

INDOLES

PART TWO

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

Editors



INDOLES PART TWO

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The Chemistry of Heterocyclic Compounds

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.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible, new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

Indoles Part Two begins the detailed coverage of the preparation, properties, reactions and tabulation of compounds containing an indole nucleus. It starts with a chapter on indole biosynthesis since this was the first and only source of indole preparations during the early years of indole chemistry.

The editor is grateful to Mrs. Maria Fanlo and Mr. Siegfried Wahrmann for library assistance and to Miss Linda Heuser for typing a portion of the manuscript.

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INDOLES

PART TWO

CHAPTER III

Biosynthesis of Compounds Containing an Indole Nucleus

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I. Introduction

Living plants produce an extraordinarily rich variety of chemical substances, many of which lack any apparent biochemical function. These

metabolites have often proved the delight (and the frustration!) of organic chemists for the challenges of structural and synthetic chemistry which they offer. With the advent of radioactive tracers and the development of more sensitive chemical and spectroscopic tools, the doors leading to a deeper understanding of the chemistry of the plant world have been opened: the investigation of natural product biosynthesis has begun. Of the fruits of a field yet in its infancy, those arising from an examination of the biosynthesis of the naturally-occurring indoles have proved among the most tantalizing, and much may be expected of the future. The present account summarizes our knowledge of the biosynthesis of compounds containing an indole nucleus, and covers the literature through November 1968.

II. Simple Indole Derivatives

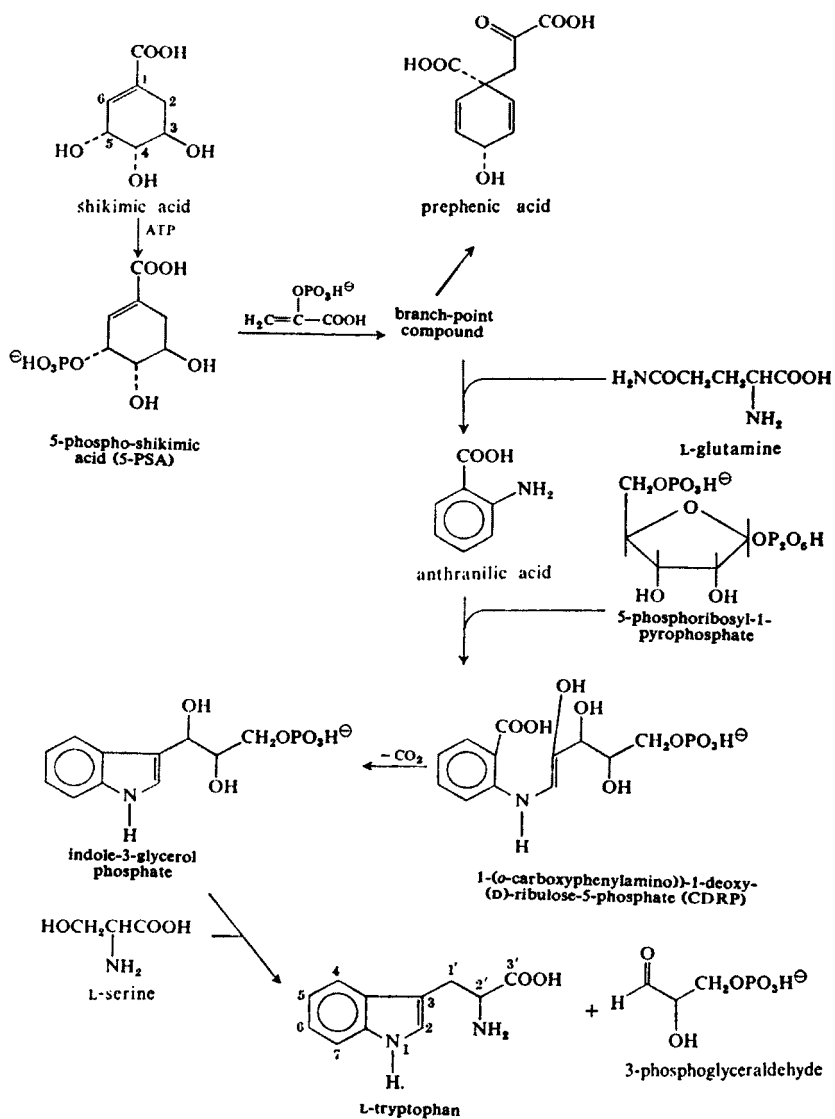
A. Tryptophan

By virtue of its ubiquitous distribution in plant and animal proteins, tryptophan may justifiably be regarded as the most important of the naturally-occurring indoles. Extensive explorations aimed at unraveling the tangled thread of its biosynthesis are a consequence of this importance. These investigations have been limited almost exclusively to microorganisms, and disappointingly few experiments have been conducted with fungi and higher plants.

The subject of tryptophan biosynthesis in microorganisms was carefully reviewed in 1960 by Doy¹; Scheme 1 summarizes the metabolic picture presented by the experimental evidence available at that time. More recent work has supplied some of the significant detail absent from this picture.

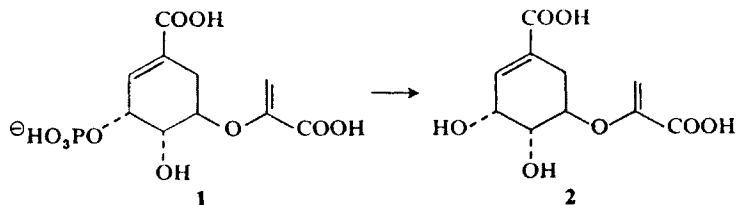
The enzyme which phosphorylates shikimic acid to 5-phosphoshikimic acid (5-PSA) has been isolated from *Escherichia coli* by Fewster.² Its optimum pH is 7.0 and it exhibits a requirement for divalent magnesium or manganese. Neither the formation of the enzyme nor its activity is affected by the ultimate products of the aromatic biosynthetic pathway. The same author also reported evidence for the presence of this enzyme system in a variety of microorganisms known to synthesize aromatic amino acids.

One of the most fascinating problems in tryptophan biosynthesis, the nature of the so called branch point compound leading either to prephenic acid or to anthranilic acid, has yielded to the patience of the investigators. Early experimental evidence³ suggested that at least one additional substance, called Z₁ and formulated⁴ as the 5-enolpyruvyl ether of shikimic acid, was produced from 5-PSA before the branch point. Later work by Srinivasan⁵



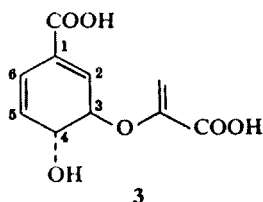
Scheme 1

indicated, however, that Z_1 was not in fact an intermediate in the conversion of 5-PSA to anthranilic acid in cellfree extracts of *E. coli*, and Levin and Sprinson⁶ found that Z_1 is not converted to prephenic acid by extracts of the same organism. These authors present additional data suggesting that the first product formed from 5-PSA and phosphoenolpyruvic acid is 3-enolpyruvylshikimate-5-phosphate (1), which is then dephosphorylated to Z_1 , proposed to be the 3-enolpyruvyl ether of shikimic acid (2). In the presence

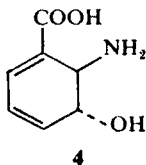


of fluoride ion, the dephosphorylation reaction is inhibited, and Z_1 -phosphate, **1**, accumulates. Since prephenate formation from 5-PSA and phosphoenolpyruvic acid could be demonstrated, it follows that Z_1 -phosphate is probably the active intermediate leading to prephenate. Evidence implicating Z_1 -phosphate as a precursor of anthranilic acid was also forthcoming. Cellfree extracts of *Aerobacter aerogenes*⁷ converted shikimic acid or 5-PSA in the presence of phosphoenolpyruvic acid to a substance with properties identical to those of Z_1 -phosphate as reported by Levin and Sprinson. By using mutants of the same organism which were unable to convert 5-PSA to Z_1 -phosphate, to anthranilic acid, or to phenylpyruvic acids, the formation of these acids in a cell extract containing Z_1 -phosphate could be detected. Treatment of the Z_1 -phosphate containing extract with alkaline phosphatase followed by acid produced a substance supporting the growth of an *E. coli* mutant requiring shikimic acid. Neither treatment alone produced a growth factor, but either destroyed the substrate for anthranilic acid formation. Addition of fluoride ion improved the yield of anthranilic acid from the substrate. The role of Z_1 -phosphate in anthranilic acid biosynthesis in *E. coli* has been studied by Rivera and Srinivasan.⁸ Ammonium sulfate or protamine sulfate treatment of a crude anthranilate forming enzyme preparation from an *E. coli* mutant gave two fractions. One of these contained an enzyme, named 3-enolpyruvylshikimate 5-phosphate synthetase, that condensed 5-PSA and phosphoenolpyruvic acid to give Z_1 -phosphate. This enzyme fraction further converted Z_1 -phosphate to a new, unidentified substance which was itself converted to anthranilic acid by the second enzyme fraction in the presence of L-glutamine, divalent magnesium, nicotinamide adenine dinucleotide (NAD^+), and a nicotinamide adenine dinucleotide, reduced form ($NADH$) regenerating system. The second fraction was unable to convert Z_1 -phosphate to anthranilate.

Gibson and Gibson^{9, 10} also reported the presence of a new intermediate in aromatic ring biosynthesis in extracts of an *A. aerogenes* mutant. This substance could be converted by mild chemical treatment into prephenic acid, *p*-hydroxybenzoic acid, and phenylpyruvic acid; enzymically, it was transformed into anthranilic, prephenic, phenylpyruvic, *p*-hydroxyphenylpyruvic, and *p*-hydroxybenzoic acids. On the basis of this evidence, the substance was judged to be the elusive branch point compound, and was named chorismic acid (chorismic = separating). The obtention of a multiply-blocked auxotroph of *A. aerogenes* which accumulated the acid allowed its isolation¹¹ as the barium salt and formulation^{11, 12} as the 3-enolpyruvyl ether of *trans*-3,4-dihydroxycyclohexa-1,5-diene carboxylic acid (3). Chorismic acid has also been isolated from a *Saccharomyces cerevisiae* mutant by Lingens and Luck.¹³

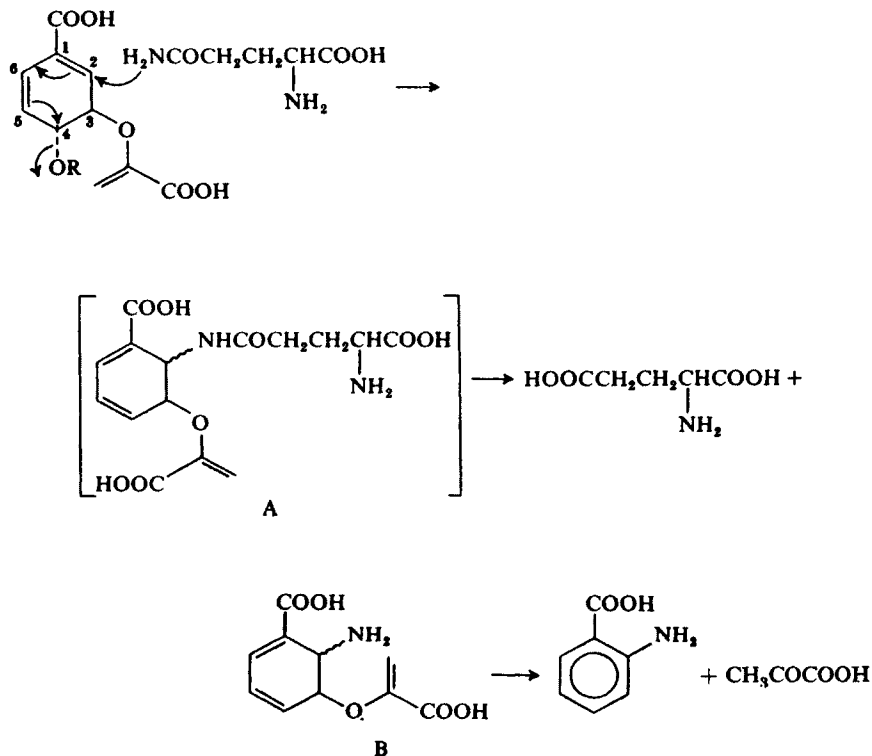


The problem of the conversion of chorismic acid into anthranilic acid is still under investigation. Srinivasan and Rivera,¹⁴ working with *E. coli* mutants, demonstrated that an NADH regenerating system and either divalent magnesium or iron were required in addition to L-glutamine; the amino group of anthranilic acid was found to be derived from the amide nitrogen atom of glutamine. More recently, some very informative results have been obtained¹⁵ by feeding 3,4-¹⁴C-glucose to an *E. coli* mutant accumulating anthranilic acid. Earlier isotopic studies of the incorporation of 3,4-¹⁴C-glucose into shikimic acid established that the carboxyl carbon and carbons 3 and 4 become labeled.¹⁶ Utilizing this information, degradation of the labeled anthranilic acid produced from the radioactive glucose showed that the carboxyl group of shikimic acid becomes the carboxyl group of anthranilic acid, and that the amination of chorismic acid occurs at C-2 rather than at C-6. Examination of *trans*-2,3-dihydro-3-hydroxyanthranilic acid (4), which has been isolated from *Streptomyces aureofaciens*,¹⁷ as a



possible anthranilate precursor in cellfree extracts of *E. coli* gave negative results, indicating that the actual intermediate probably still bears the

enolpyruvyl moiety. These results were rationalized by the scheme shown in Scheme 2. In a recent report, Lingens et al. claim to have isolated a substance corresponding to A from a mutant of *Saccharomyces cerevisiae*.¹⁸

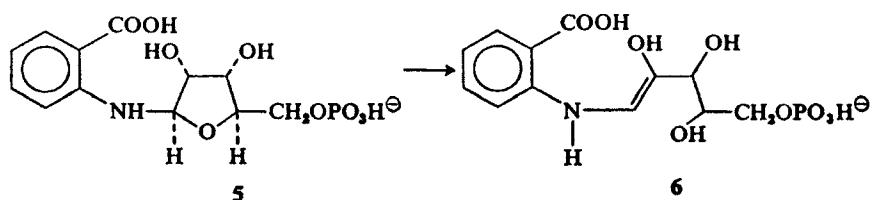


Scheme 2

DeMoss¹⁹ has investigated the formation of anthranilic acid in *Neurospora crassa*. Cellfree extracts will convert shikimic acid into anthranilic acid after an inhibitor that is present has been removed by ammonium sulfate precipitation. The cofactors required for the transformations are identical to those of the bacterial systems studied except that nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) is needed in place of NADH. Omission of L-glutamine from the incubation mixture led to the accumulation of chorismic acid. The enzyme catalyzing the chorismate to anthranilate conversion was purified 83-fold and appeared to be homogeneous. Its activity was completely inhibited by low concentrations of L-tryptophan, and this inhibition was competitively reversed by chorismic acid, suggesting that the conversion of chorismic acid to anthranilic acid is specifically involved in tryptophan biosynthesis.

The L-glutamine requirement does not appear to be obligatory. Gibson et al.²⁰ have recently recorded anthranilate biosynthesis that does not require glutamine. A strain of *E. coli* was obtained that required both glutamine and tryptophan. Cell suspensions of this organism were able to synthesize anthranilic acid by using glucose as the carbon source and ammonium ions as the only nitrogen source; addition of DON (6-diazo-5-oxo-6-norleucine), a glutamine antagonist to the cell suspensions, caused no inhibition of anthranilate formation. It was suggested that the un-ionized form of ammonia may be available for transfer reactions normally requiring glutamine.

The steps leading from anthranilic acid to tryptophan have been carefully scrutinized. Yanofsky proposed²¹ that the first intermediate resulting from the reaction of anthranilic acid and 5-phosphoribosyl-1-pyrophosphate should be *N*-*o*-carboxyphenylribosylamine-5-phosphate (5), also known as *N*-(5'-phosphoribosyl)anthranilic acid or PRA. An Amadori rearrangement²² of this substance to 1-(*o*-carboxyphenylamino)-1-deoxyribulose-5-phosphate (CDRP) (6) was postulated. Early failures to detect the presence of PRA^{1, 23}

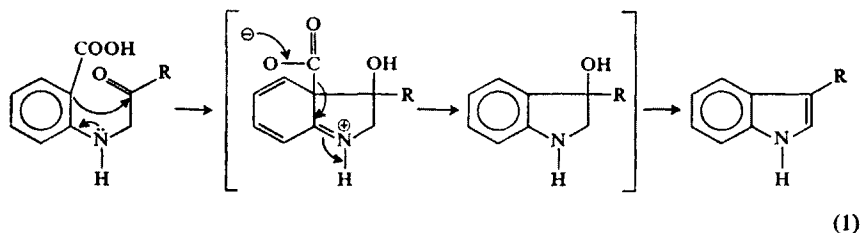


were ascribed to the lability of anthranilic acid glycosylamines.^{1, 24} Evidence supporting this instability was subsequently provided by Doy and co-workers.²⁵ The half-life of synthetic PRA at 37°C in aqueous solution, pH 6, was found to be 6 min. The sensitivity of the substance increased with decreasing pH and decreased with increasing pH. This ease of hydrolysis predicts that mutants blocked between PRA and CDRP will appear to accumulate anthranilic acid unless special precautions are taken. An investigation by Doy et al.²⁵ confirms this prediction; extracts of certain mutant microorganisms (*E. coli*, *A. aerogenes*, *Salmonella typhimurium*), which in whole cell experiments accumulated anthranilic acid, were found to catalyze a reaction between anthranilic acid and 5-phosphoribosyl-1-pyrophosphate leading to an acid labile substance, less fluorescent than anthranilic acid, and readily hydrolyzing back to that compound. The substance was converted enzymically to indole-3-glycerol phosphate, and was surmized to be PRA. Doy²⁶ also reported similar behavior in two tryptophan auxotrophs of *Pseudomonas aeruginosa* which are phenotypically identical, i.e., both require indole or tryptophan for growth and accumulate anthranilic acid. The two strains, however, differ genotypically, because one is blocked between anthranilic acid and PRA while the other is blocked between PRA

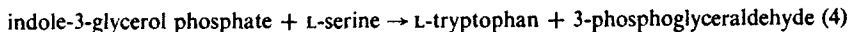
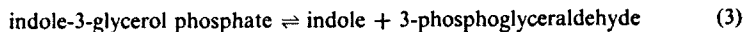
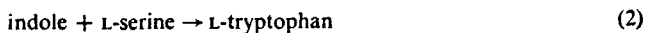
and CDRP. The rapid hydrolysis of accumulating PRA results in the apparent accumulation of anthranilic acid by the second mutant.

