Cl, 1-COC_6H_5	Vilsmeier–Haack on oxindole	—	-	82
Bisthiosemicarbazone		—	>300	82
Bis-*N*-methylthiosemicarbazone		—	254–256d	82
Bisguanylhydrazone		—	>300d	82

TABLE V. MISCELLANEOUS INDOLINECARBOXALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
5-CHO	Vilsmeier–Haack	—	Oil	576
5-CHO, 1-CH_3	Photochemical Reimer–Tiemann	27	Oil	46
Semicarbazone		—	212–214	46
6-CHO, 1-CH_3	Vilsmeier–Haack	52	39	22
7-CHO, 1-CH_3	Photochemical Reimer–Tiemann	14	Oil	46
5-CHO, 1-C_4H_9, 2-CH_3	Vilsmeier–Haack	—	Oil	577
3-CHO, 2-C_6H_5- 4,5,6,7-H_4	Vilsmeier–Haack	75	217–218	23
Oxime		—	210–211	23
3-CHO, 2-CH_3, 1-C_4H_9, 4,5,6,7-H_4	Vilsmeier–Haack	60	bp_4 168–169	23
3-CHO, 2-C_6H_5, 1-C_2H_5, 4,5,6,7-H_4	Vilsmeier–Haack	89	132–133	23

TABLE VI. INDOLE-2-ACETALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
5-OCH_3	Redn. of acid chloride	—	—	187
α,α-$(CH_3)_2$	Oxidn. of alcohol	—	68–70	184

TABLE VII. α-METHYLENEINDOLINE-ω-CARBOXALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1,3,3-$(CH_3)_3$	Vilsmeier–Haack	95	112–115	174, 175
1,3,3-$(CH_3)_3$, ω-CN	Vilsmeier–Haack	70	154–156	176
1,3,3-$(CH_3)_3$, 5-C_6H_5, ω-CN	Vilsmeier–Haack	—	252–253	177
1,3,3-$(CH_3)_3$, 5-OCH_3, ω-CN	Vilsmeier–Haack	—	198–199	176
1,3,3-$(CH_3)_3$, 5-Cl, ω-CN	Vilsmeier–Haack	—	180–181	176

TABLE VIII. INDOLE-3-ACETALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
None	$NaIO_4$ cleavage of glycol	—	Oil n_D^{20} 1.6178	185, 579
Bisulfite adduct	NaOCl oxidn. of tryptophan, followed by $NaHSO_3$	—		178
Oxime	Hydrolysis of imidazoline, followed by H_2NOH	86	140–142	578
	H_2NOH on bisulfite adduct	—	140–141	199
Semicarbazone	Directly from aldehyde	—	142–50	579
	Hydrogenation of nitrile in presence of semicarbazide	60	150	198
Phenylhydrazone			112–113	578
1-$COCH_3$				
Oxime	Reduction of nitrile	—	137–138	578
Phenylhydrazone		—	121–124	578
Semicarbazone		—	201–202	578
2-CH_3	NaOCl oxidn. of tryptophan	—	—	179
Semicarbazone	Reduction of nitrile in presence of semicarbazide	—	179–181	189
α-CH_3	Oxidn. of indolymycin	—	—	
Semicarbazone		—	182	186
1,α-$(CH_3)_2$	Oxidn. of alcohol	65	69–70	183
Semicarbazone		—	208–209	183
α-NH_2	Sodium amalgum redn. of methyl tryptophanate			
2,4-DNP, HCl		—	173–174	192
5-OH	LAH redn. of acyl pyrazole			
2,4-DNP		—	168–169	190
α-OH	LAH redn. of glyoxalyl-amide	—	72–73	191
Semicarbazone		—	260	191
5-$OCH_2C_6H_5$	NaOCl oxidn. of tryptophan deriv.			
Bisulfite adduct		—	—	580
Semicarbazone		—	150–151	580
α-CO		—	—	206
5-CH_3O, 2-CH_3,	Cleavage of β-OH ester	—	118–120	195
1-COC_6H_4Cl	Oxidative cleavage of tryptophan deriv.	—	118–120	181
α-CF_3, 5-CH_3O, 2-CH_3,	Cleavage of β-OH ester	—	—	196

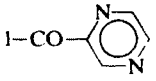


TABLE VIII. *(Continued)*

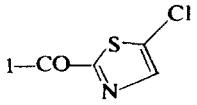
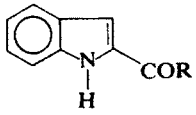
Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
α-CF_3, 5-CH_3O, 2-CH_3, 1-COC_6H_4Cl	Cleavage of glycidic ester	—	—	200
α-CF_3, 5-CH_3O, 2-CH_3,	Cleavage of glycidic ester	—	—	222
				
α,β-Dehydro	Elimination from triethoxypropyl	—	155–156	197

TABLE IX. INDOLE-4-ACETALDEHYDES

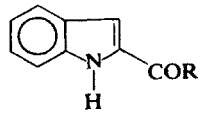
Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
None	Ring closure of an aldehyde, followed by $NaHSO_3$	—	—	531
Bisulfite adduct			72	531
Semicarbazone		70	209	531
1-$COCH_3$		35	64–66	202
1-$SO_2C_6H_4CH_3$		56	104	203

TABLE X. 2-INDOLYL KETONES



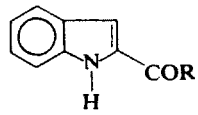
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
CH_3; none	Redn. of 2-diazoaceto deriv.	—	150–151.5	323
	Ac_2O and BF_3	25	144–145	217
	Ac_2O and $Mg(ClO_4)_2$	50	—	214
	Reductive cyclization of nitro compound	16	—	593
	Fischer	7	190	324

TABLE X. (*Continued*)



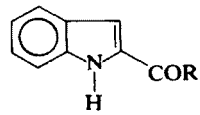
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
Phenylhydrazone		—	311	323
CH_3; 1-CH_3	Fischer	68	71	324
CH_3; 3-CH_3	Fischer	—	—	325
Hydrazone		—	142–144	291
CH_3; 1,3-$(CH_3)_2$	Ac_2O and PPA	78	86–87	
CH_3; 5-$COCH_3$, 3-CH_3	Fischer	39	202–205	217
CH_3; 5-$COCH_3$, 1,3-$(CH_3)_2$	Methylation	95	127–128	217
CH_3; 3-C_6H_5	Fischer	Nearly quant.	151	275
CH_3; 1-C_6H_5	Fischer	49	102	324
CH_3; 3-(2-phthalimidoethyl)	Fischer	Nearly quant.	214	275
CH_3; 5-OCH_3, 3-(2-phthalimidoethyl)	Fischer	—	218	275
CH_3; 3-C_6H_5, 5,6-$(OCH_3)_2$	Fischer	~100	181	163
CH_3; 3,3-dimethylindolenine	Autoxidation			269
CH_3; 3,3-trimethylene-indolenine	Autoxidation	~100	129–130.5	268, 269
CH_3; $COCH_3$	Photooxygenation of heterocycle			274
C_2H_5; 3-CHO, 1-CH_3	Photooxygenation of heterocycle			274
C_6H_5; none	Intramolec. nitrene insertion	73	—	290
	Nitrile on lithio-indole	26	147–148.5	273
C_6H_5; 3-CH_3	Vilsmeier-Haack	—	138.5–140	235
C_6H_5; 1-CH_3	Fischer	81	140–140.5	279
C_6H_5; 1-C_2H_5	Ethylation	—	62–64	593
C_6H_5; 1,3-$(CH_3)_2$	Fischer	96	55–56	279
C_6H_5; 3,5-$(CH_3)_2$	Fischer	95	131–132	279
C_6H_5; 1,3,5-$(CH_3)_3$	Fischer	95	69–70	279
C_6H_5; 5-OCH_3, 3-CH_3	Fischer	33	157–158	279
C_6H_5; 5-Cl, 3-CH_3	Fischer	58	160–161	279
C_6H_5; 5-Cl, 1,3-$(CH_3)_2$	Fischer	94	85–86	279
C_6H_5; 1-CH_2OCH_3	Acid chloride on lithioindole	84	56–57.5	273
C_6H_5; 1-$SO_2C_6H_5$	Acid chloride on lithioindole	65	142–144	273
	Ester on lithio-indole	26	142–144	273

TABLE X. (*Continued*)



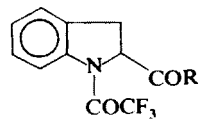
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
4-$CH_3OC_6H_4$; none	—	—	—	325
4-$CH_3OC_6H_4$; 3-CH_3	Fischer	94	155–156	279
4-$CH_3OC_6H_4$; 1-CH_3	—	—	—	325
4-$CH_3OC_6H_4$; 1-CH_2OCH_3	Nitrile on lithio-indole	70	97–98.5	273
4-$CH_3OC_6H_4$; 3,5-$(CH_3)_2$	Fischer	80	154–155	279
4-$CH_3OC_6H_4$; 5-Cl, 3-CH_3	Fischer	57	173–173.5	279
4-$CH_3OC_6H_4$; 5-OCH_3, 3-CH_3	Fischer	46	161–162	279
3,4-$(CH_3O)_2C_6H_3$; 3-CH_3	Fischer	47	162–163	279
3,4$(CH_3O)_2C_6H_3$; 5-OCH_3, 1,3-$(CH_3)_2$	Fischer	98	133–134	279
3,4-$(CH_3O)_2C_6H_3$; 3,5-$(CH_3)_2$	Fischer	75	193–194	279
4-ClC_6H_4; 3-CH_3	Fischer	83	167–167.5	279
4-ClC_6H_4; 3,5-$(CH_3)_2$	Fischer	78	179–180	279
4-ClC_6H_4; 5-Cl, 3-CH_3	Fischer	79	210–211	279
4-$CH_3C_6H_4$; none	—	—	—	325
4-$CH_3C_6H_4$; 3-CH_3	Fischer	84	150–151	279
4-$CH_3C_6H_4$; 1-CH_3	—	—	—	325
4-$CH_3C_6H_4$; 3,5-$(CH_3)_2$	Fischer	78	183–184	279
4-$CH_3C_6H_4$; 5-OCH_3, 3-CH_3	Fischer	48	177–178	279
4-$CH_3C_6H_4$; 1,3,5-$(CH_3)_3$	Fischer	91	83–85	279
CH_2I; none	Cu_2I_2 on diazoketone	8	245–246	271
CH_2Cl; none	HCl on diazoketone	89	208–210	271
CH_3; none	Diazomethane on acid chloride	92	d > 150	595
CH_2-(1-Piperidyl); none	From α-chloroketone	—	250–255d (HCl)	271
CH_2-(1-Pyrrolidinyl); none	From α-chloroketone	—	245–250d (HCl)	271
CH_2Cl; 3-CH_3	$ClCOCH_2Cl$ on Grignard	—	—	224
CF_3; 3-CH_3	Modified Hoesch	40	116	258
CH_2OH; 3-CH_3	KOH on halide	—	198–200	224
CHO; none	Hydrol. of ald. ammonia	—	115	584
Phenylhydrazone		—	223	584
CHO; 3-CH_3	Hydrol. of ald. ammonia	—	137	584
2-Pyridyl; none	nitrile on lithio-indole	36	134.5–136	273

TABLE X. (*Continued*)



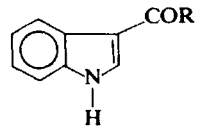
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
	Intramolecular nitrene insertion	51	—	289
2-Pyridyl; 1-CH_2OCH_3	Nitrile on lithioindole	56	92–93.5	273
3-Pyridyl; none	Nitrile on lithioindole	22	171–173	273
3-Pyridyl; 1-$SO_2C_6H_5$	Acid chloride on lithioindole	60	128–129	273
4-Pyridyl; none	Nitrile on lithioindole	31, 26	172–174	273
	Fischer	33	172–174	276
4-Pyridyl; 1-CH_2OCH_3	Nitrile on lithioindole	56	90–91	273
4-(2-Ethylpyridyl); none	Fischer	70	151–153	278
(4-Piperidyl)methyl; none	Hydrol. of benzoyl	—	167–169	283
4-(*N*-Benzoylpiperidyl) methyl; none	Redn. of nitro ketone	13	154–156	283

TABLE XI. 2-INDOLINYL KETONES



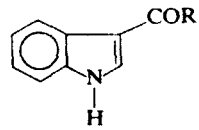
Substituent R	Method of synthesis	Yield (%)	mp (°C)	Ref.
CH_3	Redn. of CH_2Br	87	108.5–109.5	272
CH_2Br	HBr on diazoketone	90	121.5–123	272
CHN_2	Diazomethane on acid chloride	86	124.7–125.7	272