1(-*o*-Carboxyphenylamino)-1-deoxyribulose, the dephosphorylated Amadori product, was originally detected in cell suspensions of *A. aerogenes* and in *E. coli* mutants.^{27, 29} Its identity was based upon R_F values, color reactions, absorption spectra, and a DNP derivative as compared with synthetic material. On the basis of Yanofsky's scheme,²¹ the substance is most reasonably considered as an artifact, derived from the actual tryptophan precursor by loss of the 5-phosphate group. Smith and Yanofsky²³ have since provided evidence for this by detecting what appears to be the phosphorylated compound in extracts of *E. coli* and *S. typhimurium* mutants; impure CDRP was obtained synthetically from anthranilic acid and the sodium salt of ribose-5-phosphate; its properties compared reasonably well with those of the naturally occurring substance. Both the synthetic and natural compounds were converted to indole-3-glycerol phosphate in the extracts.

The mechanism of the conversion of CDRP to indole-3-glycerol phosphate appears to have been little studied. Smith and Yanofsky²³ prepared the decarboxylated analog of CDRP, but found that it was not transformed into indole-3-glycerol phosphate by appropriate cell extracts. This implies that the decarboxylated substance is not a free intermediate in the reaction. Mechanistically, it seems reasonable to suppose that the decarboxylation may not occur until after ring closure has taken place, so that this biochemical inertness of the decarboxylated analog need occasion no surprise (Eq. 1).



Studies of the tryptophan synthetase enzyme system have elucidated some of the details of the last step in tryptophan biosynthesis. The enzyme obtained from *E. coli* has been shown to consist of two protein subunits, A and B,^{28, 29} which catalyze three reactions³⁰ (Eqs. 2-4):



The B subunit will catalyze Reaction (2) in the absence of the A subunit,³¹ and the A subunit will catalyze Reaction (3).²⁸ Reaction (4) only occurs in

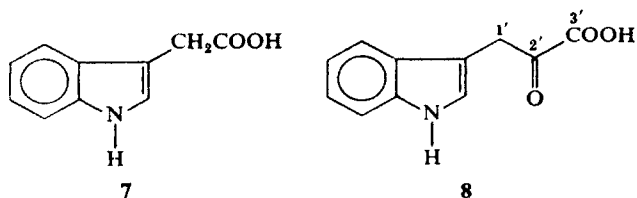
the presence of the AB complex, and indole is evidently not a free intermediate in the reaction.²⁸

The A protein has been obtained crystalline,³² characterized,^{33, 34} and the complete amino acid sequence deduced.³⁵⁻³⁹ The B subunit has likewise been purified;⁴⁰ it is of much higher molecular weight (ca. 108,000) than the A subunit (ca. 29,000) and requires pyridoxal phosphate as a cofactor to the extent of 2 moles of cofactor to each mole of B protein. The apoenzyme is unable to catalyze Reaction (2), but retains its ability to facilitate Reaction (4) when combined with the A protein. The evidence points to an AB complex containing two A protein units per molecule of B protein.

The tryptophan synthetase enzyme system of *N. crassa* appears to be quite similar to the *E. coli* system.⁴¹ The *N. crassa* enzyme catalyzes the same three reactions discussed above, with a pyridoxal phosphate requirement for Reactions (2) and (3). The conversion of indole-3-glycerol phosphate to tryptophan by the enzyme does not appear to involve free indole as an intermediate.

B. 3-Indoleacetic Acid

The discovery of the remarkable plant hormonal properties of 3-indoleacetic acid (7) in 1934⁴² and its subsequent isolation from a higher plant⁴³ have stimulated an extensive amount of research on the mode of action and metabolism of this substance. These investigations have been the subject of a number of detailed reviews,⁴⁴⁻⁵⁰ so that the discussion here will be limited to the more relevant papers with emphasis placed on recent work.

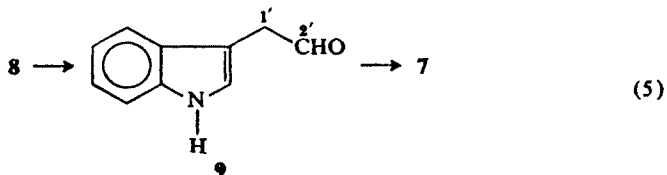


1. Biosynthesis in Higher Plants

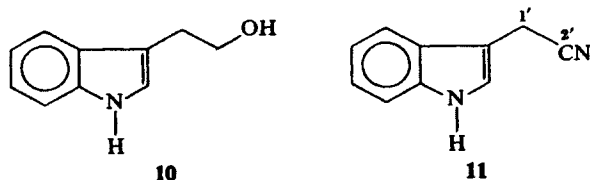
The evidence currently available regarding 3-indoleacetic acid biosynthesis in higher plants strongly suggests that the substance is derived from tryptophan. Murakami and Hayashi,⁵¹ for example, have shown that the juice from immature rice-grains will convert tryptophan into 3-indoleacetic acid, and that the conversion is stimulated by α -ketoglutaric acid. More recently, Libbert⁵² demonstrated the conversion of tryptophan to 7 by pea sprouts in

the presence of α -ketoglutaric acid, and isolated⁵³ an enzyme system from the plants which effects the same conversion.

There have been various proposals as to the nature of the intermediates involved in 3-indoleacetic acid biosynthesis. One intermediate frequently suggested⁵⁴⁻⁵⁸ is 3-indolepyruvic acid (8), the product resulting from transamination of tryptophan. The requirement for α -ketoglutarate noted in the transformations above supports this suggestion. Subsequent decarboxylation of 8 would produce 3-indoleacetaldehyde (9), oxidation of which would yield



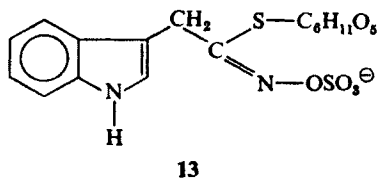
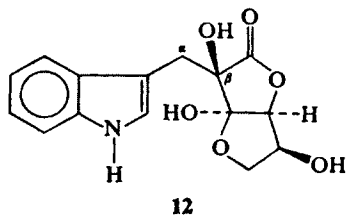
3-indoleacetic acid. The possible intermediacy of 9 in the biosynthesis derives credibility from its detection^{50, 59} in a number of plants, and from the occurrence of an enzyme system in plants⁶⁰ which will convert 9 into 7 (Eq. 5). The detection of 3-indolepyruvic acid in plant extracts proves more difficult as the substance decomposes readily during chromatography,^{50, 61} though the patterns of decomposition are apparently quite characteristic.⁵⁸ 3-Indolepyruvic acid has been tentatively identified in maize,^{56, 62} and in watermelon tissue⁶³ after the feeding of tryptophan. In a careful chromatographic analysis carried out by Libbert and Brunn⁶⁴ on the products from the metabolism of tryptophan by an 3-indoleacetic acid synthesizing enzyme from pea plants, 3-indolepyruvic acid and tryptophol (10) were detected.



Another intermediate along the path from tryptophan to 7 may well be 3-indoleacetonitrile (11). This substance was originally isolated from cabbage (*Brassica oleracea*)⁶⁵ and evidence presented for its occurrence in other members of the *Cruciferae*. A variety of other simple indoles including 7, 3-indolecarboxaldehyde, 3-indolecarboxylic acid, and ascorbigen (12), were also found to occur in *B. oleracea*. Libbert and Ballin⁶⁶ have since detected 11 in a variety of higher plants and found evidence in many for its enzymatic hydrolysis to 3-indoleacetic acid. Earlier work by Thimann⁶⁷ and by Seeley and coworkers⁶⁸ also provides evidence for the presence of an enzyme system effecting the conversion of the nitrile to 3-indoleacetic acid.

An interesting problem resides in the mechanism of the conversion of 3-indolepyruvic acid into 3-indoleacetonitrile. A number of proposals have been made^{50, 56, 65, 69} and the most attractive of these involve the intermediacy of oximes. Dannenburg and Liverman⁶³ postulated the decarboxylation of 3-indolepyruvic acid to **9** followed by oximation and dehydration to **11**. Evidence favoring this hypothesis has been reported by Mahadevan and coworkers^{70, 71} who observed the conversion of 3-indoleacetaldehyde oxime into 3-indoleacetonitrile in banana-leaf tissue and in cellfree preparations of cabbage leaves. Furthermore, Underhill⁷² has recently discovered the conversion of phenylalanine into phenylacetaldehyde oxime in *Tropaeolum majus*, and Kindl et al. have stated⁷³ that 3-indoleacetaldehyde oxime is a product of tryptophan metabolism in *B. oleracea*. Alternatively, Stowe⁵⁰ has offered the oxime of 3-indolepyruvic acid as a possible biosynthetic intermediate. The principal support that can be mustered for this idea derives from the *in vitro* conversion of this oxime to the nitrile under simulated physiological conditions,⁶⁹ from the known occurrence of α -ketoacid oximes in plant tissue,⁷⁴ and from the discovery of a transoximase system catalyzing the transfer of an oximino moiety between α -ketoacids.^{75, 76}

Further indications of a biochemical thread running from tryptophan through 3-indoleacetonitrile to **7** have been supplied by Wightman.⁷⁷ Radioactive 2'-¹⁴C-tryptophan (see Section II.A for numbering) was incorporated by 15-week old cabbages into 3-indoleacetonitrile and 3-indoleacetic acid, as well as into 3-indolecarboxaldehyde, 3-indolecarboxylic acid, and ascorbigen. These substances were also obtained radioactive when 1'-¹⁴C-3-indoleacetonitrile was administered to the cabbages. It is of some interest that no evidence could be found for the intermediacy of 3-indolepyruvic acid or its oxime in these transformations; additional tracer experiments indicated that neither 2'-¹⁴C-tryptamine (tryptophan numbering) nor 1'-¹⁴C-3-indoleacetaldehyde were converted to radioactive **11** in the cabbage tissue. More recent investigations, dealing with ascorbigen, discussed in Section II.D, complicate the interpretation of these results; it now appears^{78, 79} that ascorbigen is an artifact produced during the extraction of the cabbage tissue by enzymic hydrolysis of the mustard-oil glucoside, glucobrassicin (**13**). This



hydrolysis also produces **11**, and the feeding of 1'-¹⁴C-tryptophan to cabbages apparently does not produce any radioactive **11** or ascorbigen when the

proper precautions are taken during the subsequent extraction. The natural occurrence of **11** in cabbage tissue must therefore be questioned.

As indicated earlier, evidence does exist for the presence of 3-indoleacetonitrile in plants other than *B. oleracea*, and an enzyme catalyzing the conversion of the nitrile to 3-indoleacetic acid has been found in various plants, isolated, and purified.⁸⁰ It is active in the absence of oxygen and is not deactivated by sulfhydryl or heavy metal reagents. Interestingly enough, 3-indoleacetamide, the presumed intermediate in the conversion, is not liberated in detectable concentration during the enzymic hydrolysis, and is itself not readily attacked by the enzyme. Complete hydrolysis thus appears to take place before the enzyme-substrate complex dissociates. This behavior may perhaps explain the observation of Eifert and Eifert⁸¹ when testing the growth stimulating activity of various substances on the vine, *Vitis vinifera*. Tryptophan, **8**, **9**, **11**, and tryptamine all produced stimulation while 3-indoleacetamide had an inhibitory effect; the amide probably competes with 3-indoleacetonitrile for the hydrolyzing enzyme, and blocks it by virtue of the difficulty with which it is hydrolyzed.

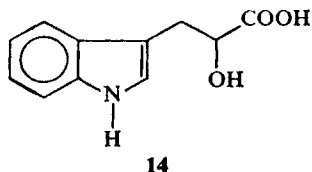
The transformation of tryptophan into 3-indoleacetamide in the presence of horse-radish peroxidase and pyridoxal phosphate has been observed by Riddle and Mazelis,⁸² and by Kleambt.⁸³ The reaction is very similar to the conversion of methionine into 3-methylthiopropionamide by the same enzyme and cofactor as reported by Mazelis, Ingraham, and Weston.⁸⁴ In a more detailed study,⁸⁵ Riddle and Mazelis report that cabbage seedling homogenates contain natural inhibitors of peroxidase activity which are removable by dialysis. After such treatment, the homogenates will convert tryptophan into 3-indoleacetamide with a small amount of 3-indoleacetic acid also being produced. Whole cabbage seedlings were shown to convert 1'-¹⁴C-tryptophan into radioactive **11** and **7**, but 3-indoleacetamide could not be detected. In view of the work described earlier, the occurrence of **11** in cabbage seedlings should be questioned. On the other hand, infiltration of 1'-¹⁴C-indoleacetamide (numbered as **11**) into the cabbage seedlings resulted in significant hydrolysis to 3-indoleacetic acid after 12 hr. Homogenates of cabbage seedlings were also capable of the same transformation unless dialyzed. These experiments point to the presence of 3-indoleacetamide, which may or may not be derived from 3-indoleacetonitrile, as an intermediate leading to 3-indoleacetic acid in cabbages.

To complete this rather complex picture of 3-indoleacetic acid biosynthesis, an alternative pathway needs mention. There is indirect evidence indicating that tryptamine may serve as an 3-indoleacetic acid precursor in higher plants. The presumed pathway involves decarboxylation of tryptophan to tryptamine, transamination of the latter to 3-indoleacetaldehyde, and oxidation of the aldehyde to the corresponding acid. In support of this

hypothesis, the natural occurrence of a variety of tryptamines⁸⁶ in higher plants speaks for the presence of a tryptophan decarboxylase system in the Angiosperms. In addition, Skoog⁸⁷ has demonstrated an auxin activity for tryptamine in oats, and Winter⁸⁸ has found that tryptamine produces a marked stimulation of growth in *Avena sativa* coleoptiles, which stimulation was inhibited by the addition of amine oxidase inhibitors. Curiously, tryptophan showed no growth stimulating properties when applied to the coleoptiles. The case is given further strength by the isolation of an amine oxidase from peas which converts tryptamine to 3-indoleacetaldehyde,⁸⁹ and by Libbert's report⁹⁰ of the formation of tryptamine from tryptophan in crude enzyme preparations from pea plants. On the other hand, Gordon has stated⁵⁷ that, in some plant tissues, inhibitors of amine oxidase do not affect 3-indoleacetic acid formation from tryptophan, and he concludes that tryptamine is not a normal intermediate. Libbert's detection of the production of tryptamine from tryptophan has also recently been questioned⁹¹ on the grounds that no precautions were taken to exclude bacterial contamination. The question of the role of tryptamine in 3-indoleacetic acid biosynthesis thus does not appear to be settled as yet, and its importance as a precursor may in fact vary with different plants.

2. Biosynthesis in Lower Plants

The occurrence of 3-indoleacetic acid in the lower plants seems to be rather widespread,^{44, 92} and the biosynthetic pathways, in so far as they have been elucidated, generally parallel those existing in the higher plants. Srivastava and Shaw⁹³ have shown, for example, that the fungus *Melampsora lini* will convert 2'-¹⁴C-tryptophan into **7**; 3-indoleacetaldehyde and probably 3-indolepyruvic acid appeared to be intermediates in the process while tryptamine and 3-indoleacetonitrile were not. The metabolism of tryptophan by *Taphrina deformans* also appears to produce **8** as well as **7**, **10**, and 3-indolelactic acid (**14**),⁹¹ but no tryptamine, as had been originally reported.⁹⁴



Cellfree preparations of *Acetobacter xylinum* are also said^{95, 96} to metabolize tryptophan to tryptophol (**10**) and 3-indoleacetic acid, with 3-indoleacetaldehyde being trapped when sodium bisulfite is added to the medium;

α -ketoglutaric acid was required and the production of all three indoles was stimulated by the addition of pyridoxal phosphate. Still another example is provided by *Endomycopsis vernalis*⁹⁷ which converts tryptophan to **7**, **8**, **14**, **10**, 3-indolecarboxaldehyde, and 3-indolecarboxylic acid; when cellfree preparations were utilized, 3-indoleacetaldehyde could be detected. In the case of the crown-gall organism, *Agrobacterium tumefaciens*, the reported production of **8** during the biosynthesis of **7**⁵⁸ is fortified by a subsequent isolation of an amino transferase⁹⁸ exhibiting broad specificity in transferring an amino group from tryptophan, valine, leucine, or isoleucine to phenylpyruvic acid; the tryptamine pathway is apparently absent in this organism.

An unusual pathway to 3-indoleacetic acid has been discovered in *Pseudomonas solanacearum*.⁹⁹ A wild, pathogenic strain converted 1-¹⁴C-tryptophan into 3-indoleacetic acid which was only weakly labeled; under the same circumstances, the chain-labeled tryptophan was efficiently incorporated into cellular protein. When ring-labeled tryptophan was employed, the resulting 3-indoleacetic acid displayed a considerably higher level of radioactivity, and radioactive products of the kynurenine pathway for tryptophan metabolism were formed. The results led to the suggestion that the organism may synthesize **7** through the kynurenine pathway rather than by the usual routes. Strangely, a mutant, nonpathogenic strain of the same organism employed the more conventional routes to **7** as both ring- and chain-labeled tryptophan led to radioactive acid.

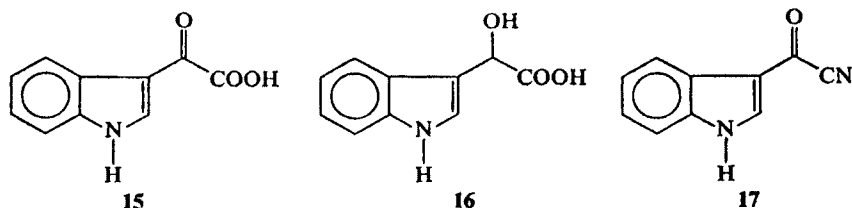
C. 3-Indolecarboxaldehyde and 3-Indolecarboxylic Acid

The biosynthesis of these substances has been discussed by Stowe,⁵⁰ and only the more recent developments are mentioned here.

3-Indolecarboxaldehyde and the corresponding acid seem to be formed biologically from either 3-indoleacetic acid or 3-indoleacetonitrile. Flowering heads of cauliflower,¹⁰⁰ for example, will metabolize both **7** and **11** to 3-indolecarboxaldehyde and the corresponding acid; the acid appears to be produced from the aldehyde as the aldehyde is itself converted to the acid by cauliflower tissue. A 3-indoleacetic acid oxidase system isolated¹⁰¹ from the root tips of *Lens culinaris* converts ring-labeled **7** into labeled 3-indolecarboxaldehyde. Another 3-indoleacetic acid oxidase system is present in *Lupinus albus*¹⁰² and, when coupled to a cytochrome oxidase system, will also transform **7** into 3-indolecarboxaldehyde. The intermediate in this conversion may be presumed to be 3-indoleglyoxylic acid (**15**), though its presence in these systems was not ascertained. The glyoxylic acid has been tentatively identified in cabbages⁷⁷ as a product of tryptophan metabolism, and young

tomato plants have been observed¹⁰³ to convert **7** into **15**, 3-indoleglycolic acid (**16**), 3-indolecarboxaldehyde, and 3-indolecarboxylic acid.

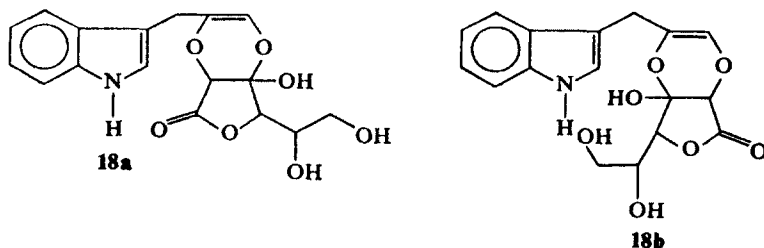
The conversion of 3-indoleacetonitrile to 3-indolecarboxaldehyde and



3-indolecarboxylic acid in pea and wheat tissue has been reported.¹⁰⁴ The reaction was suggested to proceed by α -oxidation of the nitrile to either the acyl cyanide (**17**) or the corresponding cyanohydrin; neither intermediate could be detected, however. The conversion of 3-indolecarboxaldehyde into the corresponding acid in the same tissues was noted. A crude enzyme preparation transforming **11** into 3-indolecarboxylic acid has also been isolated from pea seedlings.¹⁰⁵ Schiewer and Libbert¹⁰⁶ have observed the conversion of **11** into 3-indolecarboxaldehyde and the acid by three species of brown algae; no 3-indoleacetic acid was detected.

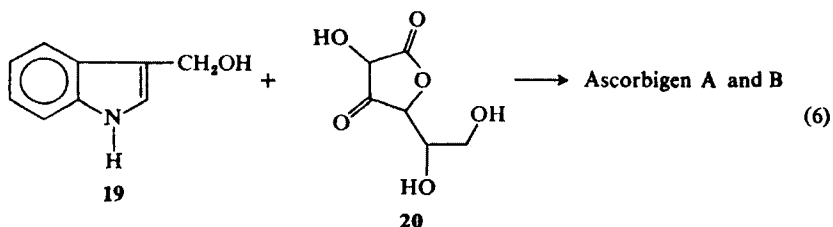
D. Ascorbigen

This curious substance was originally isolated from *Brassica oleracea* and one of the two alternative structures, **18a** or **18b**, allotted to it.¹⁰⁷ Subsequent



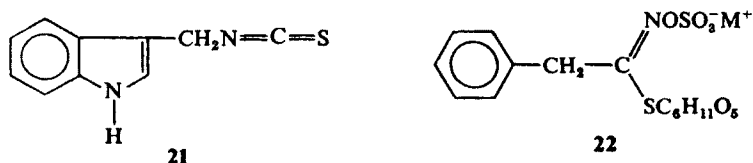
work by Gmelin and Virtanen⁷⁸ and by Kutacek and coworkers⁷⁹ has revealed that the substance is in fact an artifact produced during the isolation process, and casts doubt on the original structural proposal. A boiling methanolic extract of intact cabbage leaves was found to yield no ascorbigen, but only the mustard-oil glucoside, glucobrassicin (**13**). Myrosinase, an enzyme present in cabbage tissue, hydrolyzes this glucoside to 3-hydroxymethylindole (**19**), **11**, and various other products whose relative proportions are pH dependent. If the enzymic hydrolysis is conducted in the presence of ascorbic

acid (20), which is also present in cabbage tissue, ascorbigen results, and indeed, an excellent yield of ascorbigen can be produced synthetically by the near room temperature reaction of ascorbic acid and 3-hydroxymethylindole.¹⁰⁸ Feeding 1'-¹⁴C-tryptophan to the cabbage plants yielded only radioactive glucobrassicin; no radioactive ascorbigen or 3-indoleacetonitrile was detected. Furthermore, α -¹⁴C-ascorbigen and 1'-¹⁴C-3-indoleacetonitrile were not incorporated into glucobrassicin. These results contrast with the earlier report by Kutacek and coworkers¹⁰⁹ where, care not being taken to avoid enzymic hydrolysis, radioactive ascorbigen and 3-indoleacetonitrile were produced from 1'-¹⁴C-tryptophan while no glucobrassicin, either active or inactive, was detected. The data led Gmelin and Virtanen⁷⁸ to suggest that the original structural proposal was incorrect, and the structure has in fact been reexamined.¹¹⁰ The product resulting from the reaction of 3-hydroxymethylindole and ascorbic acid is formulated as a mixture of epimers and ascorbigens A and B, differing only at the configuration of the β -carbon; ascorbigen A (12) is the naturally occurring isomer (Eq. 6).



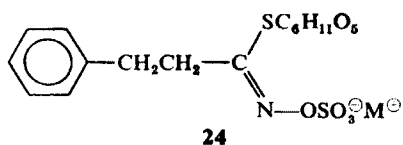
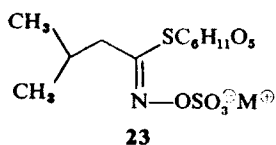
E. Glucobrassicin

Glucobrassicin (13) is a representative of a large group of unusual thioglucosides possessing the common property of hydrolyzing to glucose, sulfuric acid, and an isothiocyanate in the presence of the enzyme myrosinase. The chemistry and botanical distribution of this interesting class of natural products has been reviewed.^{111, 112} Recent biosynthetic work suggests that glucobrassicin is derived from tryptophan. 1'-¹⁴C-Tryptophan is incorporated into the skeleton of the thioglucoside by *B. oleracea*,⁷⁹ and ³⁵S-sulfur dioxide labels the thioether moiety when administered to cauliflower plants¹¹³; hydrolysis of the radioactive thioglucoside labeled in this fashion gives the radioactive isothiocyanate 21. Schraudolf and Bergmann¹¹⁴ similarly observed



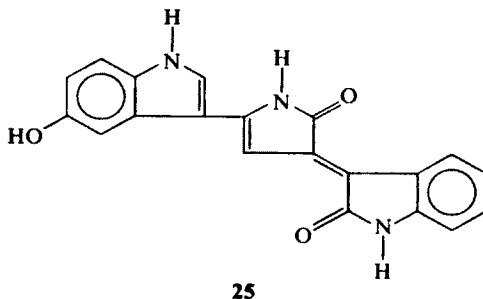
the incorporation of Ar- ^{14}C -DL-tryptophan into **13** by *Sinapis alba*; ^{35}S -sulfate was rapidly utilized in the formation of the thioether group; only L-tryptophan was transformed into **13**; D-tryptophan was converted into D-N-malonyl-tryptophan.

Tracer experiments on the related thioglucoside glucotropaeolin (**22**) shed some light on possible intermediates in glucobrassicin biosynthesis. 2'- ^{14}C -DL-phenylalanine is an efficient precursor of the thioglucoside aglucone¹¹⁵⁻¹¹⁷ and ^{14}C - ^{15}N -L-phenylalanine is incorporated as a unit, except for the loss of C-3' (tryptophan numbering).¹¹⁸ Subsequent experiments^{72, 117} indicated that phenylacetaldehyde oxime is a more efficient precursor of glucotropaeolin aglycone than phenylalanine, and the conversion of phenylalanine to the aldehyde oxime in *Tropaeolum majus* was demonstrated.⁷² It is stated that analogous experiments in *B. oleracea* detected 3-indoleacetaldehyde oxime as a product of L-tryptophan metabolism.⁷³ Furthermore, isobutyraldehyde oxime and 3-phenylpropionaldehyde oxime act as efficient precursors of the mustard-oil glucosides, glucoputranjivin (**23**) and gluconasturtiin (**24**),⁷² respectively. Thus, a common biosynthetic sequence for the formation of these thioglucosides appears to be operating in a variety of plants, and 3-indoleacetaldehyde oxime is probably the precursor of glucobrassicin in *B. oleracea*. Studies of the nature of the amino acid to oxime conversion for glucotropaeolin suggest that the N-hydroxyamino acid is an intermediate.¹¹⁹

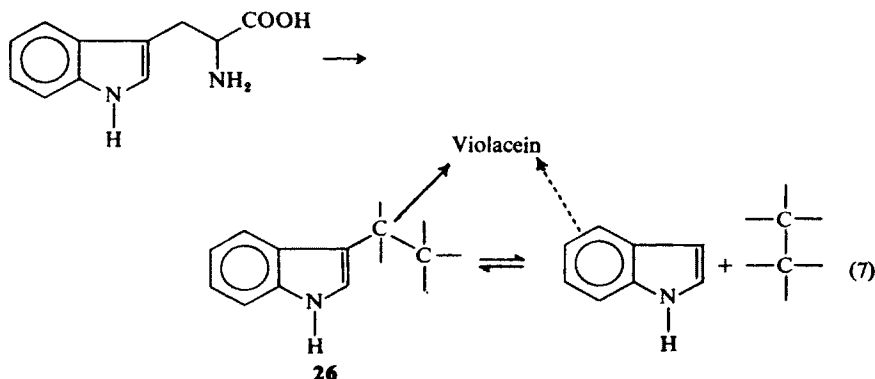


F. Violacein

This unusual pigment of structure **25** is obtained from *Chromobacterium violaceum*.¹²⁰ Its biosynthesis has been studied by two groups. DeMoss and



Evans^{121, 122} found that L-tryptophan was required as the sole carbon source for nonproliferating cells of *C. violaceum*, synthesizing the pigment; oxygen was also required, while D-tryptophan was not converted to the pigment. The incorporation of L-tryptophan labeled with ¹⁴C in either carbons 1', 2', or 3' (Scheme 1) of the side chain proceeded with loss of the carboxyl carbon and retention of the two remaining carbon atoms of the side chain though their activity was diluted somewhat by an unknown endogenous carbon source. 5-Hydroxytryptophan, which is reported¹²³ to be formed by *C. violaceum*, was not incorporated. Sabek and Jäger¹²⁴ also reported the conversion of L-tryptophan into violacein by *C. violaceum*; in addition, they found that lyophilized preparations of the washed cells synthesized indole from tryptophan, and that washed, nonlyophilized cells incubated in an atmosphere of indole vapors rapidly produced violacein. From these results, they concluded that tryptophan is converted to violacein through the intermediacy of indole. This conclusion is incompatible with DeMoss and Evan's results and appears to be unwarranted. The results of both groups may be explained by assuming that tryptophan loses its carboxyl carbon to give an intermediate (26) which

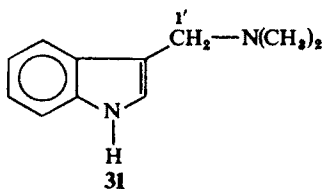
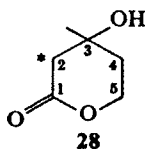
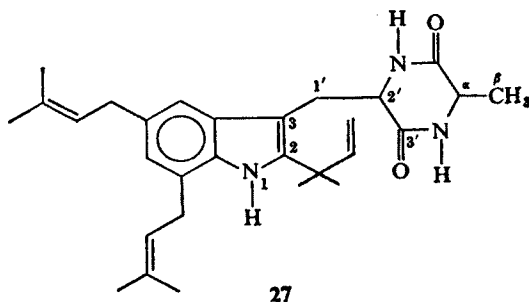


is in equilibrium with indole and a two-carbon fragment. The dilution of the activity of the side-chain carbons observed by DeMoss and Evans might then be a consequence of the incorporation of an inactive, endogenous two-carbon unit into the intermediate 26 via its equilibration with indole (Eq. 7). Both groups of authors tested the ability of *C. violaceum* to convert a wide variety of likely precursors into violacein; negative results were obtained in every case. The nature of the steps leading from tryptophan to the pigment thus remains a mystery.

G. Echinulin

The mold metabolite echinulin (27) was first isolated and investigated by Quilico and his school.¹²⁵ Birch and his collaborators¹²⁶ subsequently employed

tracer studies as an aid to the elucidation of the structure of the molecule. Feeding 2-¹⁴C-mevalonic lactone (28) to *Aspergillus amstelodami* produced

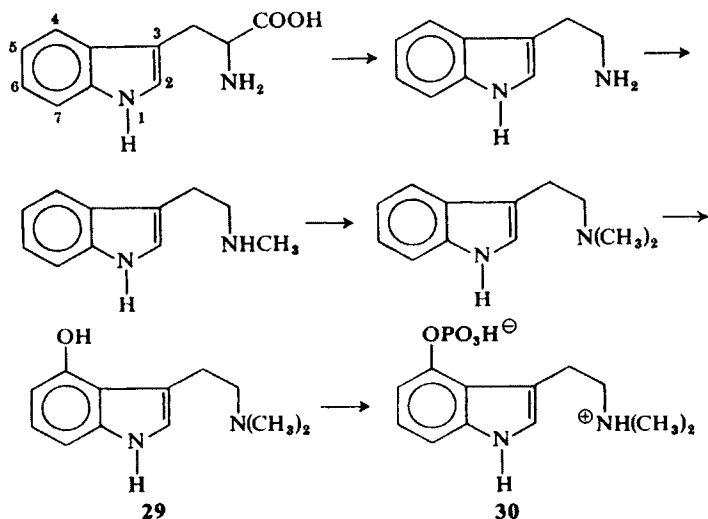


radioactive echinulin, degradation of which indicated the presence of three isoprene units in the metabolite. β -¹⁴C-DL-Alanine was shown to be efficiently incorporated into the alanine-derived portion of the diketopiperazine moiety. Birch and Farrar¹²⁷ also found significant incorporation of 1'-¹⁴C-DL-tryptophan into echinulin, a result taken to indicate that isoprenylation occurs at a stage later than tryptophan in echinulin biosynthesis. MacDonald and Slater¹²⁸ have since verified this result and have shown that the incorporation of ¹⁴C-DL-tryptophan labeled at the 2-position of the indole ring or in either the 2' or 3' positions of the side chain proceeds as anticipated. 1'-¹⁴C-L-Tryptophan was found to be incorporated about twice as efficiently as the D-isomer. This last result is in support of a very recent ORD study¹²⁹ which concluded, on the basis of the Cotton effects exhibited below 250 m μ by echinulin and a series of model diketopiperazines, that echinulin contains an L-tryptophan unit. This conclusion is at variance with that derived earlier from ORD studies limited to the region above 290 m μ .¹³⁰

H. Psilocybin

The biosynthesis of psilocybin (30), the active principle in certain Mexican hallucinogenic fungi of the genus *Psilocybe*,¹³¹ has only recently been scrutinized. The incorporation of labeled tryptophan into psilocybin was first

recorded by Hofmann's group,¹³² and subsequently confirmed by Agurell and coworkers^{133, 134}; the latter authors also investigated the utilization of other likely precursors by *Psilocybe cubensis*. Tryptamine, which is synthesized from tryptophan by the same fungus, was found to be a more efficient precursor than the amino acid, even when it was assumed that only the L-amino acid was utilized. *N*-Methyltryptamine was a still more efficient precursor, while *N,N*-dimethyltryptamine was relatively inefficient; this last result was attended with some ambiguity however, as the amine was poorly absorbed by the fungus. 4-Hydroxytryptamine also proved to be an inefficient progenitor, suggesting ring hydroxylation at a later stage in the biosynthesis; psilocin (**29**), which also occurs in the fungus, was readily converted into psilocybin. The authors summarized the data in terms of the diagram presented in Scheme 3.