TABLE XII. 3-INDOLYL KETONES



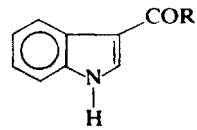
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
Alkyl				
CH_3; none	CH_3CO_2Et on indolyl	Low	189	36
	Grignard	—		
	Fischer	20–50	190	324
	Ac_2O, vinyl acetate	66		211
	Ac_2O, $HClO_4$	30		212
	Ac_2O, $SiCl_4$	21	191	120
	AcOH, pentamethyl-dioxolane	51		263
Oxime			149	582
Oxime			95	582
2-Aminoethoxime hydrochloride			174–177	292
Hydrazone			260–270	583
CH_3; 1-CH_3	Fischer	68	108	324
	Ac_2O	—	—	216
	Methylation	—	95	322
	Tosyhydrazone of diacetylmethyl-cyclohexane	—	—	288
CH_3; 1-C_2H_5	Alyklation	—	88	322
CH_3; 1-C_4H_9	Alkylation	—	119	322
CH_3; 1-$COCH_2COCH_3$	Ac_2O	13	178–179	581
CH_3; 2-CH_3	Hydrol. of sulfamoyl cpd.	91	240.5–242.5	
	Ac_2O	40	—	215, 216
	Vilsmeier–Haack	98		
2,4-DNP			263–264	215
CH_3; 1,2-$(CH_3)_2$	Ac_2O	—	103–104	215, 216
CH_3; 1-C_6H_5	Fischer	35	141–143	324
CH_3; 2-C_6H_5	Ac_2O	—	275–277	194, 215
	Vilsmeier–Haack	76	222–223	247
	CH_3COCl on Grignard	32		
CH_3; 2-$N(CH_3)_2$	AcCl, pyridine	75	195	241
CH_3; 5-CN	AcCl, $SnCl_4$	70	300	243
CH_3; 1-CH_2OH	HCHO, Na_2CO_3	—	115–116	318
CH_3; 2-C_6H_5, 5-CH_3O	Vilsmeier–Haack	91	247	247
CH_3; 2-C_6H_5, 5-Br	Bromination	—	246	247
CH_3; 5-$OCH_2C_6H_5$	Vilsmeier–Haack	71	189–190	249
CH_3; 1-C_2H_5	Vilsmeier–Haack	76	87–90	249
CH_3; 2-CH_3, 5-OH, 1-*p*-tolyl	Nenitzescu cond.	37	264	285
CH_3; 2-CH_3, 5-OH, 1-*p*-anisyl	Nenitzescu cond.	50	262	285

TABLE XII. (*Continued*)



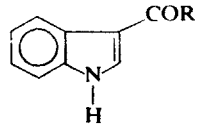
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
CH_3; 2-CH_3, 5-OH, 1-*p*-dimethylaminophenyl	Nenitzescu cond.	57	285–287	285
CH_3; 2-CH_3, 5-OH, 1-(2-hydroxethylbenzyl)	Nenitzescu cond.	—	234–236	285
CH_3; 1-(3-D-glucosyl)	Friedel–Crafts	—	—	242
CH_3; 2-CH_3, 4,5,6,7-H_4	Cond. of α-oximinocyclohexanone with acetylacetone	—	203	287
CH_3; 5-$COCH_3$	Vilsmeier–Haack	10		280, 220
CH_3; 1,5-$(COCH_3)_2$	Ac_2O, 140°	75		280
CH_3; 2-CH_3, 1-$(CH_2)_3NH_2$	Fischer	—	—	281
CH_3; 2-$NHCO_2C_6H_5$	Vilsmeier–Haack	—	155–156	254
C_2H_5; none	Vilsmeier–Haack	86	171–173	249, 317
C_2H_5; 1-CH_3	Methylation	—	80.5–81.5	317
C_2H_5; 5-CN	Acid chloride, $SnCl_4$	69	262–264.5	243
C_2H_5; 1-$CH_2CH_2CH_2N(CH_3)_2$ Oxime	Alkylation	—	Oil	287
		—	135–137	287
C_2H_5; 1-$CH_2CH_2N(CH_3)_2$ Oxime	Alkylation	—	Oil	287
			145	287
C_2H_5; 1-$CH(CH_3)CH_2N(CH_3)_2$ Oxime	Alkylation	—	Oil	287
			164	287
C_3H_7; none	—	—	175	287
C_3H_7; 2-CH_3	Houben–Hoesch	—	150–154	11
$CH(CH_3)_2$; 2-CH_3	Houben–Hoesch	—	186	11
$CH(CH_3)_2$; 5-CN	Acid chloride, $SnCl_4$	65	250–252.5	243
$CH(CH_3)_2$; 2-$NHCO_2C_6H_5$	Vilsmeier–Haack	—	128–129	254
C_4H_9; none	—	—	—	287
$C(CH_3)_3$; 2-CH_3	Vilsmeier–Haack	49	134–135	249
$CH(CH_3)C_2H_5$; 2-CH_3	Vilsmeier–Haack	18	101–103	249
$CH_2CH(CH_3)_2$; 2-CH_3	Vilsmeier–Haack	62	139–141	249
Cyclohexyl; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	172	594
Aryl and aralkyl				
C_6H_5; none	Vilsmeier–Haack	51	241–243.5	152
	Acid chloride on Grignard	47	237–239	236
	Houben–Hoesch	100	238	261
	Phenylthiomethyl-1,3-dithiane, $CuCl_2$	64	—	264
C_6H_5; 1-$CH_2CO_2C_2H_5$	Alkylation	—	216–218	264
C_6H_5; 2-CH_3	Houben–Hoesch	33	195–196	256
C_6H_5; 1,2-$(CH_3)_2$	Methylation	—	139–140	305
C_6H_5; 2-CH_3, 1-$CH_2CH_2NH_2$	Fischer	—	—	281

TABLE XII. (*Continued*)



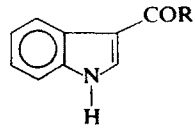
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
C_6H_5; 5-CN	Acid chloride, $SnCl_4$	55	289–290	243
$CH_2C_6H_5$; none	—		207	243, 305
$CH_2C_6H_5$; 2-CH_3	Houben–Hoesch	80	196–197	256
$CH_2C_6H_5$	Acid chloride, $SnCl_4$	38	259–261	243
2-$CH_3C_6H_4$; none	Acid chloride on Grignard	—	190–192	235
3-$CH_3C_6H_4$; none	Vilsmeier–Haack	62	234–236	235
4-$CH_3C_6H_4$; none	Acid chloride on Grignard	65	179–181	235
C_6H_5; 2-C_6H_5	Hydrol. of sulfamoyl cpd.	100	237–239	286
C_6H_5; 2-$N(CH_3)_2$	AcCl, pyridine	47	190	241
C_6H_5; 2-$NHCO_2C_6H_5$	Vilsmeier–Haack	—	170–171	254
C_6H_5; 2-$NHCO_2C_6H_5$, 5-Cl	Vilsmeier–Haack	—	167–168	254
$CH_2CH_2C_6H_5$; none	Fischer	—	161	233
	Redn. of epoxide	95	—	304
$CH_2CH_2C_6H_5$; 2-CH_3	Fischer	—	147	233
$CH_2CH_2C_6H_4$-4-CH_3; none	Fischer	—	139	233
$CH_2CH_2CH_2C_6H_5$; 2-CH_3	Fischer	—	158	233
$CH_2CH_2C_6H_4$-4-Cl; none	Fischer	—	198	233
$CH_2CH_2C_6H_4$-4-Cl; 2-CH_3	Fischer	—	165	233
2-FC_6H_4; none	Vilsmeier-Haack	17	195–198	248
	Acid chloride on Grignard	46		
2-FC_6H_4; 1-CH_3	Methylation	64	105–107	248
4-ClC_6H_4; 2-$NHCO_2C_6H_5$	Vilsmeier–Haack	—	189–190	254
o-(Benzylamino)phenyl; 1-CH_3	Rearrgt.	—	—	248
4-$C_2H_5C_6H_4$; none	Acid chloride on Grignard	—	199	248
4-$CH_3OC_6H_4$; 2-$NHCO_2C_6H_5$	Vilsmeier–Haack	—	157–158	254
4-$CH_3C_6H_4$; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	217	594
4-FC_6H_4; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	228	594
4-$F_3CC_6H_4$; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	222	594
4-$CH_3OC_6H_4$; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	191	594
4-$CH_3SC_6H_5$; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	195	594
4-ClC_6H_4; 6-Cl, 2-CH_3	Vilsmeier–Haack	—	225	594
4-ClC_6H_4; 6-OC_4H_9, 2-CH_3	Vilsmeier–Haack	—	175	594
2-ClC_6H_4; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	228	594
4-$CH_3OC_6H_4$; 6-Cl, 2-CH_3	Vilsmeier–Haack	—	224	594
4-ClC_6H_4; 2-CH_3	Vilsmeier–Haack	—	189	594
4-$CH_3SO_2C_6H_4$; 6-OCH_3, 2-CH_3	Vilsmeier–Haack	—	244	594

TABLE XII. (*Continued*)



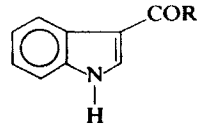
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-Napthyl; none	Acid chloride on Grignard	—	236	237
2-Naphthyl; none	Acid chloride on Grignard	—	257	237
1-Naphthylmethyl; none	Acid chloride on Grignard	—	229	237
2,3-Dimethylbenzyl; none	Acid chloride on Grignard	15	214–216	232
2,3-Dimethylbenzyl; 2-CH_3	Nitrile on Grignard	42	168–169	232
3,4-Dichlorobenzyl; none	Acid chloride on Grignard	37	218–220	232
3,4-Dimethylbenzyl; 5-Br	Acid chloride on Grignard	9	253	232
3,4-Dichlorobenzyl; 2-CH_3	Nitrile on Grignard	70	168–169	232
2,4-Dichlorobenzyl; 2-CH_3	Nitrile on Grignard	42	209–211	232
2,3,4-Trimethoxybenzyl; none	Acid chloride on Grignard	48	246–248	232
2,3-Dimethoxybenzyl; none	Acid chloride on Grignard	33	196–197	232
3-Methoxybenzyl; none	Acid choride on Grignard	9	160–162	232
3,4-Methylenedioxybenzyl; 2-CH_3	Nitrile on Grignard	48	202–204	232
3,4-Methylenedioxybenzyl; 5,6-methylenedioxy	Acid chloride on Grignard	10	256	232
2-Cl-3,4-Dimethoxybenzyl; none	Acid chloride on Grignard	30	237–239	232
5-Cl-3,4-Dimethoxybenzyl; none	Acid chloride on Grignard	24	216–217.5	232
2-Cl-4,5-Dimethoxybenzyl; none	Acid chloride on Grignard	41	226–227	232
2-Br-4,5-Dimethoxybenzyl; none	Acid chloride on Grignard	31	218–219.5	232
3-Methoxybenzyl; 5-Br	Acid chloride on Grignard	5	193–194	232
5-Cl-3,4-Dimethoxybenzyl; 5-Br	Acid chloride on Grignard	25	240–242	232
2-Br-4,5-Dimethoxybenzyl; 5-Br	Acid chloride on Grignard	Trace	258–260	232
Vinyl				
$CH{=}CHC_6H_5$; none	Dehydration of alcohol	—	233	307
$CH{=}CH{-}C_6H_4$-4-CH_3; none	Dehydration of alcohol	—	201	307

TABLE XII. (*Continued*)



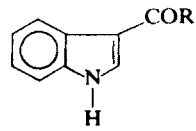
Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
CH=CH-C_6H_4-2-OCH_3; none	Dehydration of alcohol	—	206	307
CH=CH-C_6H_4-4-OCH_3; none	Dehydration of alcohol	—	204	307
CH=CH-C_6H_4-4-OH; none	Dehydration of alcohol	—	211	307
CH=CH-C_6H_4-2-Cl	Dehydration of alcohol	—	238	307
CH=CH-2-quinolyl	Dehydration of alcohol	—	275	307
CH=CH-2-naphthyl	Dehydration of alcohol	—	241	307
CH=CH-2-thienyl	Dehydration of alcohol	—	229	307
CH=CH-2-pyridyl	Dehydration of alcohol	—	220	307
CH=CH-3-pyridyl	Dehydration of alcohol	—	216	307
Haloalkyl				
F_3C; none	Modified Hoesch	—	214	258
	$(CF_3CO)_2O$, DMF	63–95	—	221
F_3C; 1-CH_3	Modified Hoesch	100	105	258
F_3C; 2-CH_3	Modified Hoesch	—	152	258
F_3C; 7-CH_3	Modified Hoesch	—	214	258
F_3C; 7-CH_3, 1-$CH_2C_6H_5$	Modified Hoesch	—	140	258
F_3C; 5-CN	Acid chloride, $SnCl_4$	88	269–271	243
F_3C; 5,6-$(OCH_3)_2$	Modified Hoesch	—	207	258
F_3C; 5,6-OCH_2O	Modified Hoesch	—	268	258
F_3C; 2-CH_3, 5-OCH_3	$(F_3CCO)_2O$	50	185–185.5	222
Cl_3C; none	Modified Hoesch	—	235–237	258
	Acid chloride on Grignard	—	228	229
	Acid chloride in pyridine	71	235–237	240
Cl_3C; 7-CH_3	Modified Hoesch	—	202	258
Cl_3C; 5-OCH_3	Acid chloride in pyridine	85	210–212	240
$ClCH_2$; 2-CH_3	Acid chloride on Grignard	—	196	310
$ClCH_2$; 1-CH_3	Vilsmeier–Haack	68	151–154	252
$ClCH_2$; 5-OCH_3	Acid chloride in pyridine	75	210–212	210
$ClCH_2$; 5-$COCH_3$	Vilsmeier–Haack	—	—	253
$ClCH_2$; 5-$COCH_2Cl$	Vilsmeier–Haack	—	—	253
$ClCH_2$; 2-$NHCO_2CH_2C_6H_5$	Vilsmeier–Haack	—	184–185	311
$ClCH_2$; 2-$NHCO_2C_6H_5$	Vilsmeier–Haack	—	184–185	254
$ClCHCH_3$; none	Acid chloride in pyridine	56	193–194	240
$ClCH_2$; none	Acid chloride on Grignard	—	230–232	224, 225

TABLE XII. (*Continued*)



Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
	Vilsmeier–Haack	36	233–234	249, 251
Cl_2CH; none	Acid chloride on Grignard	—	202	229
$BrCH_2$; none	Bromination	75	230	308
Br_2CH; none	KBr on dichloro cpd.	—	—	229
Aminoalkyl				
H_2NCH_2; none	NH_3 on chloromethyl	—	237	310
$(CH_3)_2NCH_2$; none	Amine on bromomethyl	84	208–209	308
		71	203–205	243
$(C_2H_5)_2NCH_2$; none	Amine on bromomethyl	85	136–137	308
CH_3NHCH_2; none	Amine on bromomethyl	58.5	197.8	308
$C_4H_9NHCH_2$; none	Amine on chloromethyl	—	148	309
$H_2C{=}CHCH_2NHCH_2$; none	Amine on chloromethyl	—	175	309
Cyclohexyl-$NHCH_2$; none	Amine on chloromethyl	—	175	309
$C_6H_5NHCH_2$; none	Amine on chloromethyl	—	201–202	309
$C_6H_5CH_2NHCH_2$; none	Amine on chloromethyl	—	221	309
γ-Picolyl$NHCH_2$; none	Amine on chloromethyl	—	248–250	309
H_2NCH_2; 2-CH_3	NH_3 on chloromethyl	—	240	310
$CH_3NHCH_2CH_2CH_2$; none	$POCl_3$ and N-methyl pyrrolidone	19	108–113	250
Piperidino-CH_2; none	Amine on bromomethyl	75	169–170	308
Piperidino-CH_2; 1-CH_3 HCl	Amine on chloromethyl	—	266–268	252
Morpholino-CH_2; none	Amine on bromomethyl	89	167	308
Morpholino-CH_2; 1-CH_3 HCl	Amine on chloromethyl	—	234–237	252
$(CH_3)_2NCH_2$; 5-NO_2	Amine on bromomethyl	61	250–255	243
$(CH_3)_2NCH_2$; 5-CN	Amine on bromomethyl	83	252–255	243
$(C_2H_5)_2NCH_2$; 5-CN	Amine on bromomethyl	88	196.5–198.5	243
Piperidino-CH_2; 5-CN	Amine on bromomethyl	49	207–213	243
Morpholino-CH_2; 5-CN	Amine on bromomethyl	83	220–224	243
$(CH_3)_2NCH(CH_3)$; 5-CN	Amine on bromomethyl	50	219–222	243
Pyrrolidinyl-CH_2; 2-$NHCO_2CH_2C_6H_5$	Amine on chloromethyl	—	164–165	311
Piperidino-CH_2; 2-$NHCO_2CH_2C_6H_5$	Amine on chloromethyl	—	160–161	311
Morpholino-CH_2;	Amine on chloromethyl	—	187–188	311
4-Methylpiperazino-CH_2' 2-$NHCO_2CH_2C_6H_5$	Amine on chloromethyl	—	176–177	311
4-(β-OH-Ethyl)piperazino-1-CH_2; 2-$NHCO_2CH_2C_6H_5$	Amine on chloromethyl	—	167–168	311

TABLE XII. (*Continued*)



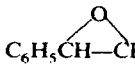
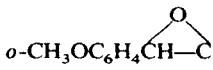
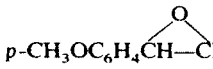
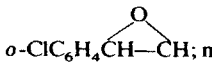
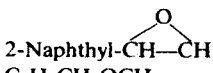
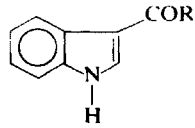
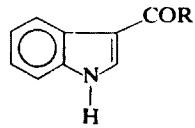
Substituent	Method of synthesis	Yield (%)	mp (°C)	Ref.
$(C_2H_5)_2NCH_2$; 2-$NHCO_2CH_2$-C_6H_5	Amine on chloromethyl	—	179–180	311
Other nitrogen				
$NCCH_2$; 2-CH_3	KCN on chloromethyl	—	249	224, 310
N_3CH_2; none	Azide on bromoethyl	92	184–186	243
N_3CH_2; 5-CN	Azide on bromomethyl	72	220–225	243
$N_3CH(CH_3)$; 5-CN	Azide on bromoethyl	31	190–192	243
Hydroxy and ether				
$HOCH_2$; none	Hydrogenolysis of benzyl ether	—	90–91	303
$HOCH_2$; 1-CH_3	Alkylation	—	80–81	303
$HOCH_2$; 2-CH_3	KOH on chloromethyl	—	196	224, 310
$HOCH_2$; 1-CH_2OH	$HCHO + Na_2CO_3$	—	152–154	318
$HOCH_2$; 5-$COCH_2OH$	—	—	—	253
$HOCH_2$; 5-$COCH_3$	Hydrol. of acetate	—	—	253
CH_3OCH_2; 5-$COCH_3$	NaOAc on halide	—	—	253
$CH_3CO_2CH(CH_3)$; 1-CH_2OH	$HCHO + Na_2CO_3$	—	129-131	318
C_2H_5O; 2-CH_3	$C_2H_5OCH_2COCl$ on Grignard	—	157	230
$C_6H_5CH(OH)CH_3$; none	Cond. with benzaldehyde	20	159	307
p-$O_2NC_6H_5CH(OH)CH_2$; none	Cond. with p-$O_2NC_6H_4CHO$	—	229–233	307
 none	H_2O_2, NaOH on vinyl	—	204–205	304, 307
 none	H_2O_2, NaOH on vinyl	—	221	307
 none	H_2O_2, NaOH on vinyl	—	209	307
 none	H_2O_2, NaOH on vinyl	—	230	307
 none	H_2O_2, NaOH on vinyl	—	220	307
$C_6H_5CH_2OCH_2$; none	Acid chloride on Grignard	50	212	231
3,4-$(CH_3O)_2C_6H_3CH_2$; 5-Br	Acid chloride on Grignard	37	228–230	232

TABLE XII. *(Continued)*



Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
2-NO_2, 3-CHO, 4-CH_3 —$C_6H_2CH_2$; 5-Br	Nitration	—	250	232
3,4-$(OCH_2O)C_6H_3CH_2$; none	Acid chloride on Grignard	95	145–146	232
2-NO_2, 3,4-$(OCH_2O)C_6H_3$-CH_2; none	Nitration	—	239–240	232
3,4-$(OCH_2O)C_6H_3CH_2$; 5-Br	Acid chloride on Grignard	38	256–258	232
2-NO_2, 3,4-$(OCH_2O)C_6H_3$-CH_2; 5-Br	Nitration	—	266	232
Heterocyclic				
2-Furyl; none	Ester on Grignard	—	188–189	228
	Acid chloride on Grignard	—	—	226
2-Furyl; 1-CH_3	Methylation	—	128	226
2-Furyl; 2-CH_3	Acid chloride on Grignard	—	165	237
2-Thienyl; none	Acid chloride on Grignard	—	181	226
2-Thienyl; 1-CH_3	Methylation	—	145	226
2-(3-Methylthienyl); none	Acid chloride on Grignard	—	165	226
2-(5-Methylthienyl); none	Acid chloride on Grignard	—	226–227	226
2-Thienyl; 2-CH_3	Acid chloride on Grignard	—	167	237
3-Pyridyl; none	Acid chloride on Grignard	—	210–211	238
	SeO_2 oxidation of methylene	25	191	265
HCl			178–180	238
2-Pyridyl; 1-β-D-glucosyl	Friedel–Crafts	—	—	242
3-(2-Chloropyridyl); none	Nitrile on Grignard	—	234.5–236.5	250
2-Quinuclidinyl; none	Cyclization of precursor	63	267–269	239
4-(1-benzyloxycarbonylpiperidino)-propionyl; none	Acid chloride on Grignard	47	162–165	239
(3-Indolyl)ethyl; none	β-Chloro ester on Grignard	low	199–200	585
Oxo				
CHO; none	Oxidn. of chloromethyl	—	105–110	193, 206

TABLE XII. *(Continued)*



Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Bisulfite adduct		52	—	206
Aldoxime		26	206d	206
CHO; 2-CH_3	SeO_2 oxidn. of methyl	—	188	194
Oxime		—	190	194
Phenylhydrazone		—	168	194
Semicarbazone		—	232	194
CHO; 2-C_6H_5	—	—	247	194
Oxime		—	189	194
Phenylhydrazone		—	189	194
Semicarbazone		—	243	194
$CH_3COCH(C_5H_5)$; none	Keto ester on Grignard	—	144–145	228
CH_3COCH_2; none	Diketene	40	146-148	259
CH_3COCH_2; 1-CH_3	Diketene	51	164–166	259
CH_3COCH_2; 1-$COCH_2COCH_3$	Diketene	—	—	259
$CH_3COCH(CH_3)$; none	Ethylation	75	140–141	259
$CH_3COCH(C_2H_5)$; none	Methylation	78	142–143	259

TABLE XIII. 3-INDOLINYL KETONES

Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
C_6H_5; 1-CH_3, 2-C_6H_5	C_6H_5MgBr on ketone	—	115.5–116	305
C_6H_5; 1,2-$(CH_3)_2$, 2-C_6H_5	C_6H_5MgBr on ketone	—	139–140	305

TABLE XIV. OTHER INDOLYL KETONES WITH THE CARBONYL GROUP ON THE SIX-MEMBERED RING

Carbonyl position; other substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
4-OCH_3; 1-$COCH_3$	Diazomethane on aldehyde	—	127.5–128	189
4-$COCH_3$; 1-$COCH_3$, 3-CH_2CHO	Many steps	—	83	189
5-$COCH_3$; 1,2-$(CH_3)_2$	$AlCl_3$, CH_3COCl	—	157	215
2,4-DNP		—	263–264	215
5-$COCH_3$; 1,2,3-$(CH_3)_3$	$AlCl_3$, CH_3COCl	—	123	215
2,4-DNP		—	258	215

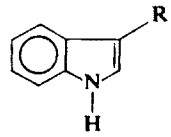
TABLE XIV. (*Continued*)

Carbonyl position; other substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
5-$COCH_3$; 2,3,4,6-$(CH_3)_4$	$AlCl_3$, CH_3COCl	—	152	215
2,4-DNP		—	256–257	215
4-$COCH_3$; 2,3-$(CH_3)_2$, 7-OCH_3	$AlCl_3$, CH_3COCl	—	159	215
Picrate		—	192–193	215
4-COC_6H_5; 2,3-$(CH_3)_2$, 7-OCH_3	$AlCl_3$, CH_3COCl	—	183	215
2,4-DNP		—	206–207	215
6-$COCH_3$; 2,3-$(CH_3)_2$	From 1,6-diacetyl	—	153	215, 533
6-$COCH_3$; 2,3-$(CH_3)_2$, 1-$COCH_3$	$AlCl_3$, CH_3COCl	—	115–116	215, 533
	Acetic Ac_2O			219
5-$COCH_3$; 3-$COCH_3$	Ac_2O	—	—	280
	Vilsmeier–Haack	10	—	280
5-$COCH_3$; 3-CH_3, 2-$COCH_3$	Fischer	7	220–225	217
5-$COCH_3$; 1,3-$(CH_3)_2$, 2-$COCH_3$	Methylation	99	127–128	217
5-$COCH_3$; 1,3-$(COCH_3)_2$	Ac_2O	75	—	280
5-$COCH_3$; 3-(2-aminoethyl)	From carboline	—	140–142	282
6-$COCH_3$; 3-(2-aminoethyl)	From carboline	—	148–150	282
5-$COCH_3$; 2,3-$(4\text{-}CH_3OC_6H_4)_2$	$CdCl_2$ on acid chloride, CH_3I	—	—	270
5-$COCH_3$; 2,3-$(4\text{-}CH_3OC_6H_4)_2$, 1-CH_3	$CdCl_2$ on acid chloride, CH_3I	—	—	270
5-$COCH_3$; 2,3-$(4\text{-}CH_3OC_4H_6)_2$, 1-$COCH_3$	$CdCl_2$ on acid chloride, CH_3I	—	—	270
5-$COCH_2Cl$; none	—	—	—	62

TABLE XV. OTHER INDOLINYL KETONES WITH THE CARBONYL GROUP ON THE SIX-MEMBERED RING

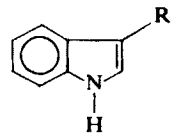
Carbonyl position; other substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
5-$COCH_3$; none	From 1,5-diacetyl	—	70.5–71	246
5-$COCH_3$; 1-$COCH_3$	$AlCl_3$, CH_3COCl	100	146–147	246
5-$COCH_3$; 2-CH_3	From 1,5-diacetyl	65	140.5–141	246
5-$COCH_3$; 2-CH_3, 1-$COCH_3$	$AlCl_3$, CH_3COCl	70–95	96.5–97	246
7-COC_6H_5; none	—	—	—	315
7-COC_6H_5; 1-$COCH_2Br$	Acylation	—	—	315
5-$COCH_2Cl$; none	From 1,5-disubstituted	43	139–140	246
5-$COXH_2Cl$; 1-$COCH_2Cl$	$AlCl_3$, $ClCH_2COCl$	—	149-5-.50	246
5-$COCH_2Cl$; 2-CH_3	From 1,5-disubstituted	56	153–156	246
5-$COCH_2Cl$; 2-CH_3, 1-$COCH_2Cl$	$AlCl_3$, $ClCH_2COCl$	—	107–107.5	246
4-$COCH_2Cl$; 7-OH, 1-$COCH_3$	$AlCl_3$, $ClCH_2COCl$	—	190–192	62