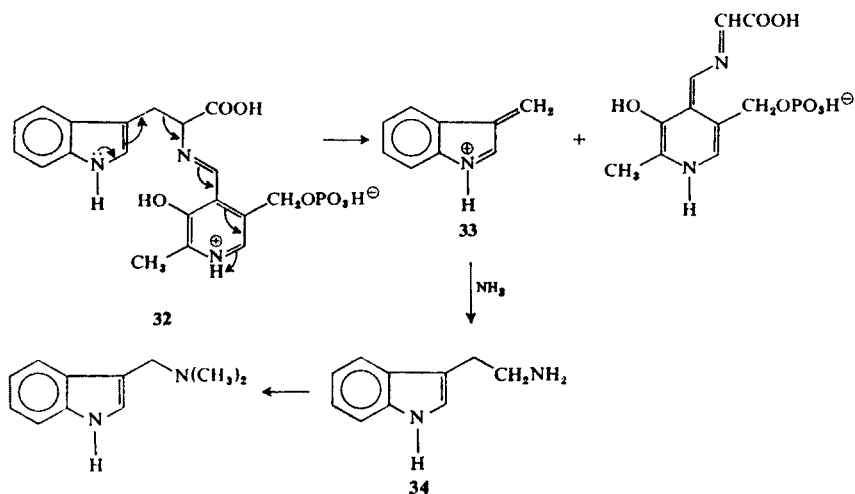
Scheme 3

III. Indole Alkaloids

A. Gramine

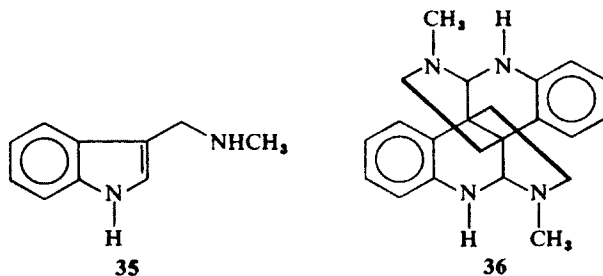
The simple indole alkaloid gramine (**31**) is present in the sprouting barley plant (*Hordeum vulgare*).^{135, 136} Initial work^{137, 138} on its biosynthesis revealed the ability of sprouting barley plants to convert 1'-¹⁴C-tryptophan into gramine; a continuation of the investigations¹³⁹ verified the incorporation

of the indole ring and C-1' as a unit. By feeding a mixture of DL-tryptophan labeled at C-2 of the indole ring and DL-tryptophan labeled at C-1', gramine was obtained which was labeled solely at the expected positions and with a ratio of activities identical to that in the original tryptophan mixture. S-Methyl- ^{14}C -methionine has been shown to be the source of the *N*-methyl groups in gramine.¹⁴⁰ An examination of various plausible intermediates¹⁴¹ between tryptophan and gramine indicated that 1'- ^{14}C -3-indolepyruvic acid and 1'- ^{14}C -3-indoleacrylic acid could act as precursors. The incorporations of these acids were specific, but quite poor. 3-Indoleacetic acid, 3-indoleglyoxylic acid, 3-indolecarboxaldehyde, and 3-indoleacetamide each failed to give rise to gramine. In the light of more recent work, 3-indoleacrylic acid can be dismissed as an intermediate. Very low incorporation was found when the labeled acid was fed to excised barley shoots,¹⁴² and the level of radioactivity was in fact higher in the isolated tryptophan than in the gramine. This suggests prior conversion of the acrylic acid to the amino acid before incorporation. O'Donovan and Leete¹⁴³ have published more conclusive evidence. Administration of a mixture of 1'- ^3H -DL-tryptophan and 1'- ^{14}C -DL-tryptophan to intact barley seedlings yielded radioactive gramine labeled only at C-1', and with the same $^3\text{H}/^{14}\text{C}$ ratio as the original tryptophan mixture. Since no loss of tritium was observed, the 1'-methylene group of tryptophan must maintain its integrity during the conversion of the amino acid to gramine. The result may also invalidate 3-indolepyruvic acid and 3-indoleacetic acid as possible precursors since the tritium atoms in these substances would be born by a carbon atom adjacent to a carbonyl function and might therefore be exchanged.



Scheme 4

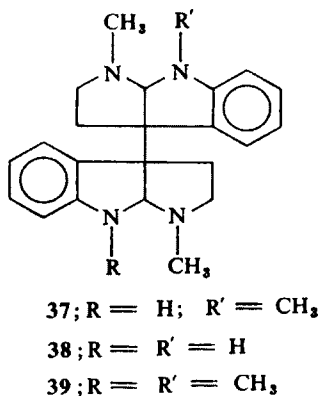
This evidence is compatible with an attractive hypothesis proposed by Wenkert¹⁴⁴ for the conversion of tryptophan to gramine. Tryptophan was postulated to condense with pyridoxal phosphate to yield the Schiff's base **32** which could undergo fragmentation to the protonated 3-methylene-indolenine **33**; addition of ammonia to this highly reactive entity would yield 3-aminomethylindole (**34**), methylation of which would afford gramine (Scheme 4). Support for this scheme derives from two sources. First, 3-aminomethylindole and 3-methylaminomethylindole (**35**) have in fact been



isolated from barley seedlings and an enzyme preparation obtained from barley shoots which methylates 3-aminomethylindole to **35** and gramine.¹⁴⁵ Second, Gower and Leete¹⁴⁶ have prepared 2-¹⁴C-3-aminomethylindole and 2-¹⁴C-3-methylaminomethylindole and administered them to excised barley shoots. The incorporations of the two amines were quite high, being 14.2 and 24.5% respectively, and the radioactive gramine so obtained was labeled exclusively at C-2.

B. Calycanthus Alkaloids

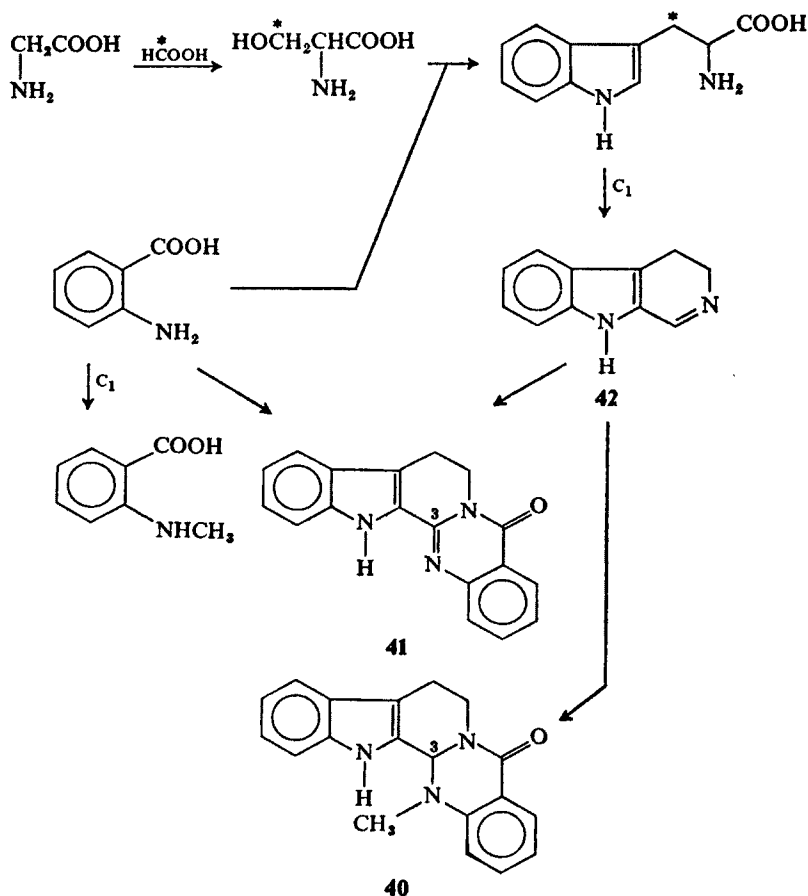
Biosynthetic work on the Calycanthus alkaloids¹⁴⁷ appears to be limited to a single investigation. Schutte and Maier¹⁴⁸ report the incorporation of



1'-¹⁴C-tryptophan into calycanthine (36), calycanthidine (37), chimonanthine (38), and folicanthine (39) by *Calycanthus floribunda*, though the identifications of the alkaloids were uncertain. Additional work on these interesting alkaloids is clearly needed.

C. Evodia Alkaloids

Two papers by Yamazaki and coworkers^{149, 150} explore the formation of alkaloids in the fruit of *Evodia rutaecarpa*.¹⁵¹ 1'-¹⁴C-Tryptophan led to radioactive evodiamine (40) and rutaecarpine (41) whose degradation indicated that most of the activity resided in the tryptamine portion of the bases.



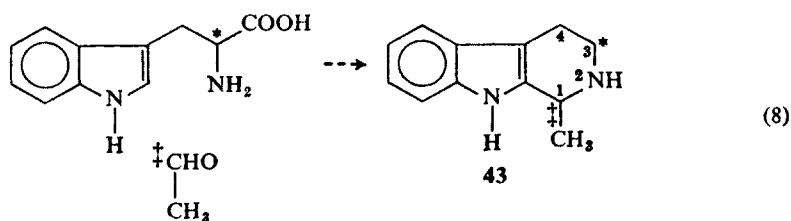
Scheme 5

^3H -Anthranilic acid was utilized in the formation of both **40** and **41**, but the radioactive alkaloids were not degraded. Sodium ^{14}C -formate was incorporated primarily into C-3 of rutaecarpine with the remainder of the activity localized in the tryptamine portion of the molecule, a result attributed to *in vivo* condensation between the labeled formate and glycine to give radioactive serine which subsequently transformed into tryptophan. In the case of evodiamine, the formate label was located primarily at C-3 and in the *N*-methyl group. Methyl- ^{14}C -methionine supplied radioactivity exclusively to C-3 and the *N*-methyl group of evodiamine, and solely to C-3 of rutaecarpine. The specific activity of the evodiamine formed when these C_1 donors were fed was lower in comparison with that of rutaecarpine than would have been anticipated on the basis of the presence of two C_1 -derived carbons in the former alkaloid. This was interpreted to mean that evodiamine does not arise from *N*-methylation of a rutaecarpine-like precursor, but rather by the introduction of a C_1 unit at an earlier stage of the biosynthesis to give *N*-methylantranilic acid which could be diluted by nonlabeled, endogenous *N*-methylantranilic acid. The biosynthetic network illustrated in Scheme 5 was proposed by the authors, though no evidence was provided for dihydronorharman (**42**) being an intermediate.

D. Carboline Alkaloids

The known carboline bases constitute a group of alkaloids derived from simple variations in the oxidation state of the β -carboline ring system.¹⁵² These alkaloids have long been a subject of biosynthetic speculation, beginning with the farsighted proposal by Perkin and Robinson in 1919¹⁵³ that they arise *in vivo* from a Mannich condensation between a tryptamine derivative and acetaldehyde. Only three papers have thus far appeared that provide experimental data on carboline alkaloid biosynthesis.

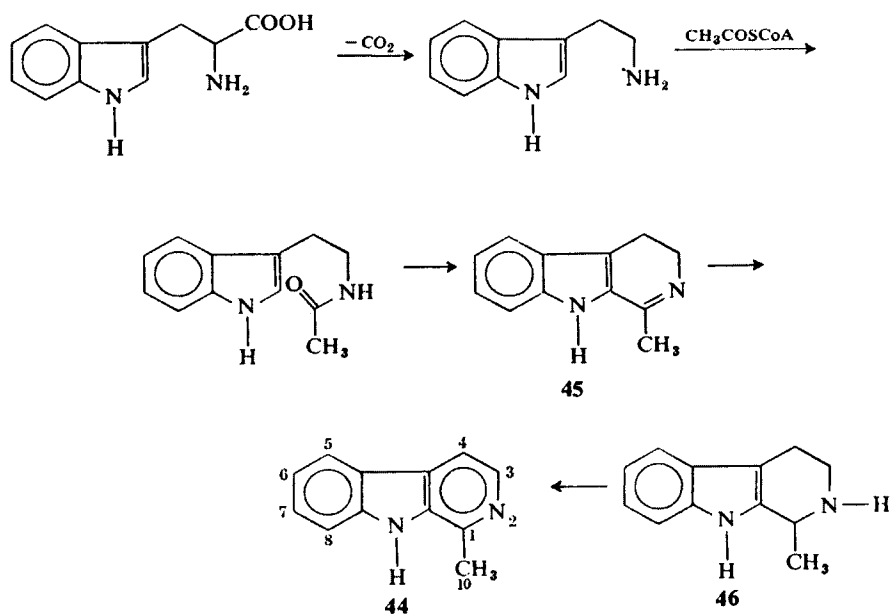
O'Donovan and Kenneally¹⁵⁴ examined the formation of eleagine (**43**), the



simplest member of the series, in *Elaeagnus angustifolia*. 2'- ^{14}C -DL-Tryptophan and sodium 1- ^{14}C -acetate were incorporated to give radioactive alkaloid

labeled exclusively at C-3 and C-1, respectively, in support of the Perkin-Robinson hypothesis (Eq. 8). The extent of incorporation of the two precursors was surprisingly low (0.01 and 0.003%, respectively), however, in view of their apparently close chemical kinship to the alkaloid.

A thorough study of the biosynthesis of harman (**44**) in *Passiflora edulis* has recently appeared. Slaytor and McFarlane¹⁵⁵ procured convincing evidence that tryptamine and *N*-acetyltryptamine are intermediates in the tryptophan to harman conversion. *N*-Acetyl-2'-¹⁴C-tryptophan was shown not to serve as a precursor for harman, while 1'-¹⁴C-tryptamine and *N*-acetyl-1'-¹⁴C-tryptamine were both utilized to form specifically labeled alkaloid. Free tryptamine was detected in the plant, but the presence of *N*-acetyltryptamine could not be directly established. Its presence in the plant was effectively demonstrated, however, by the use of radiochemical dilution. Unlabeled *N*-acetyltryptamine was administered to the plant and followed in 24 hr by either labeled tryptophan or tryptamine. The *N*-acetyltryptamine reisolated after 3 days was radioactive. When ³H-¹⁴C-L-tryptophan was administered, the radioactive *N*-acetyltryptamine obtained had the same ³H/¹⁴C ratio as did the amino acid, indicating intact incorporation. The participation of *N*-acetyltryptamine in harman biosynthesis suggests harmalan (**45**) as the penultimate biosynthetic intermediate. In fact, the authors demonstrated the efficient incorporation of ¹⁴C-harmalan into harman, but



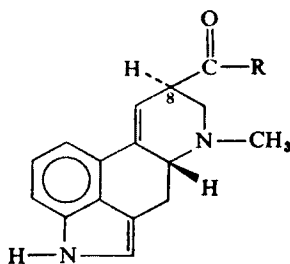
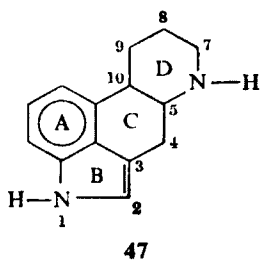
Scheme 6

the presence of harmalan in the plant tissues could not be proven, even by isotopic dilution experiments. A crude homogenate prepared from an acetone powder was able to transform harmalan to harman, nevertheless. ^{14}C -Tetrahydroharman (**46**) was also able to serve as a precursor for harman. The data were rationalized in terms of the scheme illustrated (Scheme 6). The principal difference between this pathway and that originally suggested by Perkin and Robinson is that harmalan rather than tetrahydroharman is the first tricyclic intermediate; though the conversion of tetrahydroharman to harmalan and harman was found to occur in *P. edulis*, no tetrahydroharman was detected in the plant.

Stolle and Gröger^{155a} have investigated the biosynthesis of harmine (7-methoxy **44**) in *Peganum harmala*. Both tryptophan and tryptamine specifically labeled in their side chains with ^{14}C and ^{15}N were incorporated with unchanged $^{14}\text{C}/^{15}\text{N}$ activity ratios. A specific incorporation into C-1 of harmine was observed on feeding 2- ^{14}C -pyruvic acid while 3- ^{14}C -pyruvate led to specific labeling of C-10 of harmine. An unspecific labeling pattern resulted from the administration of 1- or 2- ^{14}C -acetate, and 1,2,3,4-tetrahydroharman-3-carboxylic acid did not serve as a harmine precursor.

E. Ergot Alkaloids

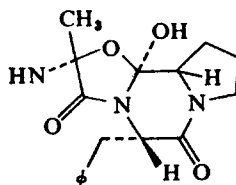
Fungi of the genus *Claviceps* elaborate a number of indole alkaloids based upon the ergoline skeleton (**47**). These alkaloids may be divided into two groups; one group contains the ergot alkaloids which are amides of



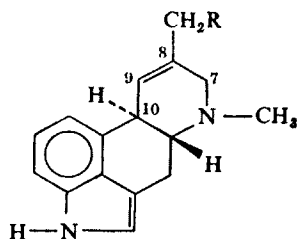
48; R = OH

49; R = NHCH(CH₃)CH₂OH

50; R =

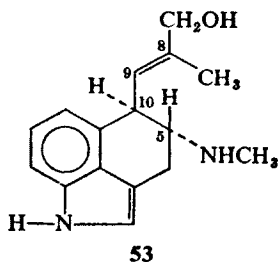


lysergic acid (48), ranging in structural complexity from such simple derivatives as ergometrine (49) to the intricate cyclic peptides, of which ergotamine (50) is representative; the other group is that of the clavine alkaloids, the most important members of which are agroclavine (51), elymoclavine (52),



51; R = H

52; R = OH



53

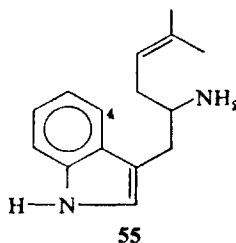
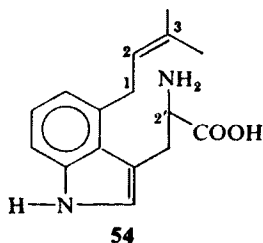
and chanoclavine-I (53). A great deal of the structural work on these substances is due to Stoll and Hoffmann, who have recently reviewed the field.¹⁵⁶

The biosynthesis of the ergot alkaloids was reviewed in 1962 by Weygand and Floss,¹⁵⁷ and again in 1966 by Agurell.¹⁵⁸ The present account focuses attention on recent developments in the field, but necessarily retraces some of the ground previously covered.

Early investigations demonstrated the ability of both tryptophan¹⁵⁹⁻¹⁶⁶ and mevalonic lactone^{160, 167-171} to serve as precursors for the ergot bases. Baxter and coworkers¹⁷¹ and Plieninger¹⁶⁴ each obtained evidence indicating that mevalonic lactone was incorporated via either isopentenyl or dimethylallyl pyrophosphate. Baxter's data demonstrated that the radioactivity derived from 2-¹⁴C-mevalonic lactone (28) was diluted in the presence of nonradioactive isopentenyl or dimethylallyl pyrophosphate, and that the carboxyl group of 1-¹⁴C-mevalonic lactone was not incorporated into the alkaloids. Plieninger reported that deuterated isopentenyl pyrophosphate was utilized in the formation of the clavine alkaloids. Recently, additional substantiation was provided¹⁷² when methyl-¹⁴C-dimethylallyl pyrophosphate was shown to be incorporated into agroclavine and elymoclavine. The *N*-methyl group of the ergot alkaloids has been found to be efficiently derived from methyl-¹⁴C-methionine, or less effectively, from sodium ¹⁴C-formate.^{173, 174}

Relatively little additional information on the formation of ring C of the ergot alkaloids has been deduced since Weygand's review. Electronic arguments favor a direct electrophilic attack of dimethylallyl or isopentenyl pyrophosphate at either the 5- or 7-position of the indole nucleus rather than at the requisite 4-position. This supposition receives support from the great

disparity between the numbers of naturally occurring 4- or 5-substituted indole derivatives. The work of both Baxter¹⁶² and Plieninger¹⁶⁴ has cast doubt on an earlier proposal that the 4-position might be suitably activated by hydroxylation at the 5-position. Structural arguments nevertheless require the attachment of an isoprene unit at C-4. This requirement might be met in one of two ways. Electrophilic attack may in fact occur directly at C-4 under enzymic mediation to give 4-(γ,γ -dimethylallyl)tryptophan¹⁶⁹ (**54**); or, alternatively, condensation might take place at C-2' of tryptophan to yield the substance **55**.¹⁵⁷ The latter substance can suffer ring closure only at C-4

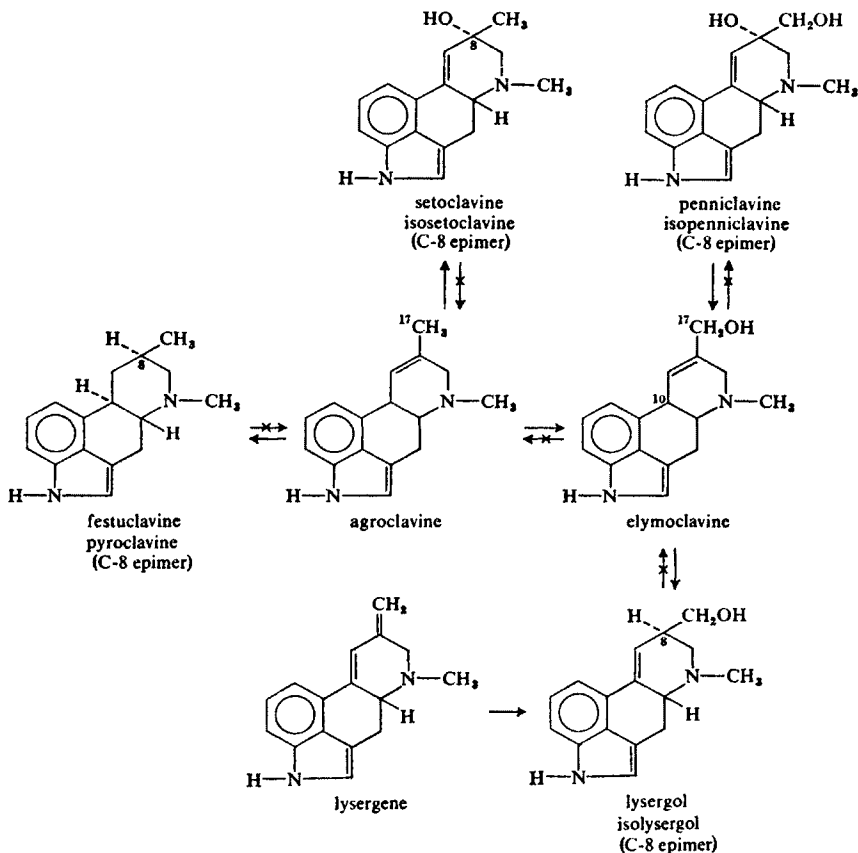


for stereochemical reasons. Plieninger has synthesized **54** containing ¹⁴C and found¹⁷⁵ that it is incorporated into elymoclavine with modest efficiency. Weygand, Floss, and Mothes¹⁷⁶ prepared **55** and compared its effectiveness as a precursor in competition with **54**; the latter substance was always more efficiently utilized. More recently, Plieninger's group synthesized **54** labeled with ¹⁴C at C-1 of the allyl side-chain and with ³H at C-2' of the alanine side-chain; the doubly-labeled substance was incorporated into agroclavine and elymoclavine without a change in the ³H/¹⁴C ratio, indicating an intact utilization of the compound.¹⁷² ¹⁴C-4-(γ,γ -Dimethylallyl)tryptamine was by contrast only poorly incorporated into the clavine alkaloids, and in fact served as an inhibitor of alkaloid formation. This result speaks in favor of isoprenylation occurring before the decarboxylation and *N*-methylation processes, a conclusion that harmonizes with other experimental evidence.^{173, 177} Very recently, Agurell and Lindgren¹⁷⁸ have found **54** in a *Pennisetum* derived ergot culture supplied with tryptophan and ethionine. The substance was detected as its *N*-trifluoroacetyl methyl ester by comparison with authentic, synthetic material using a combination of gas chromatographic and mass spectral analysis.

A greater volume of experimental data bearing on the biosynthetic relationships between the various ergot alkaloids is available. Rochelmeyer proposed¹⁷⁹ in 1958 that the clavine alkaloids serve as precursors for the lysergic acid derivatives, a hypothesis that subsequently received thorough experimental vindication. The application of ³H-elymoclavine to the sclera of an ergotamine producing strain of rye ergot, for example, led to specific rates of incorporation (= 100 $\times$ specific molar activity of product/specific molar

activity of precursor) into that alkaloid of up to 74%; similarly, using submerged cultures of a strain of *C. paspali*, the specific rates of elymoclavine incorporation into simple lysergic acid amides reached 30%.¹⁸⁰ Complimentary evidence is supplied by Agurell and Johansson¹⁸¹; both ¹⁴C-elymoclavine and ¹⁴C-agroclavine were utilized by the mycelium of *C. purpurea* in the synthesis of ergotamine, ergotaminine (50 epimeric at C-8), and ergometrine. The data indicate that the lysergic acid derivatives may be derived by the oxidation of the clavine alkaloids.

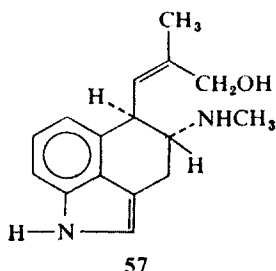
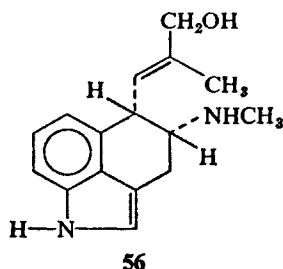
The interrelationships between the clavine alkaloids have been the object of some study. A *Claviceps* strain isolated from *Pennisetum typhoideum* irreversibly converts¹⁸² agroclavine and elymoclavine into penniclavine and isopenniclavine. Using the same ergot strain, the biosynthetic interconversions of a variety of ergot bases were unraveled; these relationships are summarized in Scheme 7. Similar data are available from Baxter.¹⁸³



Scheme 7

More recent experiments supply some interesting details regarding these interconversions. An intermediate in the enzymic oxidation of elymoclavine to penniclavine and isopenniclavine has been isolated and identified as 10-hydroxyelymoclavine.¹⁸⁴ The substance is transformed under mild conditions *in vitro* to the final products. The analogous transformation of agroclavine to setoclavine and isosetoclavine has been accomplished using horse-radish peroxidase, and some evidence presented implicating a peroxidase in the natural biological processes.¹⁸⁵ On the other hand, it has recently been argued¹⁸⁶ that the claim of a correlation of the peroxidase content of *Claviceps* mycelium with the ratio of elymoclavine to agroclavine¹⁸⁷ was ill-founded since the method of peroxidase analysis utilized primarily measures the catalase activity. Furthermore, it was found that mycelial homogenates containing both catalase and peroxidase activity would not convert ¹⁴C-agroclavine into radioactive elymoclavine in the presence of hydrogen peroxide. The oxygen atoms that must be introduced in the conversion of 4-(γ,γ -dimethylallyl)-tryptophan to chanoclavine-I and of agroclavine to elymoclavine do not derive from water¹⁸⁸; this suggests that they are introduced by direct hydroxylation and are derived from atmospheric oxygen. Such a process finds ample precedent in the microbial hydroxylations of steroids.¹⁸⁹

One of the more intriguing and puzzling problems in ergot alkaloid biosynthesis concerns the role of chanoclavine within the metabolic network. Much of the available experimental data is contradictory, and the discovery¹⁹⁰ in 1964 of the stereoisomeric chanoclavine bases points a finger of suspicion at all these early results since it is not clear to which stereoisomers the results apply, if indeed pure substances were always utilized. The structures of the three isomeric chanoclavine alkaloids, chanoclavine-I (53), chanoclavine-II (56), and isochanoclavine-I (57), are shown here; the absolute configuration



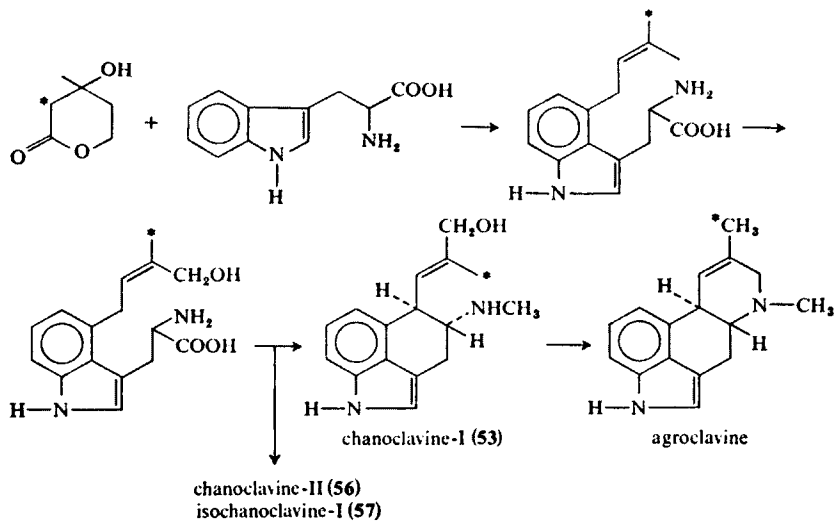
of chanoclavine-I at C-5 and C-10 was determined by Hofmann's group¹⁹¹ by correlation with festuclavine, while the configurations of the other two alkaloids are due to Stauffacher and Tscherter.¹⁹⁰ The stereochemistry assigned to chanoclavine-I and isochanoclavine-I was recently confirmed by Arigoni *et al.*¹⁹²

Though it is not yet certain whether chanoclavine-I is an obligatory intermediate in ergot alkaloid biosynthesis, the ability of the base to serve as an efficient precursor of the tetracyclic ergolines has been amply demonstrated; the incorporation levels into agroclavine, elymoclavine, and lysergic acid amide in *C. paspali* range to 40%.¹⁹³

The details of these transformations have begun to assume a remarkable complexity. Arigoni and collaborators recently reported¹⁹⁴ that sodium 2-¹⁴C-DL-mevalonate is incorporated by a *Claviceps* strain from *P. typhoideum* into agroclavine and elymoclavine to give alkaloids carrying over 90% of their respective activities at C-17. This is in accord with previous experimental data¹⁶⁹ and with the stereochemistry expected for the conversion of mevalonic acid to dimethylallyl pyrophosphate.¹⁹⁵ The radioactive chanoclavines isolated had, by contrast, over 90% of their activity in the C-methyl group, regardless of the geometry of the 8,9-double-bond. Chanoclavine-I therefore bore an unexpected *trans*-relationship of the labeled atom and the olefinic proton. This labeling pattern and stereochemistry suggested that isochanoclavine-I should be the precursor of the tetracyclic alkaloids. Further experiments proved that this supposition was incorrect, however. Biosynthetically labeled elymoclavine was converted chemically into chanoclavine-I bearing greater than 90% of its activity in the hydroxymethylene carbon. The incorporation of this substance gave labeled agroclavine, shown by degradation to carry over 96% of the activity at C-7. The conversion of chanoclavine-I into agroclavine must therefore be accompanied by a *trans* to *cis* isomerization of the 8,9-double-bond. Experiments under similar conditions with hydroxymethylene labeled isochanoclavine-I failed to disclose any significant incorporation of the compound into the tetracyclic ergolines.

Floss and coworkers¹⁹⁶ have furnished confirmation of these most interesting results as well as additional experimental information. Chanoclavine-I bearing tritium at C-9 or C-10 as well as a ¹⁴C reference label was prepared biosynthetically from the requisite labeled mevalonic acid. Conversion of the doubly-labeled alkaloid into elymoclavine by *Claviceps* strain SD58 proceeded with 100% retention of the label at C-10 and 92% retention of label at C-9. Hence, a double-bond shift to the 9,10-position during the isomerization process does not occur. The importance of chanoclavine-I as a precursor of the tetracyclic bases was emphasized by the relative efficiencies of conversion of various clavines into elymoclavine; in replacement cultures, the specific incorporations of agroclavine, chanoclavine-I, isochanoclavine-I, and chanoclavine-II (each biosynthetically labeled with tritium in the indole ring) were 9.6, 9.0, 1.9, and 0.6%, respectively. On the basis of these findings, and the additional observations of Arigoni *et al.*¹⁹⁷ that desoxychanoclavine-I and its *N*-demethylation product are not incorporated into elymoclavine, the biosynthetic sequence involving two isomerizations shown in Scheme 8 was proposed.

The alternative to this proposal, that the isopentenyl pyrophosphate isomerase reaction in *Claviceps* follows an unexpected steric course, has been ruled out by still further experimentation.¹⁹⁸ 4*R*- and 4*S*-DL-2-¹⁴C, 4-³H-Mevalonic acid were each fed to shake cultures of *Claviceps* strain SD58. The



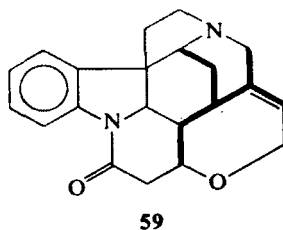
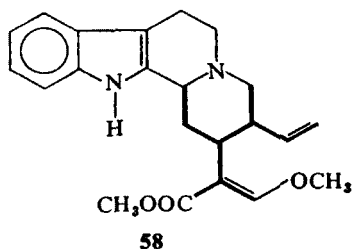
Scheme 8

elymoclavine isolated displayed ¹⁴C incorporations of 9.9 and 10.0%, respectively, and the ³H/¹⁴C ratios were such as to correspond to a 70% retention of the 4*R*-hydrogen and only 3% retention of the 4*S*-hydrogen. The loss of some of the 4*R*-hydrogens was ascribed to an isotope effect in a subsequent stage of the biosynthesis. The elimination of the 4*S*-hydrogen demonstrates that the stereochemical outcome of the isopentenyl pyrophosphate isomerase reaction in ergot alkaloid biosynthesis is the same as that observed in other biological systems.¹⁹⁹ It is therefore a reasonably safe assumption that the over-all stereochemistry of the reaction is also the same as in these systems; this assumption predicts that the label from C-2 of mevalonic lactone should be located in the *trans* methyl group of the original dimethylallyl moiety. Thus, two isomerizations of the allylic double-bond apparently occur in the formation of the tetracyclic ergolines.

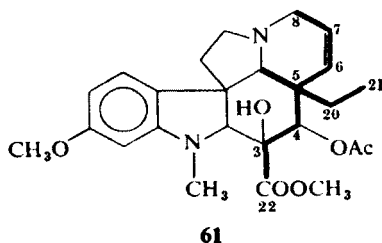
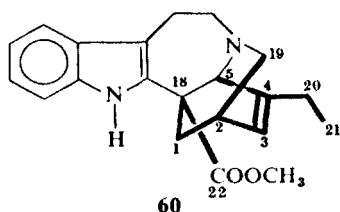
F. Monoterpene-Derived Indole Alkaloids

The family of indole bases of which corynantheine (58), strychnine (59), catharanthine (60), and vindoline (61) may be offered as representative

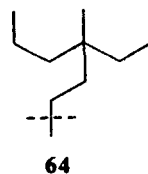
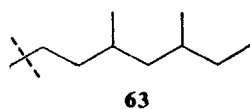
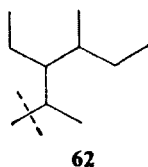
members currently includes over six hundred alkaloids^{152, 200} and undoubtedly constitutes the largest group of naturally occurring indoles. The historical background and earliest investigations dealing with the biosynthesis of these substances have been carefully summarized,^{201, 202} so that the present account places emphasis on the more recent advances in this rapidly moving area of research.



Early experimental efforts established that tryptophan could serve as the precursor for the tryptamine moiety common to almost all these alkaloids,²⁰³ and for some time the major hurdle in the way of an understanding of indole alkaloid biosynthesis was the unknown origin of the nine or ten carbon skeleton almost always found combined with tryptamine. Order was brought to the apparently endless structural variety of the alkaloids by the recognition²⁰⁴ that almost all the known examples contain the C_{9-10} skeleton in one of three arrangements. These three arrangements may be conveniently



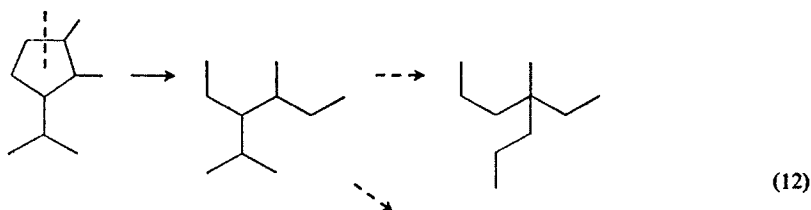
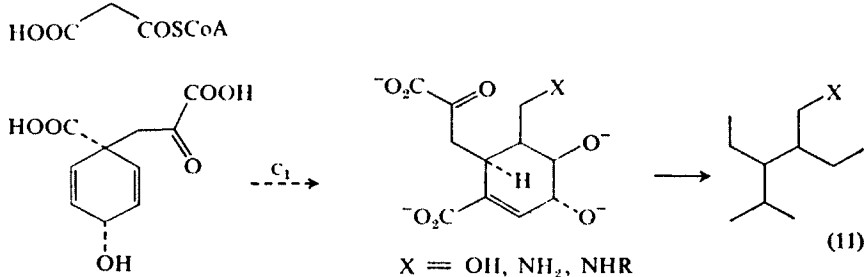
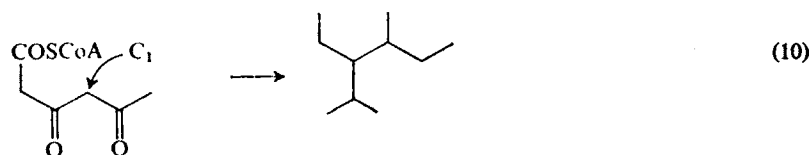
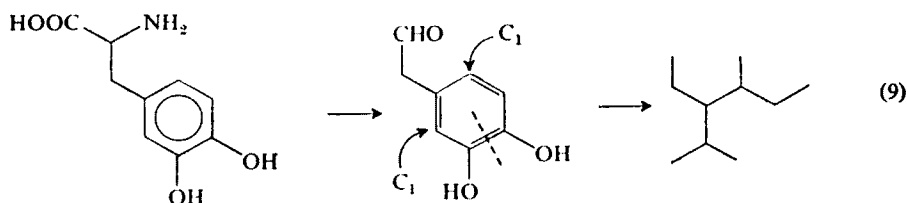
referred to as²⁰⁵ (1) the *Corynanthe* type with the C_{9-10} skeleton **62** (heavy lines in **58** and **59**), (2) the *Iboga* type, possessing the C_{9-10} unit of structure **63** (heavy lines in **60**), and (3) the *Aspidosperma* type with a C_{9-10} unit of structure **64** (heavy lines in **61**). The dashed line in each of these formulations



indicates that carbon atom which is consistently lost in those alkaloids having only nine skeletal carbons in addition to the tryptamine moiety.