TABLE XVI. INDOLES WITH SIDE-CHAIN KETONES



Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
CH_2COCH_3; none	Diazoacetone on indole	45	116.5–118.5	331
	From 1-acetyl deriv.	—	115–117.5	185
2,4-DNP		—	161–163	185
CH_2COCH_3; 1-$COCH_3$	Ac_2O on indoleacetic acid	—	Oil	185
2,4-DNP		—	194–195	185
Semicarbazone		—	208–211	185
CH_2COCH_3; 4-I	Acetoacetic ester on gramine	—	103	327
$CH_2CH_2COCH_3$; none	2-Methylsulfinyl-acetone, Al reduction	—	—	328
$CH_2CH_2COC_6H_5$; none	2-Methylsulfinyl-acetophenone, Al reduction	—	—	328
CH=$CHOCH_3$; none	Aldol cond.	54	—	122
CH=$CHCOC_6H_5$; none	Claisen	—	—	122
CH=$CHOCH_3$; 1-$CH_2C_6H_5$	Claisen	—	—	122
CH=$CHCOCH_3$; 1-$COCH_3$	Claisen	75	—	122
CH=$CHCOC_6H_5$; 5-OCH_3, 2-CH_3, 1-C_6H_5	Aldol cond.	—	—	262
CH=$CHCOC_6H_4$-4-F; 5-OCH_3, 2-CH_3, 1-C_6H_5	Aldol cond.	—	—	262
CH=$CHCOC_6H_4$-4-CH_3; 5-OCH_3, 2-CH_3, 1-C_6H_5	Aldol cond.	—	—	262
CH=$CHCOC_6H_4$-4-OCH_3; 5-OCH_3, 2-CH_3, 1-C_6H_5	Aldol cond.	—	—	262
CH=$CHCOC_6H_2$-3,4,5-$(OCH_3)_3$; 5-OCH_3, 2-CH_3, 1-C_6H_5	Aldol cond.	—	—	262
CH=$CHCOC_6H_4$-2-thienyl; 5-OCH_3, 2-CH_3, 1-C_6H_5	Aldol cond.	—	—	262
CH=$CHCOC_6H_4$-2-furyl; 5-OCH_3, 2-CH_3, 1-C_6H_5	Aldol cond.	—	—	262
$COCOC_2H_5$	Bi_2O_3 oxidn. of α-Hydroxyketone	—	—	293
$COCOCH_3$	BuONO, HCl	—	—	293
Oxime	BuONO, HCl	—	—	293
CH=$CHCOC_6H_3$-2,4-$(OCH_3)_2$; none	Aldol cond.	31	172–173	123

TABLE XVI. (*Continued*)



Substituents R; other	Method of synthesis	Yield (%)	mp (°C)	Ref.
CH=CHCOC$_6$H$_4$-4-Cl; none	Aldol cond.	75	192–193	123
CH=CHCOC$_6$H$_4$-4-Br; none	Aldol cond.	54	194	123
CH=CHCOC$_6$H$_4$-4-NO$_2$; none	Aldol cond.	55	228–229	123
CH-CHCO-1-naphthyl; none	Aldol cond.	62	214	123
CH=CHCO-2-naphthyl; none	Aldol cond.	70	218	123
CH=CHCO-4-biphenylyl; none	Aldol cond.	80	253	123
CH-CHCO-2-pyrrolyl; none	Aldol cond.	30	266	123
CH=CHCO-2-furyl; none	Aldol cond.	58	168	123
CH=CHCO-2-thienyl; none	Aldol cond.	40	164	123
CH=CHCO-3-pyridyl; none	Aldol cond.	56	191	123
CH=CHCO-4-pyridyl; none	Aldol cond.	48	257–258	123
CH(OH)COC$_6$H$_5$; none	Aldol cond.	59	170–172	260
CH(OH)CO-2-thienyl; none	Aldol cond.	—	178–180	260
CH(OH)CO-2-furyl; none	Aldol cond.	—	166–168	260
CH(OH)COC$_6$H$_4$-4-CH$_3$; none	Aldol cond.	—	234–236	260
CH(OH)CO-2-pyrrolyl; none	Aldol cond.	—	118–120	260

TABLE XVII. 4-OXO-4,5,6,7-TETRAHYDROINDOLES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
None	NH_3 on oxotetrahydrobenzofuran	90	188–190	353, 357
	Ring closure on pyrrole	—	187	362, 534
	Cyclization of aminoaldehyde	—	184–186	350
	Feist–Benary reaction	Low	187–188	353
cis-Oxime		62	181–182	360, 375
Alkyl				
1-CH_3	CH_3NH_2 on oxotetrahydrobenzofuran		85–86	357, 369
	Cyclization of aminoacetaldehyde	75	—	350
	Feist–Benary reaction	—	84–85	353
	Nitrene insertion	4	—	363

TABLE XVII. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
cis-Oxime		—	187–188	369
trans-Oxime		—	188–190	369
cis-Oxime *p*-toluene-sulfonate		—	117–120	368, 369
trans-Oxime *p*-toluene-sulfonate		—	134–136	369
2-CH_3	Cyclization of amino-acetylene	—	210–211	212
	Hydrogenation of 4-OH-indole	5	210–214	19
3-CH_3	Cyclohexanedione and α-oximinoketone	60.5	204	340
	Decarbox.	77	208–209	382
2-C_2H_5	NH_3 on oxotetrahydro-benzofuran	—	147–148	341
3-C_2H_5	Decarbox.	72	156–158	382
3-C_3H_7	Decarbox.	56	129–130	382
3-$CH(CH_3)_2$	Decarbox.	—	138–140	341
			184–185	341
3-C_4H_9	Decarbox.	—	128–129	341
1-Cyclohexyl	—	—	106–107	372
2,3-$(CH_3)_2$	Cyclohexandedione and α-oximinoketone	60	226	339
	NH_3 on oxotetrahydrofuran	90	—	357
	3-Aminocyclohexenone and diol	40	226–227	356
1,3-$(CH_3)_2$	Cyclohexanedione and α-oximinoketone	66.5	130	340
2,6-$(CH_3)_2$	NH_3 on oxotetrahydro-benzofuran	96	178–180	357
3,5-$(CH_3)_2$	Decarbox.	—	173–173.5	341
3,6-$(CH_3)_2$	NH_3 on oxotetrahydro-benzofuran	96	183–185	357
1-C_2H_5, 2-CH_3	$C_2H_5NH_2$ on acetonyl-cyclohexanedione	54	74–75	359
2-C_2H_5, 3-CH_3	Cyclohexanedione and α-oximinoketone	52	201–201.5	339, 535
3-C_2H_5, 6-CH_3	Decarbox.	—	181–182	341
3-C_2H_5, 2-CH_3	Cyclohexanedione and α-oximinoketone	—	182–183	339, 535
2-C_3H_7, 3-CH_3	Cyclohexanedione and α-oximinoketone	—	158–159.5	341
2-C_3H_7, 3-C_2H_5	Cyclohexanedione and α-oximinoketone	—	141–142.5	341
2-C_4H_9, 3-CH_3	Cyclohexanedione and α-oximinoketone	—	164–165	339

TABLE XVII. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
3-C_3H_7, 6-CH_3	Decarbox.	—	174–175	341
2-$CH(CH_3)_2$, 3-CH_3	Cyclohexanedione and α-oximinoketone	—	203.5–204.5	339
2-$CH_2CH{=}CH_2$, 3-CH_3	Cyclohexanedione and α-oximinoketone	—	149–150	341
2-$CH_2CH(CH_3)_2$, 2-CH_3	Cyclohexanedione and α-oximinoketone	—	178–179	339
2-CH_3, 3-$CH_2CH(CH_3)_2$	Cyclohexanedione and α-oximinoketone	—	180–182	339
?-C_2H_5, 3-C_3H_7	Cyclohexanedione and α-oximinoketone	—	182	339
2-CH_3, 3-C_4H_9	Cyclohexanedione and α-oximinoketone	—	174–176	339
2-CH_3, 3-$CH(CH_3)_2$	Cyclohexanedione and α-oximinoketone	—	220.5–222.5	339
2-CH_3, 3-C_3H_7	Cyclohexanedione and α-oximinoketone	—	152	339
2-CH_3, 3-C_5H_{11}	Cyclohexanedione and α-oximinoketone	—	133–134	339
2-CH_3, 3-C_6H_{13}	Cyclohexanedione and α-oximinoketone	—	122.5–124	339
6,6-$(CH_3)_2$	Cyclization of amino aldehyde	30	182–183	350
1,2,3-$(CH_3)_3$	*N*-Methylation	—	85–88	339
1-C_2H_5; 3,6,6-$(CH_3)_3$	Cyclization of *N*-(chloroallyl)-enamine	48	73–74	351
1,6,6-$(CH_3)_3$	Cyclization of amino aldehyde	70	106–107	350
2,3,6-$(CH_3)_3$	NH_3 on oxotetrahydro-benzofuran	73	205.5	357
3,6,6-$(CH_3)_3$	Decarbox.	13	162	338
2,3,6,6-$(CH_3)_4$	3-Aminocyclohexenone and diol	13	232–235	356
1-C_2H_5, 2,6-$(CH_3)_2$	NH_3 on acetonylcyclo-hexanedione	59	77–79	359, 360
1-C_2H_5, 2,5-$(CH_3)_2$	Methylation of 5-hydroxy-methylene	—	44–47	360
3-C_3H_7, 6,6-$(CH_3)_2$	From 2-nitro-oxotetra-hydrobenzofuran	66	143–144	392
2,5-$(CH_3)_2$, 3-C_3H_7	—	—	185	341
2,6-$(CH_3)_2$, 3-C_3H_7	Cyclohexanedione and α-oximinoketone	—	205–208	341
1,3-$(CH_3)_2$, 2-C_4H_9	*N*-Methylation	—	Oil	339
1-C_4H_9, 2-CH_3, 3-C_2H_5	—	—	Oil	341

TABLE XVII. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
2,3,6,6-$(CH_3)_4$	Dimedone and α-oximino-ketone	—	231–232	339
1-C_2H_5, 2,5,6-$(CH_3)_3$	Methylation of 5-hydroxy-methylene	—	97–99.5	360
1-C_2H_5, 2,6,6-$(CH_3)_3$	Ethylamine and acetonyl-dimedone	Low	97–103	380
3-C_3H_7, 2,6,6-$(CH_3)_3$	Cyclohexanedione and α-oximinoketone	—	201–204	341
Alkenyl				
5-Methylene, 2,3-$(CH_3)_2$	Hofmann elimination	—	197–198	376, 377
5-Methylene, 2-CH_3, C_2H_5	Hofmann elimination	—	217–218	376, 377
Aryl and aralkyl				
1-C_6H_5	Aniline on oxotetra-hydrobenzofuran	—	98–101	372
4-Anilino		—	130–131	372
1-*p*-Cl-C_6H_4	Aniline deriv. on oxotetrabenzofuran	—	114–116	372
1-*o*-F-C_6H_4	Aniline deriv. on oxotetrabenzofuran	—	58–71	372
1-*p*-F-C_6H_4	Aniline deriv. on oxotetrabenzofuran	—	107–110	372
2-C_6H_5	NH_3 on phenacylcyclo-hexanedione	98	232	340, 358
3-C_6H_5	Decarbox.	75	226	393
2-*p*-tolyl	NH_3 on tolacylcyclo-hexanedione	98	270	340
1-C_6H_5, 2-CH_3	Cyclization of amino acetylene	56	153	361
1-C_6H_5, 3-CH_3		—	113.5–115.5	
3-C_6H_5; 6,6-$(CH_3)_2$	Dimedone and 2-phenyl-azirine	—	—	352
1-*p*-Cl-C_6H_4, 2-CH_3	Cyclization of amino acetylene	27	166–167	361
1-*o*-Cl-C_6H_4, 2-CH_3	Aniline deriv. on oxo-tetrahydrobenzofuran	—	126–128	372
1-*m*-Cl-C_6H_4, 2-CH_3	Aniline deriv. on oxo-tetrahydrobenzofuran	—	161–163	372
1-(2,3-Cl_2-C_6H_3), 2-CH_3	Aniline deriv. on oxo-tetrahydrobenzofuran	—	130.5–132.5	372
1-*o*-F-C_6H_4, 2-CH_3	Aniline deriv. on oxo-tetrahydrobenzofuran	—	105.5–107.5	372
p-$H_3CC_6H_4$, 2-CH_3	Aniline deriv. on oxo-tetrahydrobenzofuran	—	114–116	372
1-C_6H_5, 5-CH_3	Aniline deriv. on oxo-tetrahydrobenzofuran	—	141–143	372

TABLE XVII. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-C_6H_5, 6-CH_3	Aniline deriv. on oxo-tetrahydrobenzofuran	—	123–127	372
3-C_6H_5, 2-CH_3	Cyclohexanedione and α-oximinoketone	41	261–261.5	535, 536
2-C_6H_5, 3-CH_3	Cyclohexanedione and α-oximinoketone	70	195	535
6-C_6H_5, 3-CH_3	Decarbox.	—	164–167	364
2-C_6H_5, 1-C_3H_7	—	—	—	370
2-C_6H_5, 1-cyclopropyl	—	—	—	370
2-C_6H_5, 1-cyclopropyl-methyl	—	—	—	370
1-C_6H_5, 3,6,6-$(CH_3)_3$	Cyclization of *N*-(chloroallyl)enamine	30	200–201	351
3-C_6H_5; 6,6-$(CH_3)_2$	From 2-nitro-oxotetra-hydrobenzofuran	39	200–201	351
	Dimedone and 2-phenyl-azine	42	247	352
1-(C_6H_4-4-Cl); 3,6,6-$(CH_3)_2$	Cyclization of *N*-(chloroallyl)enamine	30	142	351
1,2-$(C_6H_5)_2$	Aniline and phenacyl-cyclohexanedione	98	198	340, 213
2,3-$(C_6H_5)_2$	3-Aminocyclohexene and benzylphenylcarbinol	57	314–316	356
	Cyclohexanedione and α-oximinoketone	—	304–307	221
2,3-$(C_6H_5)_2$, 6,6-$(CH_3)_2$	3-Aminocyclohexene and benzylphenylcarbinol	24	306–309	386
2,3-$(C_6H_5)_2$, 5-$CH_2C_6H_5$	3-Aminocyclohexene and benzylphenylcarbinol	26	284–286	356
3,6-$(C_6H_5)_2$	Cyclohexanedione and α-oximinoketone	—	164–167	342
1,2,3-$(C_6H_5)_3$	Cyclohexanedione and α-aminoketone	65	171	343
1,2,3-$(C_6H_5)_3$; 6,6-$(CH_3)_2$	Cyclohexanedione and α-aminoketone	70	227	343
1-C_6H_5, 2-*p*-Cl-C_6H_4	Aniline and *p*-chloro-phenacylcyclohex-anedione	80	175–176	340
1-C_6H_5, 2-*p*-tolyl	Aniline and tolacyl-cyclohexanedione	73	196–197	340
1-$CH_2C_6H_5$	Cyclization of amino aldehyde	65–70	78–80	350
	Benzylation	76	80–81.5	360
3-$CH_2C_6H_5$	Decarbox.	77	186–189	382
		—	190–191	341

TABLE XVII. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-$CH_2C_6H_5$, 5-C_6H_5	Phenylation of 5-hydroxymethylene	54	92–98	360
1-$CH_2C_6H_5$, 5-CH_3	Methylation of 5-hydroxymethylene	82	57–58	360
2-$CH_2C_6H_5$, 3-CH_3	Cyclohexanedione and α-oximinoketone	—	193–194	341
5-$CH_2C_6H_5$; 2,3-$(CH_3)_2$	3-Aminocyclohexenone and diol	26	175–176	356
1-(2-naphthyl), 2-CH_3	Cyclization of amino acetylene	47	165–166	361
1-(2-pyridyl), 2-CH_3	Cyclization of amino acetylene	52	128	361
Halogen				
2-Br	Bromination	49	175	380
5-Br	Hydrol. of 1-benzoyl	82	170–173	360
2,3-$(Br)_2$	Bromination	31	162–163	380
		—	150–153	341
3-Br, 2-CH_3	Bromination	—	144-146	339
		—	178–180d	341
3-Br, 2-C_2H_5	Bromination	—	151–152	341
3-Br, 1-C_2H_5; 2-CH_3	Bromination	64	96–98	380
2-Cl, 3-C_2H_5	—	—	209	341
Amino (see table XVIII for Mannich base derivatives at position 5)				
3-$N(CH_3)_2$, 2-C_6H_5; 6,6-$(CH_3)_2$	Hydrazine on 3-aroyl-dimedone	60	255–257	355
3-$N(CH_2C_6H_5)_2$, 2-C_6H_5	Hydrazine on 3-aroyl-dimedone	43	205–207	355
3-*N*-morpholino, 2-C_6H_5, 6,6-$(CH_3)_2$	Hydrazine on 3-aroyl-dimedone	51	297–298	355
Oxime		—	258d	355
1-$CH_2CH_2N(CH_3)_2$; 2,6-$(C_6H_5)_2$	Amine and 2-phenacyl-cyclohexanedione	—	—	342
1-$CH_2CH_2N(CH_3)_2$; 2,6-$(C_6H_5)_2$, 3-CH_3	Alkylation	—	—	342
1-$CH_2CH_2N(CH_3)_2$, 2-$COCH_3$, 6-C_6H_5, 3-CH_3	Alkylation	—	118–119	364
1-$CH_2CH_2N(CH_3)_2$, 2-CO-CH_2H_5, 6-C_6H_5, 3-CH_3	Alkylation	—	104–106	
1-$CH_2CH_2N(C_2H_5)_2$, 2-CO-C_2H_5, 6-C_6H_5, 3-CH_3·HCl		—	184–185	364
1-$CH_2CH_2N(C_2H_5)_2$, 2-CO-C_6H_5, 6-C_6H_5, 3-CH_3·HCl	Alkylation	—	246–250	364
Other nitrogen				
2-NO_2	Nitration	32	271–272	380

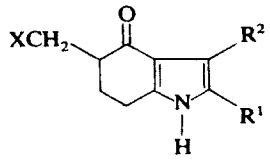
TABLE XVII. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
3-NO_2, 1-C_2H_5, 2-CH_3	Nitration	76	125–127	380
2-NO_2, 3-Br	Bromination	69	7360	380
2-NO_2, 5-Br	Bromination	91	215d	380
5-CN, 1-C_2H_5, 2-CH_3	From 5-hydroxy-methylene	35	141–145	360
5-CN, 1-C_2H_5, 2,6-$(CH_3)_2$	From 5-hydroxy-methylene	48	140–143	360
Oxygen and sulfur				
1-CH_2OH, 2-CH_3	Alkaline formaldehyde	34	145.5–147.5	366
1-CH_2OH, 3-CH_3	Alkaline formaldehyde	67	150–152	366
1-CH_2OH, 2-CH_3, 3-C_2H_5	Alkaline fromaldehyde	38	165–168	366
2-$(CHOH)_3CH_2OH$	Aminoglucose and cyclo-hexanedione	47	151–153	346
2-$(CHOH)_3CH_2OH$, 6-CH_3	Aminoglucose and methyl-cyclohexanedione	48	142–144	346
2-$(CHOH)_3CH_2OH$, 6,6-$(CH_3)_2$	Aminoglucose and dimedone	70	155–157	346
3-$(CHOH)_3CH_2OH$	Aminofructose and cyclo-hexanedione	3	174–176	346
3-$(CHOH)_3CH_2OH$, 1-$CH_2C_6H_5$	Aminofructose and cyclo-hexanedione	8	148–150	346
3-$(CHOH)_3CH_2OH$, 6-CH_3	Aminofructose and methyl cyclohexanedione	86	168–170	346
3-$(CHOH)_3CH_2OH$, 6,6-$(CH_3)_2$	Aminofructose and dimedone	13	158–160	346
5-SCH_3, 1-$CH_2C_6H_5$	From 5-hydroxymethylene	45	94–96	360
1-$SO_2C_6H_5$	Benzenesulfonyl chloride	63	117–118.5	360
1-$SO_2C_6H_5$, 5-Br	Bromination	59	94–96	360
Oxo (including tautomerized aldehydes)				
2-CHO	Periodate oxidn. of polyol	71	202–205	346
2-CHO, 6-CH_3	Periodate oxidn. of polyol	80	227-228	346
3-CHO	Periodate oxidn. of polyol	78	249–251	346
3-CHO, 1-$CH_2C_6H_5$	Periodate oxidn. of polyol	—	148–150	346
3-CHO, 6-CH_3	Periodate oxidn. of polyol	93	229–230	346
3-CHO, 6,6-$(CH_3)_2$	Periodate oxidn. of polyol	52	204–205	346
1-$COCH_3$	Acetic anhydride	90	98.5–99.5	360
1-COC_6H_5	Benzoyl chloride	63	120–123	360
1-COC_6H_5, 5-Br	Bromination	68	129–130	360

TABLE XVII. (*Continued*)

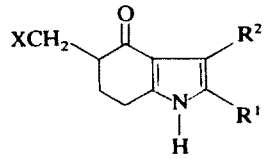
Substituent R	Method of synthesis	Yield (%)	mp (°C)	Ref.
2-$COCH_3$	Acetic anhydride and $HClO_4$	39	185–188	360
3-$COCH_3$	Cyclohexanedione and α-oximinoketone	66	209–210	344
2-$COCH_3$, 5-Br	Bromination	—	151–159	380
2-CHO, 6,6-$(CH_3)_2$	Glycol cleavage	—	191–193	345
2-CHO, 1-$CH_2C_6H_5$	Vilsmeier–Haack (anomalous)	66	114–116	360
2-$COCH_3$, 3-CH_3	Cyclohexanedione and α-oximinoketone	40	168–170	340
3-$COCH_3$, 2,6-$(CH_3)_2$	Acetic anhydride and $HClO_4$	52	203–206	380
5-(CH=OH), 1-$CH_2C_6H_5$	Ethyl formate, base	80	45–48	360
5-(CH=OH), 1-C_2H_5, 2-CH_3	Ethyl formate, base	65	82–90	360
5-(CH=OH), 1-C_2H_5, 2,6-$(CH_3)_2$	Ethyl formate, base	96	71–74	360
3-CHO, 1-C_2H_5, 2,6,6-$(CH_3)_3$	Vilsmeier–Haack	Low	97–103	380
2-$COCH_3$, 6-C_6H_5, 3-CH_3	Cyclohexanedione and α-oximinoketone	—	222–223	364
2-COC_2H_5, 6-C_6H_5, 2-CH_3	Cyclohexanedione and α-oximinoketone	—	204–204.5	364
2-COC_6H_5, 6-C_6H_5, 3-CH_3	Friedel–Crafts	—	211–212	364
2-$COCH_2Br$, 5-Br	Bromination	—	183–184	380
3-$CH_2COC_6H_5$, 6-CH_3, 2-C_6H_5	3-Aminocyclohexenone and 1,2-dibenzoylethylene	—	—	354
3-$CH_2COC_6H_5$, 6,6-$(CH_3)_2$, 2-C_6H_5	3-Aminocyclohexenone and 1,2-dibenzoylethylene	—	—	354

TABLE XVIII. MANNICH BASE DERIVATIVES OF 4-OXO-4,5,6,7-TETRAHYDROINDOLES



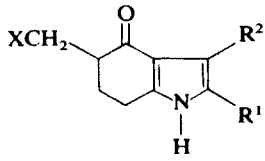
Substituents					
R^1	R^2	X		mp (°C)	Ref.
CH_3	CH_3	$N(CH_3)_2$		—	222, 376
			HCl	230	
CH_3	CH_3	Piperidino		179	222, 376
CH_3	CH_3	Morpholino		165–168	222, 376
CH_3	CH_3	4-Methylpiperidino		154–157	221, 376
			HCl	162	
CH_3	CH_3	$NHCH_2{\equiv}CH$		—	222, 376
			HCl	220	
CH_3	CH_3	*N*-Hydroxymethylpiperazino		—	221, 376
			HCl	215	
CH_3	C_6H_5	Morpholino		—	222, 376
C_4H_9	CH_3	$N(CH_3)_2$		138.5–139.5	222, 376
CH_3	C_2H_5	Piperidino		165–167	222–376
				56	377
C_2H_5	CH_3	$N(CH_3)_2$		—	222, 376
			HCl	170–175	
CH_3	C_2H_5	$NHCH_2CH_2OCH_3$		108–109	222, 376
CH_3	C_2H_5	$NHCH_2CH_2OC_2H_5$		101–102	222, 376
CH_3	C_2H_5	NHC_2H_5		150–151	222, 376
CH_3	C_2H_5	3-Morphilinopropylamino		154	222, 376
CH_3	C_2H_5	$NHCH(CH_3)CH_2OH$		172	222, 376
CH_3	C_2H_5	$NHCH_2CH_2OH$		161–163	222, 376
CH_3	C_2H_5	3-Pyridylamino		185–187	222, 376
CH_3	C_2H_5	$NHN(CH_3)_2$		202–203.5	222, 376
CH_3	C_2H_5	$NHCH(CH_3)CH_2C_6H_5$		—	222, 376
			HCl	186–189	
CH_3	C_2H_5	3-Piperidylmethylamino		142–144	222, 376
CH_3	C_2H_5	$NHCH_2CH_2CH_2N(CH_3)_2$		165–166	222, 376
CH_3	C_2H_5	4-Hydroxyphenylpiperidino		185–186	222, 376
CH_3	C_2H_5	$N(CH_3)_2$		168–169.5	222, 376
CH_3	C_2H_5	$N(C_2H_5)_2$		170–175	221, 376
CH_3	C_2H_5	Dipropynylamino		143–145	222, 376
CH_3	C_2H_5	Methallylamino		113	222, 376
CH_3	C_2H_5	Tetrahydropyranylmethylamino		135–136	222, 376
CH_3	C_2H_5	*N,N*-Hexamethylenehydrazino·HBr·*i*-PrOH		89–90	222, 376
CH_3	C_2H_5	5-Tetrazolylamino		234	222, 376
CH_3	C_2H_5	$NHCH_2C{\equiv}CH$		—	222, 376
			HCl	204–204.5	

TABLE XVIII. (*Continued*)