In the absence of experimental data, a number of ingenious hypotheses were advanced to account for the origin of the C_{9-10} unit. The essential features of the four major hypotheses are presented in Scheme 9.

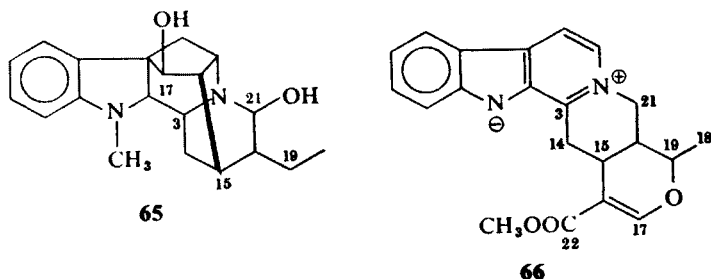
The earliest proposal derived the *Corynanthe* unit from 3,4-dihydroxyphenylalanine plus two one-carbon units utilizing a cleavage of the aromatic ring²⁰⁶ that has come to be called Woodward fission (Eq. 9); the second



Scheme 9

hypothesis²⁰⁷ suggests a derivation of the ten carbons from the condensation of three acetate units, a malonate unit, and a C_1 unit (Eq. 10); the third postulate²⁰⁸ argues for a C_{9-10} skeleton derived from prephenic acid in combination with a C_1 unit (Eq. 11); and the last suggestion^{208b, 209} proposes the cleavage of a cyclopentane monoterpene skeleton to arrive at the required C_{9-10} fragment (Eq. 12).

Experimental work by Leete's group initially appeared to substantiate the second hypothesis.^{207, 210, 211} Incorporation of sodium ^{14}C -formate into ajmaline (**65**) by *Rauwolfia serpentina* reportedly gave the alkaloid bearing 12% of its activity at C-21. Further experiments, employing sodium 1- ^{14}C -acetate, led to a labeling pattern in ajmaline in very close agreement with theory: positions 3 and 19 were each found to carry 26% of the total activity. Similarly, the incorporation of sodium 1- ^{14}C -acetate into serpentine (**66**)



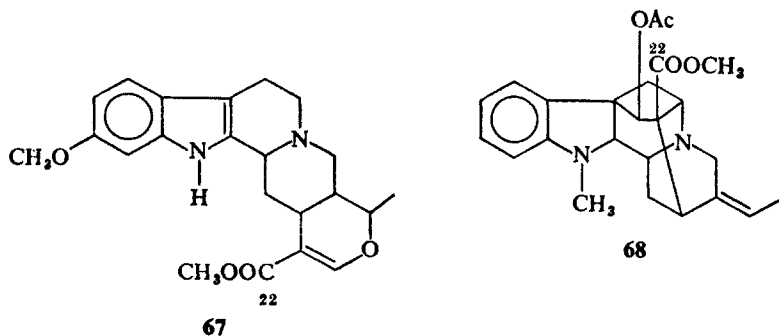
reportedly labeled C-19 with 23% of the total activity, C-22 being inactive, while 1,3- ^{14}C -malonic acid yielded serpentine with 48% of its activity at C-22, and ajmaline with 74% of its activity at C-17.

In contrast, other investigations have yielded data that argues convincingly against an acetate origin for the C_{9-10} unit. Battersby et al.²¹² reported that the radioactive ajmaline isolated when sodium 1- ^{14}C -acetate was administered to *R. serpentina* has the label scattered among the carbons of the C_{9-10} unit. Sodium ^{14}C -formate yielded ajmaline with very little activity at C-21. Goeggel and Arigoni,²¹³ testing the incorporation of sodium 1- ^{14}C acetate into vincamedine (**68**) and reserpine (**67**) by *Vinca* species, likewise observed scrambling of the label.

Finally, Barton and coworkers²¹⁴ recorded that *N*-methyltryptophan and *N*-methyltryptamine bearing ^{14}C in the *N*-methyl groups do not serve as precursors for ajmaline in *R. verticillata*. This suggests that C-21 of ajmaline cannot originate from an *N*-methyl group in a manner analogous to the formation of the C_1 bridge in the berberine alkaloids,²¹⁵ speaking in other words against the incorporation of a C_1 unit into the C_{9-10} skeleton. Administration of methyl- ^3H -DL-methionine to *R. serpentina* procured additional evidence against incorporation of a C_1 unit; the resulting ajmaline carried 97% of its total activity in the *N*-methyl group.

In the face of the unfavorable evidence, Leete reexamined his earlier results and verified the conclusions of the other investigators.²¹⁶

The data amassed in the testing of the acetate hypothesis not only speaks heavily against an acetate origin for the ubiquitous C_{9-10} unit, but also casts



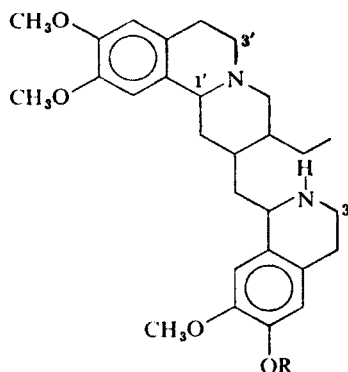
a shadow of doubt across the other two hypotheses that require the specific incorporation of a C_1 unit. Relevant data supporting this doubt was soon forthcoming. Mothes' group²¹⁷ administered $U-^{14}C$ -shikimic acid to *Vinca rosea* and degraded the radioactive vindoline (**61**) to demonstrate that over 90% of its activity resided in the benzene ring. Since shikimic acid is the usual biological precursor of prephenic acid,²¹⁸ Wenkert's suggestion that prephenic acid is the source of the nontryptophan derived portion of the indole alkaloids is untenable.

Evidence against the generation of the C_{9-10} unit by Woodward fission comes from Battersby's group.²¹⁹ The two ipecac alkaloids, cephaeline (**69**) and emetine (**70**), contain a *Corynanthe*-type skeleton, but condensed with a phenethylamine residue rather than with tryptamine; conclusions derived from tracer studies on the ipecac alkaloids may therefore be applied, with some reservations, to the indole alkaloids. When $2'-^{14}C$ -DL-tyrosine (tryptophan numbering, Section II.A) was supplied to *Cephaelis ipecacuanha*, radioactive cephaeline was produced which was specifically labeled at C-3 and C-3', but not at C-1'; hence, 3,4-dihydroxyphenylalanine is not a likely precursor for the C_{9-10} unit of these alkaloids. Administration of radioactive phenylalanine gave similar results. A scrambling of label, analogous to that observed in *R. serpentina* for the indole alkaloids, was obtained when sodium ^{14}C -formate, sodium $1-^{14}C$ -acetate, and sodium $1,3-^{14}C$ -malonate were fed to *C. ipecacuanha*.

At this point, three of the plausible pathways to the nontryptophan derived portion of the indole alkaloids had been effectively disproved, and it remained to test the validity of the fourth, implicating a cyclopentanoid monoterpene. Experiments in this area have come primarily from three laboratories, those

of Battersby, of Scott, and of Arigoni. Battersby has recently summarized his own work in the field.²⁰⁵

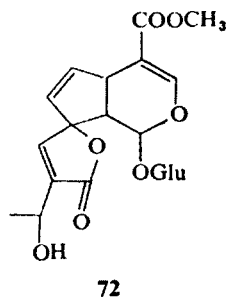
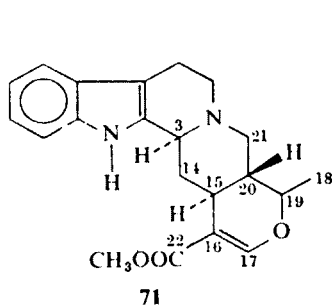
A likely precursor for a cyclopentanoid monoterpene is mevalonic acid,²²⁰ and the incorporation of this substance into the indole alkaloids has been



69; R = H

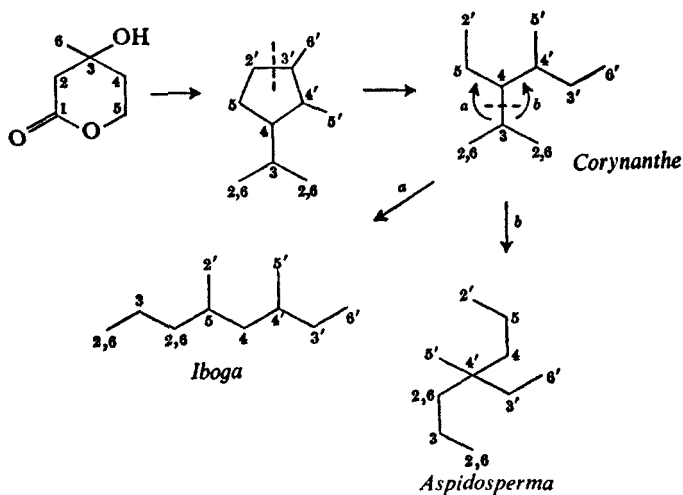
70; R = CH₃

examined with great thoroughness. Feeding of sodium 2-¹⁴C-DL-mevalonate to *Vinca* plants afforded radioactive vindoline (61),²²¹⁻²²³ reserpinine (67),²²² ajmalicine (71),²²³ and catharanthine (60),²²³ each bearing approximately one quarter of its respective total activity at C-22. These results are consonant with a specific incorporation of mevalonic acid into each of the alkaloids in such a manner that C-2 and C-6 of one mevalonate unit become equivalent, a situation previously encountered in the biosynthesis of plumeride (72).²²⁴

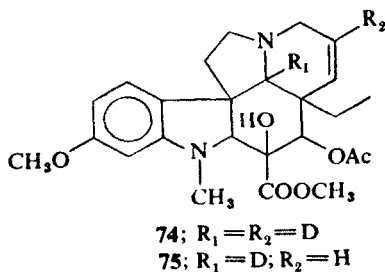


Further degradation of the catharanthine indicated that 20% of its activity was at C-1 and/or C-18, and 48% at one or more of the carbons -2, -3, -5,

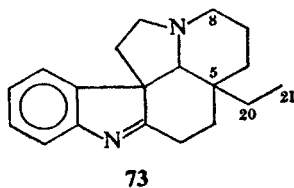
and -19. Scheme 10 presents a schematic rationalization of these labeling patterns.²⁰⁹



Scheme 10



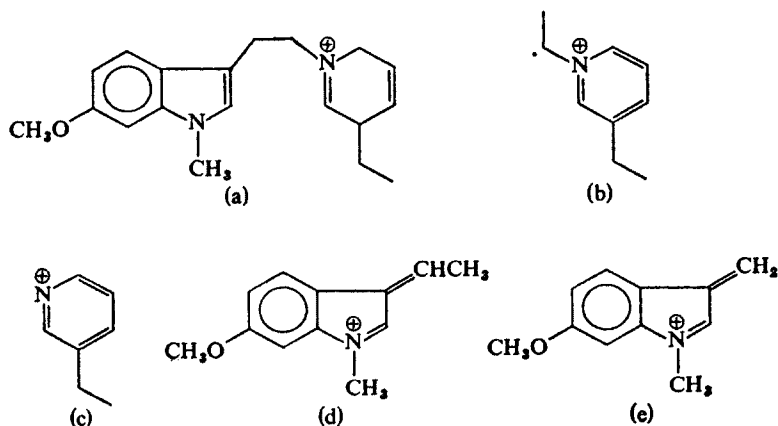
The same pattern of mevalonate incorporation was observed in another plant genus; *Rhazia stricta* utilized²²³ sodium 2-¹⁴C-DL-mevalonate in the biosynthesis of 1,2-dehydroaspidospermidine (73). Degradation revealed



that about 65% of the total activity of this alkaloid resided at C-8. Since the skeleton of the alkaloid requires the loss of one carbon atom, the anticipated value for C-8 is 67% if one of the two equivalent 2,6 carbon atoms is lost. Sodium 3-¹⁴C-DL-mevalonate was similarly incorporated by *R. stricta* into 73

with 47% (theory = 50%) of the label being located at C-20, while C-5 and C-21 were inactive.

Whatever doubts might still remain concerning the location of the mevalonate carbons in the three types of C_{9-10} units have been dispelled by additional tracer studies with *V. rosea* and labeled mevalonate. The results are in complete agreement with those predicted by Scheme 10. Thus, administration of 3- ^{14}C -mevalonate to *V. rosea* gave serpentine²²⁵ and ajmalicine²²⁶ with approximately 40% of their individual total activities at C-19; the radioactive vindoline²²⁶ generated under the same circumstances carried 47% of its label at C-20 with no activity present at C-5, -21, -22, or in the *N*- or *O*-methyl groups. Using sodium 5- ^{14}C -DL-mevalonate, radioactive vindoline and catharanthine²²⁵ unlabeled at C-5, -20, and -21, and at C-4, -20, and -21, respectively, were produced. Further scrutiny of the final location of C-5 of mevalonic acid in the *Aspidosperma* unit was achieved by mass spectral examination of the deuterio-vindoline, presumed to be **74**, produced from 5- $^2H_2$ -mevalonate by *V. rosea*; of the principal fragment ions of vindoline, ions (a), (b), and (c) showed an enrichment level corresponding to two deuterium atoms, while ions (d) and (e) showed no enrichment²²⁷ (Scheme 11).



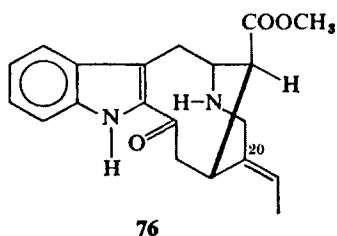
Scheme 11

When the above results are taken in conjunction with the additional studies by Battersby *et al.*²²⁸ of the incorporation of labeled mevalonate into the five *V. rosea* alkaloids ajmalicine, serpentine, catharanthine, vindoline, and perivine (**76**) (see Table I), they provide an almost complete labeling pattern for the *Corynanthe* unit; furthermore, the generation of a bond between the C-4 carbon atoms of two mevalonate units is established, supporting the formation of a cyclopentane ring.

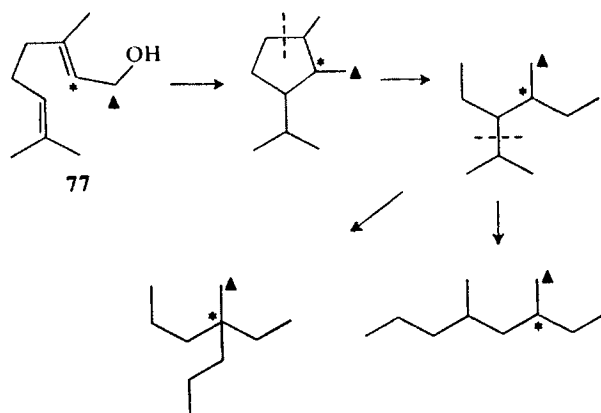
TABLE I. Administration of ^{14}C -Labeled Mevalonic Acids to *Vinca Rosea*

Position of ^{14}C in mevalonate	Alkaloid isolated	Carbon atom(s) isolated	% of total activity	
			Theory	Found
2	Serpentine (66)	3	50	43
2	Ajmalicine (71)	16-17	25	22
3	Catharanthine (60)	20-21	50	44
3	Vindoline (61)	20	50	45
4	Serpentine (66)	15	50	45
4	Perivine (76)	20	50	44
4	Catharanthine (60)	4	50	48
4	Vindoline (61)	5	50	45
5	Serpentine (66)	14	50	43

The successful incorporation of mevalonic acid into the C_{9-10} unit of the indole alkaloids provided the long sought key needed to unlock the secrets of indole alkaloid biosynthesis, and the ensuing progress has been rapid.