Substituents					
R^1	R^2	X		mp (°C)	Ref.
CH_3	C_2H_5	Cyclopropylamino		155–156	222, 376
CH_3	C_2H_5	$NHCH_2CH(OC_2H_5)_2$		95–96	222, 376
CH_3	C_2H_5	1-Morpholinylamino		137–138.5	222, 376
CH_3	C_2H_5	$N(C_4H_9)_2$		98–100	222, 376
CH_3	C_2H_5	4-Methylpiperidino		167–169	222, 376
CH_3	C_2H_5	4-Piperidinol		148-151	221, 376
CH_3	C_2H_5	4-Propylpiperidino		161–162.5	222, 376
CH_3	C_2H_5	4-Benzylpiperidino		182	222, 376
CH_3	C_2H_5	4-Carboxamidopiperidino		210–212	222, 376
CH_3	C_2H_5	$N(CH_2C_6H_5)CH_2C{\equiv}CH$		—	222, 376
			HCl	197–198	
CH_3	C_2H_5	$NHCH_2CH(C_6H_5)_2$		136–138	222, 376
CH_3	C_2H_5	$HNCH_2C_6H_4$-4-OCH_3		—	222, 376
			HCl	123–125	
CH_3	C_2H_5	(9-Acridinyl)amino		223–226	222, 376
CH_3	C_2H_5	$N(CH_3)CH_2C{\equiv}CH$		130–130.5	222, 376
CH_3	C_2H_5	Hexamethyleneimino		186–189.5	222, 376
CH_3	C_2H_5	$N(CH_3)NHC_6H_5$		—	222, 376
			HCl	187–189	
CH_3	C_2H_5	*N*-Furyl-*N*-methylamino		103–104	222, 376
CH_3	C_2H_5	4-(3-phenylpropyl)piperidine		—	222, 376
			HCl	174–176	
CH_3	C_2H_5	Pyrrolidino		165–168	221, 376
CH_3	C_2H_5	Morpholino		180–181	222, 348, 376
			HCl	192.5–193	377
CH_3	C_2H_5	$N(CH_3)CH_2C_6H_5$		130–132	222, 376
CH_3	C_2H_5	NHC_4H_9		131	222, 376
CH_3	C_2H_5	*N*-Carbethoxy-4-phenylpiperidino		188–189.5	222, 376
CH_3	C_2H_5	1-Adamantylamino		171	222, 376
CH_3	C_2H_5	4-Phenylpiperidino		169–171	222, 376
CH_3	C_3H_7	$NHCH_2C{\equiv}CH$		175–179	222, 376
CH_3	C_3H_7	$N(CH_3)_2$		150	221, 376
CH_3	C_3H_7	Piperidino		162–164	221, 376
CH_3	C_4H_9	$N(CH_3)_2$		132–134	221, 376
CH_3	C_5H_{11}	$N(CH_3)_2$		119	221, 376
			HCl	186–187.5	
C_6H_5	C_6H_5	$N(CH_3)_2$		142–146	221, 376
CH_3	C_2H_5	4,4-Methylenedioxypiperidino		—	378
CH_3	C_6H_5	$N(CH_3)_2$		177	377

TABLE XVIII. (*Continued*)



Substituents				
R^1	R^2	X	mp (°C)	Ref.
CH_3	C_6H_5	$N(C_2H_5)_2$	146	377
C_2H_5	C_6H_5	$N(CH_3)_2$	133	377
C_2H_5	C_6H_5	$N(CH_3)_2$	44	377
CH_3	C_2H_5	Morpholino	—	365
1-$CH_2CH_2COC_6H_4$-4-F				
CH_3	CH_3	Piperidino	173	377
6,6-$(CH_3)_2$				
CH_3	CH_3	Morpholino	170	377
6,6-$(CH_3)_2$				
CH_3	C_2H_5	Piperidino	64	377
CH_3	C_2H_5	Morpholino	48	377
6,6-$(CH_3)_2$				

TABLE XIX. 4-OXO-2,3,4,5,6,7-HEXAHYDROINDOLES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
3,6,6-$(CH_3)_3$	Dimedone and nitroalkylene	85	—	390
HCl			228–230	
3-C_2H_5, 6,6-$(CH_3)_2$	Dimedone and nitroalkylene	74	132–133	390
6,6-$(CH_3)_2$	Dimedone and nitroalkylene	73	155	230, 392
3-(4-HOC_6H_4), 6,6-$(CH_3)_2$	Dimedone and nitrostyrene	63	193	390
3-C_6H_5	Cyclohexanedione and nitrostyrene	80	235	392, 393

TABLE XX. 4-OXOOCTAHYDROINDOLES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-CH_3, 7-COC_6H_5	Friedel–Crafts	—	—	401
1-$COCH_3$, 3a-C_6H_5	—	35	64.5–66.5	398
1,6,6-$(CH_3)_3$, 3-(2-allyl)	Photocyclization	66	Oil	402
Picrate			142–143	402
1-CH_3, 3a-[C_6H_3-3,4-(OCH_2O)]	Annealation with methyl vinyl ketone	42	—	400
cis	—	76	110–111	399
trans	—	5.5	119.5–120.5	399
1-$CH_2C_6H_5$, 3a-[C_6H_3-3,4-(OCH_2O)]	Annealation with methyl vinyl ketone	67	98.5–101	400
1-[C_6H_2-2-Br-3,4-(OCH_2O)], HCl	—	—	123–125	240
1-[C_6H_2-2-NHCOCH_3-3,4-(OCH_2O)]	—	—	143–144	240

TABLE XXI. 6-OXO-2,3,4,5,6-HEXAHYDROINDOLES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-$CH_2C_6H_5$	Carbanion alkylation	—	—	411
1-(COC_6H_3-3,4-OCH_2O)	Benzoylation	41	202–203	410
1-CH_3, 3a-[C_6H_3-3,4-(OCH_3)$_2$]	Dehydrogenation of mesembrine	—	—	408
Methiodide		—	146–147	408

TABLE XXII. 6-OXOOCTAHYDROINDOLES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-CH_3, 3a-[C_6H_3-3,4-(OCH_3)$_2$] HCl	Acid cyclization of aminoethylcyclohexenone	70	206.5–208d	403
	Annealation with methyl vinyl ketone	—	—	404
	Redn. of 2-one	—	—	407
1-CH_3, 3a-[C_6H_3-3,4-(OCH_3)$_2$], 7-$(CH_2)_2CH(OCH_2CH_2O)$	Annealation	—	—	409
1-CH_3, 3a-[C_6H_3-3,4-(OCH_3)$_2$], 7-$(CH_2)_2CHO$	Hydrol. of ketal	52	153–154.5	409

TABLE XXIII. MISCELLANEOUS OXOINDOLES

Compound	Yield (%)	mp (°C)	Ref.
5-Oxo-4,5,6,7-tetrahydroindole	76	136–138	383
4-Methylthio-5-oxo-2-phenyl-4,5,6,7-tetrahydroindole	—	—	384
1-Methyl-5-oxo-4,5,6,7-tetrahydroindole	71	37–41	383
7-Oxo-4,5,6,7-tetrahydroindole	Low	95	385, 534
7-Oxo-4-phenyl-4,5,6,7-tetrahydroindole	—	—	386
7-Oxo-2-ethyl-3-methyl-4,5,6,7-tetrahydroindole	45	135–136	385
7-Oxo-2-ethyl-1-hydroxymethyl-3-methyl-4,5,6,7-tetrahydroindole	93	130–132	366
2,3-Dimethyl-7-oxo-4,5,6,7-tetrahydroindole	45	135–136	385
3a,5-Dimethyl-2-phenyl-3a,4,7,7a-tetrahydro-4-oxo-3H-indoline	—	92–101	395
Oxime	—	230d	395
Picrate	—	224d	395
3-Ethyl-6,6-dimethyl-3,3a,4,5,6,7-hexahydro-4-oxo-2*H*-indolenine HCl	74	228–230	390
3,6,6-Trimethyl-3,3a,4,5,6,7-hexahydro-4-oxo-2*H*-indolenine	85	132–133	390
3-(4-Hydroxy-3-methoxyphenyl)-6,6-dimethyl-3,3a,4,5,6,7-hexahydro-4-oxo-2*H*-indolenine	63	193	390
3a-Phenyl-3,3a,4,5,6,7-hexahydro-4-oxo-2*H*-indolenine	37	67–68.5	398
3a-(3,4-Methylenedioxyphenyl)-3,3a,4,5,6,7-hexahydro-4-oxoindole-2*H*-indolenine	55	119.5–121	399

TABLE XXIV. AMINOCHROMES

Substituents	Method of oxidation	Decompn. point (°C)	Ref.
1-CH_3	Ag_2O	78	419
5-Semicarbazone		198	436
5-Phenylhydrazone		226–227	418
5-Trimethylammoniumacet-hydrazone·Cl (Girard-T)		140	442
3-OH	Ag_2O	105	441
5-Semicarbazone		221	441
3-OCH_3	Ag_2O		
5-Semicarbazone		208	449
7-I	KIO_3	106	449
5-Semicarbazone		158	449

TABLE XXIV. (*Continued*)

Substituents	Method of oxidation	Decompn. point (°C)	Ref.
1-CH_3, 7-I	KIO_3	120	419
		85–87	430
1-CH_3, 3-OH (DL)	Ag_2O	125	419
	HIO_3	135–136	431
1-CH_3, 3-OH (L)	Ag_2O	115	419
5-Semicarbazone		204	431
5-Trimethylammonium-acethydrazone·Cl		160	419
		150	419
1-C_2H_5, 3-OH	Ag_2O	115	419
5-Semicarbazone	Ag_2O	215	413
5-Isonicotinic acid hydrazide		104–107	439
1-$C(CH_3)_2$, 3-OH	Ag_2O	123	417
5-Semicarbazone	$K_3Fe(CN)_6$	204	424
1,2-$(CH_3)_2$			
5-Amidinohydrazone		195–200	424
Hydrochloride		234	435
1-CH_2CH_2OH, 3-OH			
5-Semicarbazone	$K_3Fe(CN)_6$	218	427
3-OH, 7-I	Ag_2O	122–127	477
1-CH_3, 3-OH, 7-Br	Br_2	90	419
5-Oxime	Br_2	158	437
5-Semicarbazone	Br_2	190	437
1-CH_3, 3-OH, 7-I	KIO_3	120	419
5-Semicarbazone	KIO_3	150	437
1-C_2H_5, 3-OH, 7-I	KIO_3	134.5	417
2-CH_3, 3-OH, 7-I		130	476
1-$CH(CH_3)_2$, 3-OH, 7-I	KIO_3	105.5	417
1-CH_3, 3-OCH_3	Ag_2O	83	417
		86	449
5-Semicarbazone		217–218	425
1-CH_3, 3-OC_2H_5	Ag_2O	70–72	417
		79.5-81.5	449
5-Semicarbazone		211–215	425
1-CH_3, 3-OCH_3, 7-I	KIO_3	85	417
1-$CH(CH_3)_2$, 3-OCH_3		—	—
5-Semicarbazone		190.5–191	449
1-$CH(CH_3)_2$, 3-OC_2H_5		—	—
5-Semicarbazone		187.5–188.5	449
1-CH_3, 3-OC_2H_5, 7-I	KIO_3	88	417
1-CH_3, 2-SO_2Na			
5-Semicarbazone	$K_3Fe(CN)_6$	227–228	428, 429
Potassium salt		300	429
1-CH_3, 2-CO_2H, 7-I	KIO_3	85–87	421

TABLE XXIV. (*Continued*)

Substituents	Method of oxidation	Decompn. point (°C)	Ref.
2-$CO_2C_2H_5$, 7-I	KIO_3	127	430
1-CH_3, 2-$CO_2C_2H_5$, 7-I	KIO_3	80	427
5-Semicarbazone		149–150	427
1-CH_3, 3-OH, 4-H, 3a-$S(CH_2)_2CO_2H$	$HS(CH_2)_2CO_2H$ on adrenochrome	—	493

TABLE XXV. INDOLE-4,5-DIONES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
3-CH_3	Fremy's salt on 5-OH	94	>305	446
1-C_2H_5, 2-CH_3	Fremy's salt on 4-OH	12	103–107	501
1-C_2H_5, 2,6-$(CH_3)_2$	Fremy's salt on 4-OH	5	160–166	505
2-C_6H_5	Fremy's salt on 5-OH	—	>360	446, 448
1-C_2H_5, 2-CH_3, 3-CHO	Fremy's salt on 5-OH	85	198–201	511
1-C_2H_5, 6-CH_3, 3-CHO	Fremy's salt on 5-OH	—	193–195	587
1-C_2H_5, 2,6-$(CH_3)_2$, 3-CHO	Fremy's salt on 5-OH	—	214–216	587
1-C_2H_5, 2,6-$(CH_3)_2$, 3-$COCH_3$	Fremy's salt on 5-OH	—	164–166	588
2-CH_3, 3-$CO_2C_2H_5$	Fremy's salt on 5-OH	—	237	453
Oxime		—	214	453
Phenylhydrazone		—	256	453
2,6-$(CH_3)_2$, 3-$CO_2C_2H_5$	Fremy's salt on 5-OH	—	212–214	455
2,6,7-$(CH_3)_3$, 3-$CO_2C_2H_5$	Fremy's salt on 5-OH	—	217	455
Semicarbazone		—	252	453
2-CH_3, 7-Cl, 3-$CO_2C_2H_5$	Fremy's salt on hydroquinone	—	192–193	453
1,2-$(CH_3)_2$, 7-piperidino, 3-$CO_2C_2H_5$	—	—	—	523
2-CH_3, 1-C_6H_5, 7-piperidino, 3-$CO_2C_2H_5$	—	—	—	523
2-CH_3, 1-C_6H_4-3-Cl, 7-piperidino, 3-$CO_2C_2H_5$	—	—	—	523
2-CH_3, 1-C_6H_4-4-OCH_3, 7-piperidino, 3-$CO_2C_2H_5$	—	—	—	523
1,2-$(CH_3)_2$, 7-$N(CH_3)_2$, 3-$CO_2C_2H_5$	—	—	—	522
1,2-$(CH_3)_2$, 7-OH, 3-$CO_2C_2H_5$	Acid hydrol. of 7-$N(CH_3)_2$	—	—	522
2-CH_3, 1-C_6H_5, 6-Br, 3-$CO_2C_2H_5$	Nitric acid oxidn. of 5-OH	—	—	504
2-CH_3, 1-(C_6H_4-4-CH_3), 6-Br, 3-$CO_2C_2H_5$	Nitric acid oxidn. of 5-OH	—	—	504

TABLE XXVI. INDOLE-4,7-DIONES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
2-CH_3, 1-(C_6H_4-4-OCH_3), 6-Br, 3-$CO_2C_2H_5$	Nitric acid oxidn. of 5-OH	—	—	504
None	Fremy's salt on 4-OH	84	170d	19
	Fremy's salt on 7-OH			19
2,3-$(CH_3)_2$	Ag_2O on 4,7-$(OCH_3)_2$indole	30	185–195	514
2,6-$(CH_3)_2$	Fremy's salt on 4-OH	—	—	505
1-C_2H_5, 2-CH_3	Fremy's salt on 4-OH	68	86–87	501
1-C_2H_5, 2,6-$(CH_3)_2$	Fremy's salt on 4-OH	5	115–117	505
2,3-$(C_6H_5)_2$	Fremy's salt on 4-OH	—	235	451
	Fremy's salt on 7-OH	20	226–227	508
Semicarbazone		—	258	271
2,3-$(C_6H_5)_2$, 1-CH_3	Fremy's salt on 7-OH	83	220–221.5	508
5,6-$(CH_3)_2$, 2-C_6H_5	Nitrene insertion	66	291–292	520
2,3-$(C_6H_5)_2$	Fremy's salt on 4-OH	—	274–275	589
5-OH, 1-C_2H_5, 2,6-$(CH_3)_2$	Decarbox.	74	266–268	588
5-OCH_3, 1-C_2H_5, 2,3-$(CH_3)_2$	Fremy's salt on 4-OH	—	184–186	511
3-CO_2H, 5-OH, 1-C_2H_5, 2,6-$(CH_3)_2$	From 4,5,7-triacetoxy	67	220–223	587
3-CO_2CH_3, 5-OCH_3, 1-C_2H_5, 2,6-$(CH_3)_2$	Methylation with $(CH_3)_2SO_4$	65	82–83	587
3-$COCH_3$	Dichromate on hydroquinone	—	>300	519
3-COC_6H_5	Dichromate on hydroquinone	—	>300	519
3-(COC_6H_4-4-OH)	Dichromate on hydroquinone		>300	519
3-$COCH_3$, 5-OH, 1-C_2H_5, 2,6-$(CH_3)_2$	From 4,5-dione by way of 4,5,6-triacetoxy	33	172–175	588
3-$COCH_3$, 5-OCH_3, 1-C_2H_5, 2,6-$(CH_3)_2$	Methylation with $(CH_3)_2SO_4$	53	126–127	588
3-$CO_2C_2H_5$, 5-OH, 6-$(CH_3)_2$	HCl on 4,5-dione	—	212–214	453
3-CH_2Cl, 5-OCH_3, 1-C_2H_5, 2,6-$(CH_3)_2$	$SOCl_2$ on 3-CH_2OH	70	141–142	588
3-CH_2SCOCH_3, 5-OCH_3, 1-C_2H_5, 2,6-$(CH_3)_2$	$KSCOCH_3$ on 3-CH_2Cl	81	109–111	588
3-$CH(OCOCH_3)_2$, 1-C_2H_5 2-CH_3	Ac_2O on 3-CHO	47	137–138	501
5-OCH_3, 1-C_4H_9, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	16	82.5–83.0	510
5-OCH_3, 1,2-$(C_2H_5)_2$, 6-CH_3	Fremy's salt on 4-NH_2	10	76.0–77.5	510
5-OCH_3, 1,6-$(C_2H_5)_2$, 2-CH_3	Fremy's salt on 4-NH_2	22	83.0–83.5	510
5-Br, 6-OCH_3, 1-C_2H_5, 2-CH_3	Methylation of 6-OH	—	180–181	501
6-Br, 5-OCH_3, 1-C_2H_5, 2-CH_3	Methylation of 5-OH		131–135	501

TABLE XXVI. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
5-OCH_3, 1-$CHCH_2Cl$, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	58	113–114	589
5-OCH_3, 1-CH_2CH_2F, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	49	114–117	589
5-OCH_3, 1-$CH_2CH_2N_3$, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	69	78–79	589
5-OCH_3, 1-$CH_2CH_2SCH_3$, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	58	85–86	589
5-OCH_3, 1-CH_2CH_2SCN, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	30	137–138	589
5-OCH_3, 1-$CH_2CH_2OSO_2$-CH_3, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	71	143–144	589
5-OCH_3, 1-CH_2CH_2OH, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	76	129–131	589
5-OCH_3, 2-CH_2OH, 1-C_2H_5, 6-CH_3	Fremy's salt on 4-NH_2	65	128.5–130	590
5-OCH_3, 2-CH_2OCOCH_3, 1-C_2H_5, 6-CH_3	Fremy's salt on 4-NH_2	70	137–140	590

TABLE XXVII. INDOLINE-4,7-DIONES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
6-OH	Oxidn. of 6-OH dopamine	—	—	511
5-$C(CH_3)_3$, 2-$(CH{=}CHCH_3)$	Azide photolysis	96	72–73	521
5-CH_3, 2-$(CH{=}HCH_3)$, 3-CH_3	Azide photolysis	40	86–87	521

TABLE XXVIII. INDOLE-4,7-DIONE-3-CARBOXALDEHYDES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-C_2H_5, 2-CH_3	Fremy's salt on 4-OH	46	148–155	501
	Hydrolyze diacetate, add $FeCl_3$	71	148–159	501
1-C_2H_5, 2,6-$(CH_3)_2$	Fremy's salt on 4-OH	—	146–149	505
Oxime		—	204–206	505
1-C_2H_5, 2,5,6-$(CH_3)_2$	Fremy's salt on 4-OH	54.5	125–127	505
5-Br, 6-Br, 1-C_2H_5, 2-CH_3	Bromination	83	114–120	501
5-Cl, 1-C_2H_5, 2,6-$(CH_3)_2$	$POCl_3$ on 5-OH	—	—	525
5-SCH_3, 1-C_2H_5, 2,6-$(CH_3)_2$	CH_3SH on 5-OH	—	—	525
5-$SC_6H_4CH_3$, 1-C_2H_5, 2-CH_3	Addn. of *p*-$CH_3C_6H_4SH$	7	175–178	501

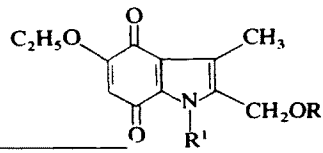
TABLE XXVIII. (*Continued*)

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
6-$SC_6H_4CH_3$, 1-C_2H_5, 2-CH_3	Addn. of *p*-$CH_3C_6H_4SH$	43	189–190	501
5-OH, 1-C_2H_5, 2,6-$(CH_3)_2$	Hydrol. and oxidn. of triacetate	—	213–215	587
6-OH, 1-C_2H_5, 2-CH_3	Hydrol. of 6-tolylthio	—	>320	501
5-OCH_3, 1-C_2H_5, 2-CH_3	Fremy's salt on 4-NH_2	48	207–208	511
6-OCH_3, 1-C_2H_5, 2-CH_3	Methylation of 6-OH	—	178–182	501
5-OCH_3, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	4	236–240	510
5-OCH_3, 1-CH_3, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	45	146–148	510
5-OCH_3, 1-C_2H_5, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	18	125–129	510
5-OCH_3, 1-C_3H_7, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	32	134–135	510
5-OCH_3, 1-$CH(CH_3)_2$, 2,6-$(CH_3)_2$	Fremy's salt on 4-NH_2	21	97–99	510

TABLE XXIX. 3-(4,7-DIOXOINDOLYL) KETONES

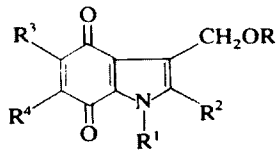
Ketone substituent	Method of synthesis	Ref.
CH_3	$K_2Cr_2O_7$ on 4,7-$(OH)_2$	519
C_6H_5	$K_2Cr_2O_7$ on 4,7-$(OH)_2$	519
C_6H_4-4-NO_2	$K_2Cr_2O_7$ on 4,7-$(OH)_2$	519
C_6H_4-4-OCH_3	$K_2Cr_2O_7$ on 4,7-$(OH)_2$	519

TABLE XXX. 2-HYDROXYMETHYLINDOLE-4,7-DIONES AND DERIVATIVES



R	R_1	mp (°C)	Ref.
H	H	213	511
H	CH_3	184.5–185.5	511
$COCH_3$	H	182–184	511
$COCH{=}CHCH_3$	H	—	511
COC_6H_5	H	—	511
$COCH_2Cl$	H	—	511
$COCHCl_2$	H	—	511
$COCH_2Br$	H	—	511
$CO_2C_6H_5$	H	193–195	511
$COCH_3$	CH_3	167–170	511
$COCH_2Cl$	CH_3	122–125	511
$COCHCl_2$	CH_3	152.5–153.5	511

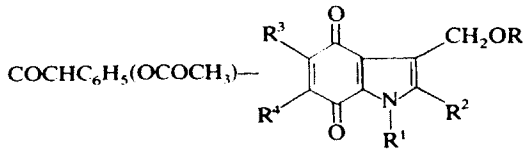
TABLE XXXI. 3-HYDROXYMETHYLINDOLE-4,7-DIONES AND DERIVATIVES



R	R^1	R^2	R^3	R^4	mp (°C)	Ref.
H	C_2H_5	CH_3	CH_3O	H	199–201	511
H	C_2H_5	CH_3	CH_3O	CH_3	85–87	591
H	C_2H_5	CH_3	C_2H_5O	CH_3	65–70	591
H	C_2H_5	CH_3	CH_3O	CH_3	78–81	591
H	C_2H_5	CO_2CH_3	CH_3O	CH_3	80–82	591
H	H	CH_3	CH_3O	CH_3	233–235	591
H	CH_3	CH_3	CH_3O	CH_3	Indef.	591
H	$CH(CH_3)_2$	CH_3	CH_3O	CH_3	76–78	591
H	C_3H_7	CH_3	CH_3O	CH_3	Oil	591
H	C_4H_9	CH_3	CH_3O	CH_3	68–70	591
H	C_2H_5	C_2H_5	CH_3O	C_2H_5	Oil	591
H	C_2H_5	CH_3	CH_3O	C_2H_5	128–129	591
H	C_2H_5	CH_2OTHP	CH_3O	C_2H_5	Oil	591
H	CH_2CH_2F	CH_3	CH_3O	CH_3	116–118	591
H	CH_2CH_2SH	CH_3	CH_3O	CH_3	Oil	591
H	CH_2CH_2Cl	CH_3	CH_3O	CH_3	Oil	591
H	CH_2CH_2OTHP	CH_3	CH_3O	CH_3	Oil	591
H	C_2H_5	CO_2CH_3	CH_3O	CH_3	83–84	591
H	C_2H_5	$CONH_2$	CH_3O	CH_3	200–202	591
H	C_2H_5	CH_2OH	CH_3O	CH_3	82–84	591
H	C_2H_5	CH_3	Cl	CH_3	110–117	591
H	C_2H_5	CH_3	$C_6H_{13}O$	CH_3	70–71	591
H	C_2H_5	CH_3	CH_3S	CH_3	66–90	591
H	C_2H_5	CH_3	H	H	90–95	591
H	C_2H_5	CH_3	Br	Br	115–122	591
H	C_2H_5	CH_3	H	CH_3	127–129	591
H	C_2H_5	CH_3	CH_3	CH_3	175–178	591
H	C_2H_5	CH_3	CH_3O	H	164–165	591
H	C_2H_5	CH_3	CH_3O	Br	114–138	591
H	C_2H_5	CH_3	CH_3O	H	164–165	591
H	C_2H_5	CH_3	Br	CH_3O	137–138.5	591

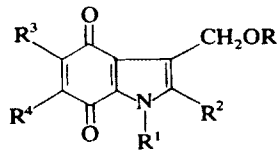
R	Substituents 1	2	5	6	mp (°C)	Ref.
CH_3	C_2H_5	CH_3	CH_3O	H	170–180	511
Acyl derivatives						
COC_2H_5	C_2H_5	CH_3	CH_3O	CH_3	127–128	592
$COCH_3$	C_2H_5	CH_3	CH_3O	H	175–180	511
COC_2H_5	C_2H_5	CH_3	CH_3O	H	120–122	511
COC_3H_7	C_2H_5	CH_3	CH_3O	H	74–76	511
$COCH(CH_3)_2$	C_2H_5	CH_3	CH_3O	CH_3	114–114.5	511
COC_6H_5	C_2H_5	CH_3	CH_3O	H	145–146	511
COC_6H_5	C_2H_5	CH_3	CH_3O	CH_3	139–141	592
CO-cyclo-hexyl	C_2H_5	CH_3	CH_3O	CH_3	127–128	592
$COCH_2OC_6H_5$	C_2H_5	CH_3	CH_3O	CH_3	96–98	592
CO-(2-furyl)	C_2H_5	CH_3	CH_3O	CH_3	156–157	592
$COCH{=}CHC_6H_5$	C_2H_5	CH_3	CH_3O	CH_3	123–123.5	592

TABLE XXXI. (*Continued*)