Knowledge of the biochemical fate of mevalonic acid²¹⁸ points to geraniol (77) as a likely precursor for the nontryptophan derived portion of the indole alkaloids, and three groups simultaneously recorded the incorporation



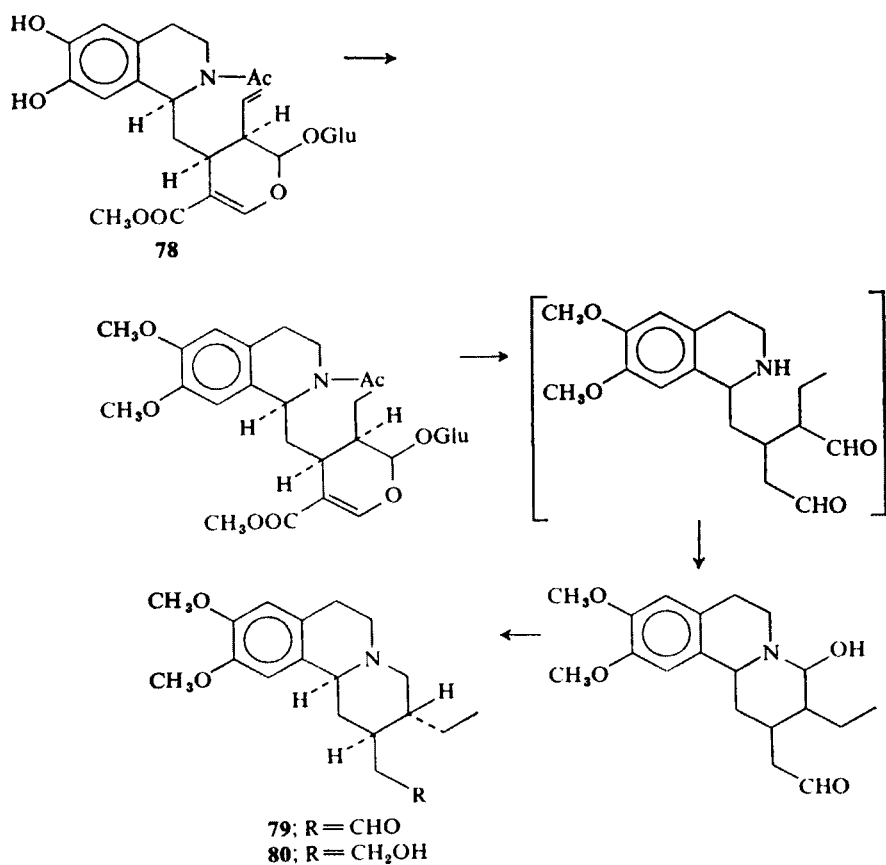
Scheme 12

of geraniol into the alkaloids of *V. rosea*. Arigoni and coworkers²²⁶ reported that 2-¹⁴C-geraniol yielded radioactive vindoline carrying all its activity at C-5; identical results were found by Battersby's²²⁵ and Scott's²²⁷ groups. In addition, Battersby established that the radioactive catharanthine produced by *V. rosea* from 2-¹⁴C-geraniol bore all of its activity at C-4, while the radioactive ajmalicine formed was labeled at one or more of the four carbons -3, -14, -20, and -21 (C-20 expected). By the use of mass spectrometry, Scott²²⁷ localized the deuterium in the vindoline generated *in vivo* from 1-²H₂-geraniol which was presumed to be **75**; ions (a), (b), and (c) each showed enrichment levels corresponding to the presence of one deuterium atom while ions (d) and (e) showed no enrichment, in agreement with expectation. The data obtained with labeled geraniol are readily accommodated by the processes of Scheme 12.

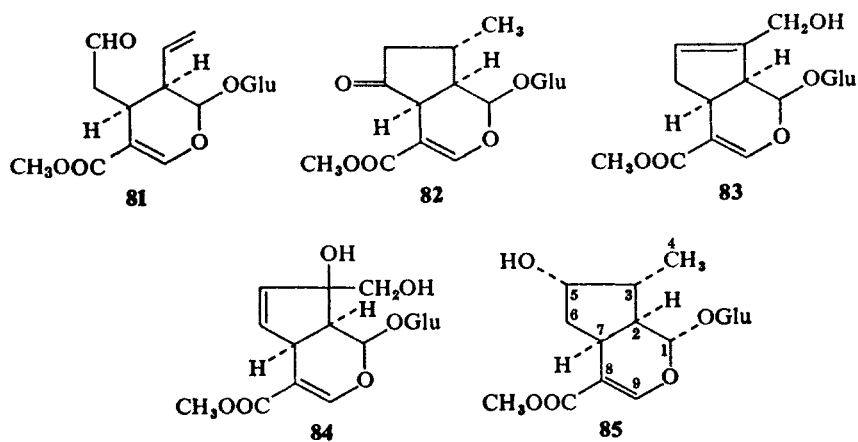
With the efficacy of geraniol as an indole alkaloid precursor amply proven, attention was next turned to the known cyclopentanoid monoterpenes in the search for a likely candidate for the postulated ring-cleavage and rearrangements. Fortunately, the field of choice was narrowed somewhat by the isolation of a glucoside called ipecoside from *Ipecacuanha* plants. The chemical and spectroscopic data led to the constitution **78** for this substance,²²⁹ and further evidence as well as its absolute stereochemistry followed from a correlation with protoemetine (**79**)²³⁰ via dihydroprotoemetine (**80**) (Scheme 13).

The success of the correlation suggests that the corresponding des-*N*-acetylipecoside may be the actual precursor of protoemetine in *Ipecacuanha*. Furthermore, the striking biogenetic similarity between protoemetine and corynantheine infers that aldehyde **81** may be the source of the C₉₋₁₀ unit in each instance. A consideration of the known cyclopentanoid monoterpenes led²⁰⁵ to the selection of four substances as likely precursors of **81**; these were verbenalin (**82**),²³¹ genepin (**83**),²³² monotropeine (shown as its methyl ester **84**),²³³ and loganin (**85**).²³⁴

Each of these terpenes has now been tested for its ability to serve as a precursor of the indole alkaloids in *V. rosea*,²⁰⁵ and the work on all but genepin has been published.²³⁵ Verbenalin was labeled by base-catalyzed exchange with tritiated water, and a portion of the radioactive compound reduced with borohydride to dihydroverbenalin. Both substances failed to serve as precursors. Methylation of monotropeine with diazomethane in the presence of tritiated water yielded the ester with tritium in the methyl group. The catharanthine, vindoline, ajmalicine, and serpentine isolated when this substance was supplied to *V. rosea* were all inactive. The result implies not only that the monotropeine system is unsuitable for *in vivo* conversion to the indole alkaloids, but it also demonstrates that the labeled methyl group has not been removed and mingled with the C₁ pool of the plant.



Scheme 13

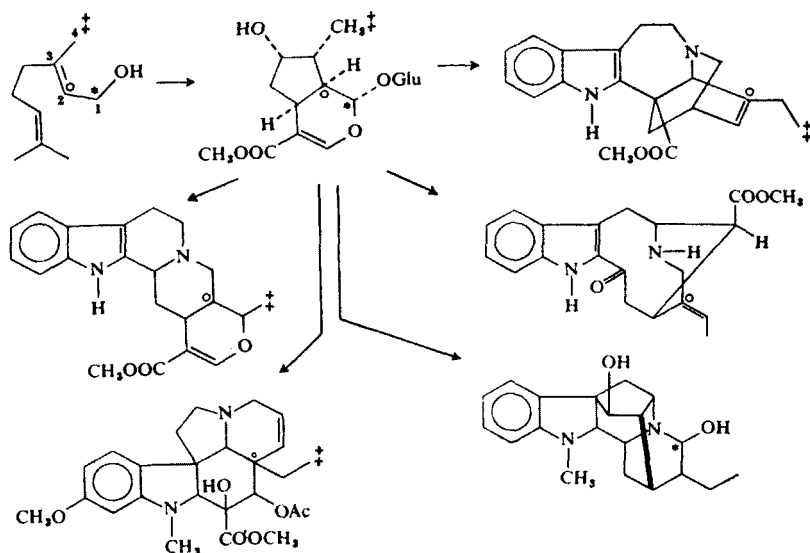


Loganin was similarly converted to *O*-methyl-³H-loganin by hydrolysis to loganic acid, and methylation with diazomethane in the presence of tritiated water. Administration of the loganin so labeled to *V. rosea* yielded radioactive catharanthine, vindoline, perivine, serpentine, and ajmalicine. Zeisel demethylation of **60**, **66**, and **71** proved that all of the radioactivity resided in the methyl group of the ester moiety in each alkaloid. Hydrolysis of the vindoline to desacetylvindoline (98% of original activity) followed by reduction with lithium aluminum hydride gave the trial which contained less than 0.1% of the original activity. No significant amount of activity was therefore present in the *N*-methyl and *O*-methyl groups, again providing evidence against *in vivo* exchange of the labeled methyl group to give the labeled C₁ pool. Hence, loganin may be said to show specific incorporation into the *Corynanthe*, *Aspidosperma*, and *Iboga* alkaloid families.

Confirmatory evidence for the role of loganin as the cyclopentanoid precursor of the indole alkaloids in *V. rosea* was supplied by the demonstration by isotopic dilution methods of its presence in *V. rosea* plants. 1-³H-Geraniol was administered and radioinactive loganin added to the plant extracts; reisolatation of the loganin as its pentaacetate, hydrolysis, and methylation of the loganic acid afforded loganin of constant specific activity corresponding to 0.02% incorporation; reconversion to the pentaacetate and further purification did not alter its specific activity.

At the time of these preliminary experiments, the structure of loganin was only tentatively established, having been derived from the application of biogenetic arguments to limited chemical data,^{231, 234} and its stereochemistry was unknown. The discovery of loganin's importance as an indole alkaloid precursor made it imperative to reexamine the substance and eliminate the uncertainties. Thus, the original structural proposal was simultaneously confirmed by two groups in 1968, and the absolute stereochemistry defined as depicted in **85**.^{236, 237} Work carried out concurrently established the mevalonate origin of loganin. 4-¹⁴C-Geraniol, on administration to the rhizomes of *Menyanthes trifoliata*, was converted into loganin bearing 85% of its label at C-4²³⁷; rather surprisingly, sodium 2-¹⁴C-DL-mevalonate was not incorporated into loganin under similar circumstances, a result best attributed to a failure of the mevalonate to reach the site of loganin biosynthesis. Using *Swertia caroliniensis*, both 2-¹⁴C-mevalonate and 1-¹⁴C-geranyl pyrophosphate were incorporated into the loganic acid found in that plant.²³⁸

The 4-¹⁴C-loganin isolated from *Menyanthes* plants supplied with 4-¹⁴C-geraniol was subsequently fed to *V. rosea*. Radioactive ajmalicine, vindoline, and catharanthine were produced; degradation revealed that the ajmalicine bore 93% of its total activity at C-18, while the vindoline and catharanthine were labeled exclusively at the positions shown (Scheme 14).²³⁹ Administration of a mixture (*ca.* 3:1) of 2-¹⁴C-geraniol and 2-¹⁴C-nerol (isomeric at the

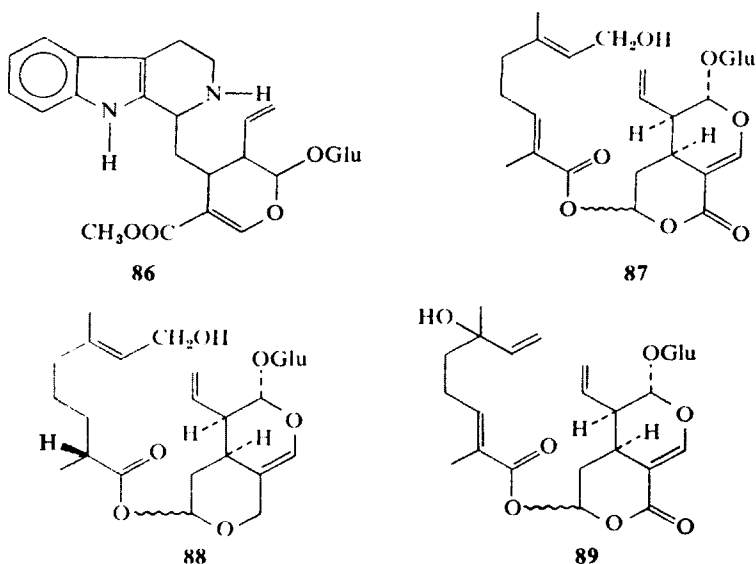


Scheme 14

2,3-double bond) to *M. trifoliata* also yielded radioactive loganin. When this labeled material was fed to *V. rosea*, radioactive serpentine, ajmalicine, catharanthine, vindoline, and perivine were produced. Degradative work demonstrated that the catharanthine was labeled solely at C-4, while the desacetylvindoline and dihydroperivine were labeled to 102 and 96% of their respective total activities at the positions indicated in Scheme 14.²⁴⁰ Similarly, 1-³H-loganin, prepared biosynthetically from 1-³H-geraniol, was supplied to *Rauwolfia serpentina*. The radioactive ajmaline isolated was shown to be specifically labeled with tritium at C-21 (see Scheme 14). Thus, a second plant species can utilize loganin as a specific precursor for a *Corynanthe*-type alkaloid.²⁴⁰

With the role of loganin as a precursor of the nontryptophan derived portion of the indole alkaloids firmly settled, the subsequent steps along the biosynthetic pathway become accessible to investigation. The constitution of ipecoside and the specific incorporation of loganin therein²⁴¹ suggest that a corresponding cleavage of the five-membered ring of loganin to aldehyde **81** followed by a condensation with tryptamine to give the β -carboline glycoside **86** represent stages in the biosynthesis of the indole alkaloids. This line of reasoning has now received experimental vindication. An extract of *Rhazia stricta* leaves has been reported²⁴² to yield an amorphous glucoside to which the constitution **86** was assigned, largely on the basis of spectroscopic data; the stereochemistry was left undefined. More recently, the natural occurrence of a glucoside corresponding to **86** has been placed on a firmer footing.

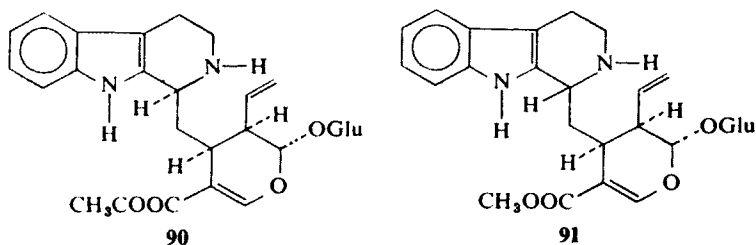
Menyanthes trifoliata has been found^{243, 244} to contain three seco-cyclopentane glucosides, called foliamenthin (**87**), dihydrofoliamenthin (**88**), and menthiafolin (**89**). Alkaline hydrolysis of menthiafolin under carefully controlled



conditions followed by methylation with diazomethane afforded seco-loganin (**81**).²⁴⁵ Repetition of the procedure using ³H-diazomethane produced *O*-methyl-³H-seco-loganin. *Vinca rosea* shoots supplied with this glucoside yielded a compliment of alkaloids: **66**, **71**, **60**, and **61**. Zeisel demethylation of **71** and **60** proved that 94 and 96%, respectively, of their total activities were localized in the methyl groups of the ester moieties; **61** yielded desacetyl-vindoline still containing 98% of the original activity, and following reduction, a triol was obtained carrying less than 1% of the former activity. The absence of significant methyl transfer to the C₁ pool was assured by the lack of activity in the *N*-methyl and aryl-*O*-methyl groups of the vindoline. Thus, the specific incorporation of seco-loganin into the three skeletal families of the indole alkaloids was demonstrated.

As a prelude to the condensation of seco-loganin with tryptamine, the ability of *V. rosea* to convert tritiated tryptamine into the three classes of indole alkaloids was established.²⁴⁶ Tryptamine was then condensed with seco-loganin to produce the two epimeric β -carboline, vincoside (**90**) and isovincoside (**91**).²⁴⁶ The use of *O*-methyl-³H-seco-loganin generated the corresponding labeled β -carboline which were fed as a mixture to *V. rosea*. Incorporation into all three types of indole alkaloids was observed. Intact incorporations were assured by the use of doubly-labeled **90** and **91** prepared

O-methyl-³*H*-loganin and *U*-³*H*-tryptamine; degradations of the radioactive alkaloids isolated in this instance disclosed that biosynthesis had taken



place without a significant alteration in the ratio of the labels present in the two halves of the β -carbolines.²⁴⁶ A separation of the *O*-methyl-³*H*-labeled glucosides **90** and **91** was subsequently achieved by partition chromatography, and feeding experiments with the individual epimers clearly indicated that only vincoside serves as the indole alkaloid precursor in *V. rosea*.²⁴⁷

Evidence for the natural occurrence of seco-loganin, vincoside, and isovincoside derives from various sources. *Vinca rosea* plants to which 5-³*H*-loganin had been administered were worked up with the addition of inactive samples of the aforementioned substances as carriers. The isolated seco-loganin fraction was treated with 3,4-dihydroxyphenethylamine to give ipecoside,²⁴⁵ whose activity corresponded to greater than 6% incorporation of loganin into seco-loganin. Acetylation of the β -carboline fraction yielded the pentaacetates of vincoside and isovincoside, each of which possessed activities as their *N*-acetyl derivatives corresponding to 1.5% incorporation.²⁴⁶ More direct evidence for the natural occurrence of vincoside has come from the isolation of its pentaacetyl derivative from an acetylated extract of *V. rosea* seedlings,²⁴⁸ and from the isolation of *N*-acetylvincoside from *V. rosea* plants.²⁴⁷

The results argue compellingly for the role of vincoside as the link between loganin and the three classes of indole alkaloids. The conversion of vincoside into the *Corynanthe*-type alkaloids poses no unusual problems, and the more intriguing questions concern the sequence and nature of the steps leading to the rearranged *Aspidosperma* and *Iboga* skeletons. Answers to some of these questions are slowly being found. Qureshi and Scott²⁴⁹ have investigated the sequential formation of indole alkaloids in germinating *V. rosea* seeds. The presence of alkaloids is detectable by thin-layer chromatography after about 26 hr, and the first alkaloids to be produced are corynantheine (**58**), corynantheine aldehyde (**58**, methyl of enol ether replaced by hydrogen), and dihydrocorynantheine (**58**, vinyl group saturated). After 45 hr, ajmalicine (**71**) appears, followed by stemmadenine (**92**) after 50 hr. The presence of stemmadenine was confirmed by the radiochemical dilution technique after

administration of 3-¹⁴C-DL-tryptophan since the amounts produced were inadequate for complete spectroscopic characterization. The *Aspidosperma*-type alkaloid tabersonine (**93**) appeared after 72 hr of incubation, and the *Ipoga*-type alkaloid catharanthine appeared along with vindoline after 168 hr. This appears to favor the order of alkaloid biosynthesis, *Corynanthe* to *Aspidosperma* to *Ipoga*, a sequence that gains further support from the studies with the labeled alkaloids summarized in Table II.²⁴⁹ In particular,

TABLE II. Administration of Labeled Indole Alkaloids to *V. Rosea* Seedlings

Alkaloid precursor	Label	³ H/ ¹⁴ C (%)	Alkaloid(s) isolated	Specific incorporation (%)	³ H/ ¹⁴ C (%)
Stemmadenine	<i>O</i> -Methyl- ³ H, 11- ¹⁴ C	—	Tabersonine	0.27	—
			Catharanthine	0.56	—
			Vindoline	1.76	—
Tabersonine	<i>O</i> -Methyl- ³ H, 11- ¹⁴ C	92.8/7.2	Tabersonine	0.10	92.3/7.7
			Catharanthine	0.30	91.8/8.2
			Vindoline	0.95	91.9/8.1
	<i>O</i> -Methyl- ³ H, 11- ¹⁴ C	—	Catharanthine	0.80 ^a	—
			Vindoline	4.80 ^a	—
			Catharanthine	0.14 ^b	95.6/4.4
Catharanthine	<i>O</i> -Methyl- ³ H	—	Vindoline	1.10 ^b	96.0/4.0
			Tabersonine	<0.001	—

^a 300 hr incubation.