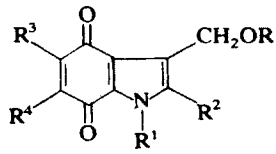
R	Substituents 1	2	5	6	mp (°C)	Ref.
$COCH{=}CHCH_3$	C_2H_5	CH_3	CH_3O	H	110–113	511
$COCH{=}CHCH_3$	C_2H_5	CH_3	CH_3O	CH_3	117–119	592
$COCH(OCOCH_3)$—$C_6H_5C_6N_5$	C_2H_5	CH_3	CH_3O	CH_3	100–101	592
$COCH_2Cl$	C_2H_5	CH_3	CH_3O	H	149–152	511
$COCHCl_2$	C_2H_5	CH_3	CH_3O	H	162–165	511
$COCH_2Br$	C_2H_5	CH_3	CH_3O	H	114–118	511
Carbonates						
CO_2CH_3	C_2H_5	CH_3	CH_3O	CH_3	137–138	593
$CO_2C_2H_5$	C_2H_5	CH_3	CH_3O	H	123–124	511
$CO_2C_2H_5$	C_2H_5	CH_3	CH_3O	CH_3	112–113	593
$CO_2C_6H_5$	C_2H_5	CH_3	CH_3O	H	73–84	511
$CO_2C_6H_5$	C_2H_5	CH_3	CH_3O	CH_3	115–117	593
Carbamates						
$CONHCH_3$	C_3H_7	CH_3	CH_3O	CH_3	170–172	592
$CONHCH_3$	C_2H_5	CH_3	CH_3O	CH_3	168–170	592
$CONHCH_3$	CH_3	CH_3	CH_3O	CH_3	209–210	592
$CONHCH_3$	$CH(CH_3)_2$	CH_3	CH_3O	CH_3	172–173.5	592
$CONHCH_3$	C_4H_9	CH_3	CH_3O	CH_3	127–129	592
$CONHCH_3$	C_2H_5	C_2H_5	CH_3O	CH_3	157–159	592
$CONHCH_3$	C_2H_5	CH_3	CH_3O	C_2H_5	142–145	592
$CONHCH_3$	C_2H_5	CH_2OTHP	CH_3O	CH_3	119–121	592
$CONHCH_3$	CH_2CH_2F	CH_3	CH_3O	CH_3	162–163	592
$CONHCH_3$	$CH_2CH_2N_3$	CH_3	CH_3O	CH_3	139–140	592
$CONHCH_3$	CH_2CH_2SH	CH_3	CH_3O	CH_3	112–115	592
$CONHCH_3$	CH_2CH_2Cl	CH_3	CH_3O	CH_3	157.5–159.5	592
$CONHCH_3$	CH_2CH_2OTHP	CH_3	CH_3O	CH_3	133.5–135	592
$CONHCH_3$	C_2H_5	CO_2CH_3	CH_3O	CH_3	175–176	592
CONH-cyclohexyl	C_2H_5	CH_3	CH_3O	CH_3	159–160	592
$CONH_2$	C_2H_5	$CONH_2$	CH_3O	CH_3O	—	592
$CONH_2$	C_2H_5	CH_3	CH_3O	CH_3O	200–202	592
$CONH_2$	C_2H_5	H	CH_3O	CH_3O	119–120	592
$CONH_2$	C_2H_5	CH_3	C_2H_5O	CH_3O	103–106	592
$CON(CH_3)CH_2$–$CH_2N(CH_3)_2$	C_2H_5	CH_3	CH_3O	CH_3O	60–61	592
$CONHC_6H_5$	C_2H_5	CH_3	CH_3O	CH_3O	117–117.5	592
CO-piperadino)	C_2H_5	CH_3	CH_3O	CH_3	163–164	592
CO-(4-methylpiperizino	C_2H_5	CH_3	CH_3O	CH_3	134–136	592
CO-aziridinyl	C_2H_5	CH_3	CH_3O	CH_3	123–125	592
$CON(C_3H_7)_2$	C_2H_5	CH_3	CH_3O	CH_3	—	592
$CONHCH_2CH_2OH$	C_2H_5	CH_3	CH_3	CH_3	—	592
$CONHCH_2CH_2CN$	C_2H_5	CH_3	CH_3O	CH_3	147–149	592
$CONH(CH_2)_3OH$	C_2H_5	CH_3	CH_3O	CH_3	125–126	592
$CONH(CH_2)_3SCH_3$	C_2H_5	CH_3	CH_3O	CH_3	116–118	592
$CONHCH_2CH_2OC_2H_5$	C_2H_5	CH_3	CH_3O	CH_3	109–110	592
$CONHNH_2$	C_2H_5	CH_3	CH_3O	CH_3	—	592

TABLE XXXI. (*Continued*)



R	1	2	5	6	mp (°C)	Ref.
CO-morpholino	C_2H_5	CH_3	CH_3O	CH_3	—	592
CO-(3-dimethyl-aminopiperazino)	C_2H_5	CH_3	CH_3O	CH_3	126–128	592
$CONHCH_3$	C_2H_5	CH_3	HO	CH_3	178–181	592
$CONHCH_3$	C_2H_5	CH_2OH	CH_3O	CH_3	144–146	592
$CONHCH_3$	C_2H_5	CH_2OH	CH_3O	CH_3	153–154	592
$CONHCH_3$	C_2H_5	CHO	CH_3O	CH_3	147–148.5	592
$CONHCH_3$	C_2H_5	$CH{=}NOCH_3$	CH_3O	CH_3	165–167	592
$CONHCH_3$	C_2H_5	$CH{=}NOH$	CH_3O	CH_3	190–190.5	592
$CONHC_6H_5$	C_2H_5	CH_3	CH_3O	CH_3	156–158	591
$CONHC_5H_{11}$	C_2H_5	CH_3	CH_3O	CH_3	124–125	591
$CONHCH_2CH{=}CH_2$	C_2H_5	CH_3	CH_3O	CH_3	121–122	591
$CONHC_3H_7$	H	CH_3	CH_3O	CH_3	275	591
$CONHCH_3$	C_2H_5	CH_3	CH_3S	CH_3	184–185	591
$CONHCH_3$	C_2H_5	CH_3	Cl	CH_3	182–183	591
$CONHC_3H_7$	C_2H_5	CH_3	CH_3O	Br	144–146	591
$CONHC_3H_7$	C_2H_5	CH_3	Br	Br	187–191	591
$CONHC_3H_7$	C_2H_5	CH_3	CH_3O	H	144–146	591
$CONHC_3H_7$	C_2H_5	CH_3	Br	CH_3O	162.5–164	591
$CONHC_3H_7$	C_2H_5	CH_3	H	CH_3O	136–138	591
$CONHCH_3$	C_2H_5	CH_3	$C_6H_{13}O$	CH_3	95.6–96.5	591
$CONHCH_3$	C_2H_5	CH_3	C_2H_4O	CH_3	156–158	591
$CONHCH_3$	C_2H_5	CH_3	CH_3	CH_3	175–178	591
$CONHCH_3$	C_2H_5	CH_3	H	CH_3	133–137	591
$CONHC_4H_7$	C_2H_5	CH_3	H	H	—	591
$CONHCH(CH_3)_2$	C_2H_5	CH_3	CH_3O	CH_3	151–153	591
$CONHC_2H_5$	C_2H_5	CH_3	CH_3O	CH_3	159–160	591
$CONHC_3H_7$	C_2H_5	CH_3	CH_3O	CH_3	129–139	591
$CONHC_4H_9$	C_2H_5	CH_3	CH_3O	CH_3	116–117	591
$CON(CH_2CO_2C_2H_5)_2$	C_2H_5	CH_3	CH_3O	CH_3	151–154	591
$CONH(m\text{-}Cl\text{-}C_6H_4)$	C_2H_5	CH_3	CH_3O	CH_3	148–149	591
$CONH(o\text{-}CH_3O\text{-}C_6H_4)$	C_2H_5	CH_3	CH_3O	CH_3	170–171	591
$CONH(1\text{-}C_{10}H_7)$	C_2H_5	CH_3	CH_3O	CH_3	169–170	591
$CONH(p\text{-}F\text{-}C_6H_4)$	C_2H_5	CH_3	CH_3O	CH_3	140–146	591
$CONH(m\text{-}CH_3\text{-}C_6H_4)$	C_2H_5	CH_3	CH_3O	CH_3	141–144	591
$CONHCH_3$	C_2H_5	CN	CH_3O	CH_3	148–149	592
$CONHCH_3$	C_2H_5	$CH{=}NNHCONH_2$	CH_3O	CH_3	212–214	592
$CONHCH_3$	C_2H_5	CH_2OCOCH_3	CH_3O	CH_3	143–145	592
$CON(C_6H_5)_2$	C_2H_5	CH_3	CH_3O	CH_3	159–161	592
$CONH_2$	C_2H_5	CH_3	CH_3NH	CH_3	137–140	592
$CONHCH_3$	C_2H_5	CH_3	C_2H_4NH	CH_3	144–148	592
$CONHCH_3$	C_2H_5	CH_3	Ethylene-imino	CH_3	168–169	592
$CONHCH_3$	C_2H_5	CH_3	$(CH_3)_2N$	CH_3	192–194	592
$CONHCH_3$	C_2H_5	CH_3	$HOCH_2\text{-}CH_2NH$	CH_3	158–160	592
$CONHC_3H_7$	C_2H_5	CH_3	NH_2	Br	136–142	592
$CONHC_3H_7$	C_2H_5	CH_3	$(C_2H_5)_2\text{-}N(CH_2)_2NH$	CH_3	149–150	592

TABLE XXXI. (*Continued*)



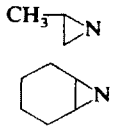
R	1	2	5	6	mp (°C)	Ref.
$CONHC_3H_7$	C_2H_5	CH_3	Br	CH_3NH	168–169	592
$CONHC_3H_7$	C_2H_7	CH_3	Br	NH_2	178	592
$CONHCH_3$	C_2H_5	CH_3	C_6H_5-CH_2NH	CH_3	170–171	592
$CONH_2$	C_2H_5	CH_3	NH_2	H	225–228	511
$CONH_2$	C_2H_5	CH_3	NH_2	CH_3	195–205	592
$CONHCH_3$	C_2H_5	CH_3	C_6H_5NH	CH_3	115–117	592
$CONHCH_3$	C_2H_5	CH_3	NH_2	CH_3	170	592
$CONH_2$	C_2H_5	CH_3	CH_3NH	H	204–207	511
$CONH_2$	C_2H_5	CH_3	CH_3NH	CH_3	237–240	592
$CONH_2$	C_2H_5	CH_3	Ethylene-imino	CH_3	230–235	525
$CONHCH_2CH_2OH$	C_2H_5	CH_3	Ethylene-imino	CH_3	136–138	525
$CONHCH_3$	C_2H_5	CH_3	CH_3NH	CH_3	213–215	525
$CONHCH_3$	C_2H_5	CH_3	OH	CH_3	190–192	525
$CONHCH_3$	C_2H_5	CH_3	CH_3O	CH_3	168–170	525
$CONHC_3H_7$	C_2H_5	CH_3	Ethylene-imino	CH_3	152–153	525
$CONHC_6H_5$	C_2H_5	CH_3	Ethylene-imino	CH_3	165–168	525
CO-(4-methylpiperazino)	C_2H_5	CH_3	Ethylene-imino	CH_3	148–151	525
$CONHCH_3$	CH_3	CH_3	Ethylene-imino	CH_3	196–198	525
$CONHCH_3$	C_3H_7	CH_3	Ethylene-imino	CH_3	128–131	525
$CONHCH_3$	$CH(CH_3)_2$	CH_3	Ethylene-imino	CH_3	180–181	525
$CONHCH_3$	CH_2CH_2F	CH_3	Ethylene-imino	CH_3	182–185	525
$CONHCH_2CH_2OH$	C_2H_5	CH_3	CH_3	CH_3	142–145	525
$CONHCH_2CH_2OH$	C_2H_5	CH_3		CH_3	162–163	525

TABLE XXXII. 5,6-DIHYDROINDOLE-4,7-DIONES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
None	$AlCl_3$ on diether	—	185	515
Semicarbazone			223	515
p-Nitrophenylhydrazone			212	515
1-CH_3	$AlCl_3$ on diether	91	—	516
1,2-$(CH_3)_2$	$AlCl_3$ on diether	—	210–213	517
2-C_6H_5	Thermal rearrangement of 4,7-dihydroxyindole	—	—	516
2-(C_6H_4-4-Cl)	$AlCl_3$ on diether	—	—	518
2-(C_6H_4-2-OCH_3)	$AlCl_3$ on diether	—	—	518
2-(C_6H_4-3-OCH_3)	$AlCl_3$ on diether	—	—	518
2-(C_6H_4-4-OCH_3)	$AlCl_3$ on diether	—	—	518
2-[C_6H_3-2,4-$(OCH_3)_2$]	$AlCl_3$ on diether	—	—	518
2-[C_6H_3-2,5-$(OCH_3)_2$]	$AlCl_3$ on diether	—	—	518
2-[C_6H_3-3,4-$(OCH_3)_2$]	$AlCl_3$ on diether	—	—	518

TABLE XXXIII. INDOLE- AND INDOLINE-6,7-DIONES

Substituents	Method of synthesis	Yield (%)	mp (°C)	Ref.
Indoles				
2-C_6H_5, 3-C_6H_5	Fremy's salt on 6-OH	—	>320	452
2,3-$(C_6H_5)_2$	Fremy's salt on 7-OH	61	>280	508
2,3-$(C_6H_5)_2$	Fremy's salt on 6-OH	—	149	452
	Fremy's salt on 7-OH	39	251–253	508
Indolines				
4-OCH_3 5-Br	Oxidn. of subst. phenethylamine	64	127.5–128.5	512

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