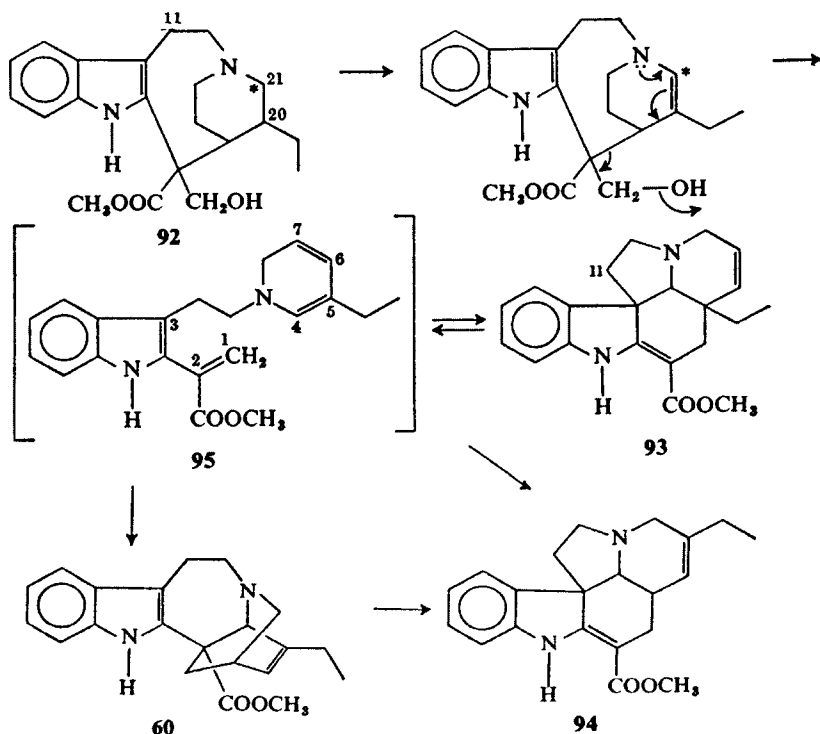
^b 168 hr incubation.

the lack of incorporation of labeled catharanthine into tabersonine is significant as the sequence stemmadenine to tabersonine to catharanthine is thereby suggested. It might also be noted that the high incorporation of tabersonine into vindoline after 300 hr points to the introduction of the 16-methoxy, *N*-(α)-methyl, and acetoxy groups at a late stage in the biosynthesis. The conversion of labeled tabersonine into catharanthine has also been observed by Kutney *et al.* in 6 month old *Vinca* plants.²⁵⁰

Qureshi and Scott were also able to provide chemical analogy for the suspected biological transformations. (—)-Tabersonine, for example, was found²⁵¹ to yield (±)-catharanthine on refluxing in acetic acid solution. (+)-Stemmadenine similarly yielded a mixture of (±)-tabersonine, (±)-catharanthine, and pseudocatharanthine (**94**), as well as unchanged starting material. These interconversions were rationalized as proceeding through the optically inactive acrylic ester **95**, and are summarized in Scheme 15.

The conversion of stemmadenine into **95** may be most easily rationalized by an isomerization of the exocyclic double-bond into the 20,21-position of

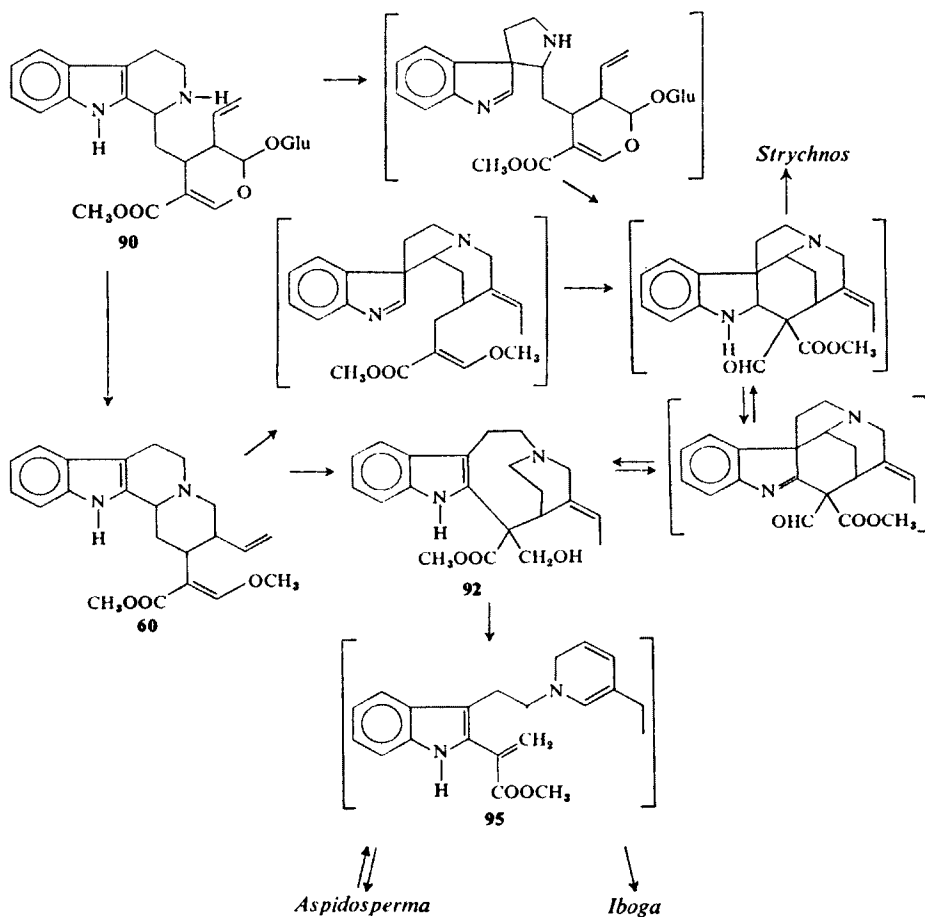
the skeleton followed by fragmentation. Evidence in support of this mechanism obtains from the feeding of *O*-methyl-³*H*-dihydrovincoside (**90** with vinyl saturated) to *V. rosea* shoots. No significant incorporation of dihydrovincoside occurred into any of the alkaloids that incorporate vincoside.²⁴⁷



Scheme 15

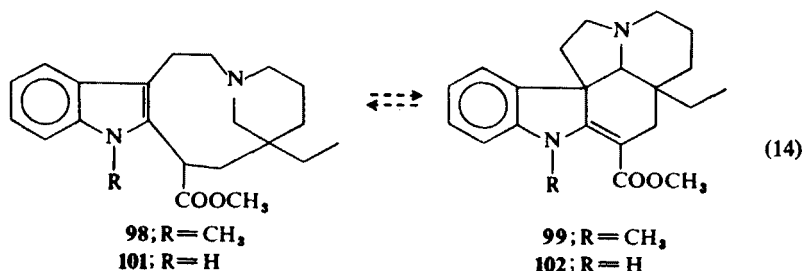
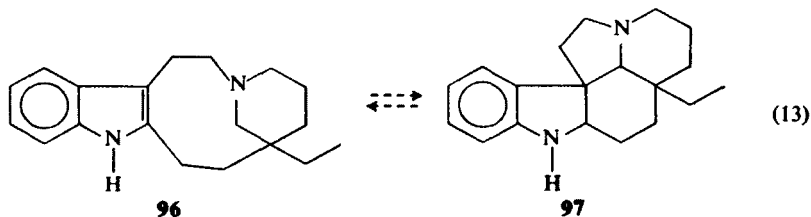
While the importance of stemmadenine as a precursor of the *Aspidosperma* and *Iboga* systems is clear from the data in Table II, the position of the *Corynanthe-Strychnos* alkaloids in the scheme is less certain. It has been suggested²⁵¹ that stemmadenine may serve as a specific precursor to the *Strychnos* family, though the alternative possibility that the *Strychnos* family is the precursor of stemmadenine deserves equal consideration. Experimentally, administration of ring *C*-³*H*-corynantheine aldehyde and *O*-methyl-³*H*-corynantheine aldehyde to young *V. rosea* plants gave insignificant incorporations into catharanthine.²⁵² Furthermore, ring *C*-³*H*-ajmalicine and *O*-methyl-³*H*-ajmalicine also gave very small incorporations into catharanthine and vindoline, though satisfactory incorporations into serpentine were observed concurrently. These results may be interpreted to mean either that

corynantheine aldehyde is a precursor of the *Iboga* and *Aspidosperma* systems, but is not reaching the site of biosynthesis, or that corynantheine aldehyde lies off the mainstream of biosynthesis leading to the rearranged alkaloids. The interpretation is rendered more complicated by experiments with *V. rosea* seedlings; in this instance, significant incorporations of *O*-methyl-³*H*-corynantheine aldehyde and ring *C*-³*H*-ajmalicine into catharanthine and vindoline were observed,²⁴⁹ a result that may imply either an easier penetration to the site of biosynthesis or the operation of alternative biosynthetic pathways in the seedlings. Current knowledge regarding the various biosynthetic interrelationships among the indole alkaloids is presented in Scheme 16 along with some plausible but as yet undetected intermediates.

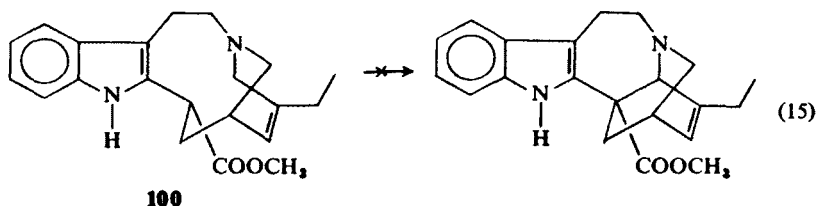


Scheme 16

Kutney and coworkers²⁵⁰ have recently begun an investigation of the biosynthesis of those *Aspidosperma* and *Iboga* type alkaloids which contain a nine-membered ring. The ease with which these substances undergo transannular cyclization *in vitro*²⁵³ indicates that similar processes might also occur *in vivo*. Radioactive quebrachamine (96) and vincaminoreine (98) were therefore prepared and tested as precursors of aspidospermidine (97) and

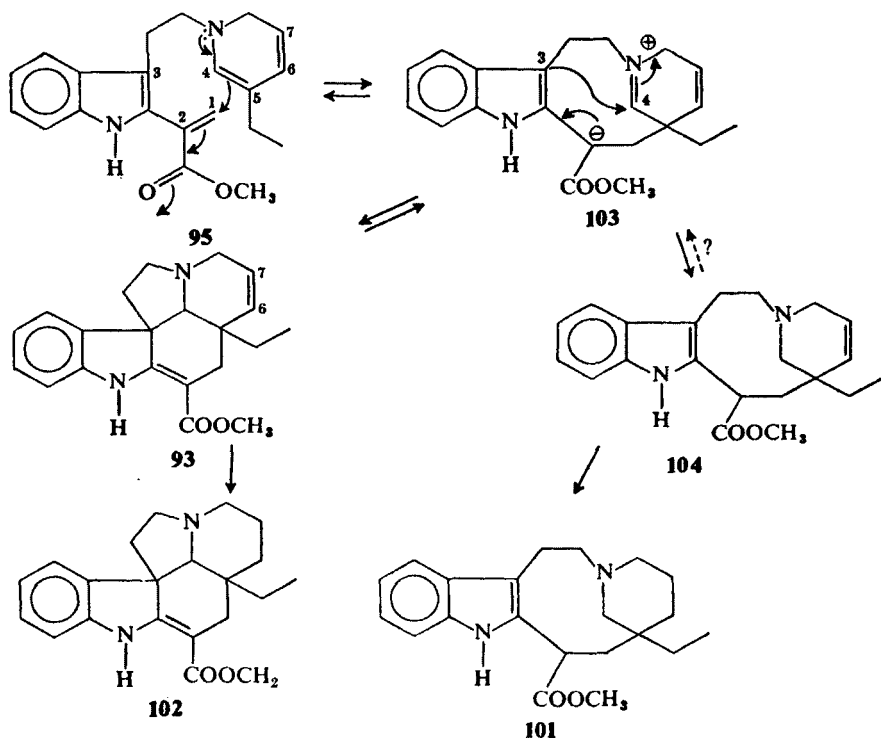


minovine (99), respectively, in *Vinca minor* (Eqs. 13 and 14). The incorporations were negligible. Similarly, radioactive carbomethoxycleavamine (100)



failed to show significant incorporation into catharanthine in *V. rosea* (Eq. 15). An examination²⁵⁴ of the relative rates of incorporation of 1'-¹⁴C-DL-tryptophan by *V. minor* into vincaminoreine (98) and vincadine (101) on the one hand, and minovine (99) and vincadiformine (102) on the other was also reported. Over a period of 14 days, the ratio of the combined activities of 98 and 101 relative to the combined activities of 99 and 102 was more or less constant. The absence of equilibration between the two alkaloid groups was proven by the essentially complete lack of incorporation of labeled minovine into vincaminoreine over a period of 1 week.

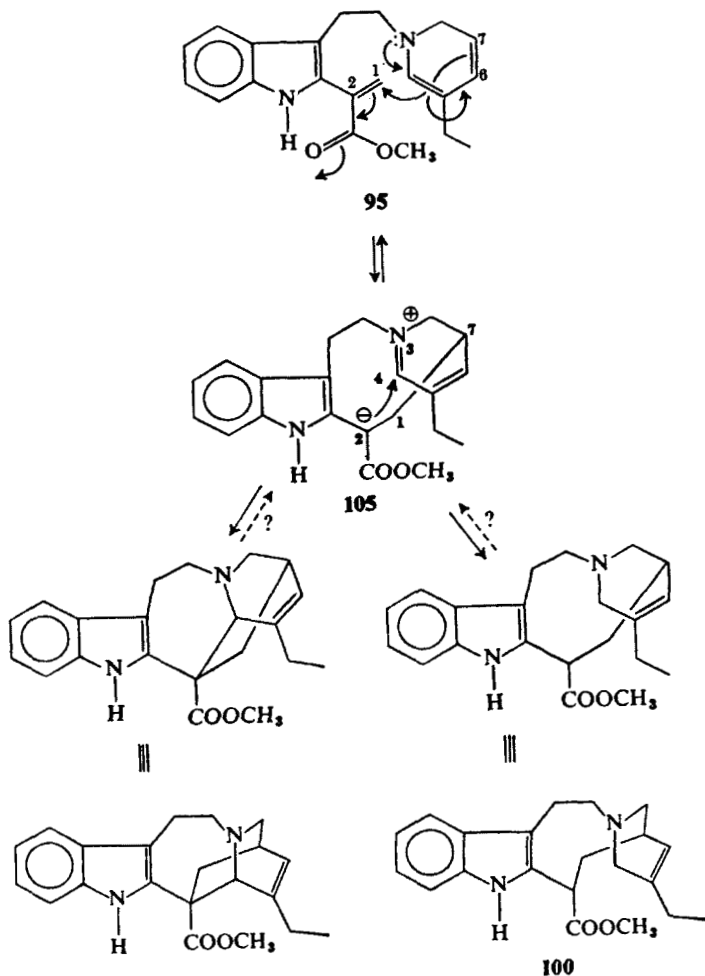
On the basis of these results, the authors arrived at two conclusions. First, it was suggested that the route to the quebrachamine-vincadine alkaloids is independent of that leading to the pentacyclic *Aspidosperma* bases with the acrylic ester **95** serving as the branch point. Second, it was proposed that in the generation of vincadifformine from **95**, the C-3, C-4 bond forms prior to or concurrently with the formation of the C-1, C-5 bond, and correspondingly, that catharanthine is produced from **95** with initial formation of the C-2, C-4 bond. These conclusions do not necessarily follow from the evidence. The pathway from **95** to vincadine (**101**) may be formulated as a Michael addition leading to bond formation between C-1 and C-5 and the generation of the dipolar species **103**; this may be reduced to vincadine in two stages with the neutral 6,7-dehydrovincadine **104** as the intermediate. Vincadifformine (**102**) may also arise from **103**; cyclization of the dipolar species with bond formation between C-3 and C-4 generates tabersonine (**93**), while reduction of the 6,7-double-bond of this substance gives vincadifformine (**102**) (Scheme 17). The observed lack of equilibration between



Scheme 17

the two groups of alkaloids then follows if the final reduction of the 6,7-double-bond is irreversible in each case.

The evidence favoring an *in vivo* conversion of tabersonine into catharanthine^{249, 250} suggests that the cyclization of **103** to tabersonine may be reversible; on the other hand, the reduction of **103** to the neutral species, **104**, may be irreversible. A similar pair of processes may be formulated for the conversion of **95** into the *Iboga* alkaloids. Cyclization of the acrylic ester with bond formation between C-1 and C-7 leads to the dipolar intermediate **105**; addition of C-2 to C-4 then gives catharanthine by a process which, on the basis of the observed lack of incorporation of catharanthine into



Scheme 18

tabersonine,²⁴⁹ may well be irreversible. Reduction of **105** gives carbomethoxycleavamine (**100**); if this latter process is irreversible, the lack of incorporation of **100** into catharanthine observed by Kutney and coworkers²⁵⁰ is explained (Scheme 18).

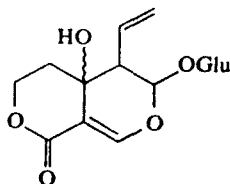
Additional insights into the mechanism of loganin biosynthesis and its conversion to the three families of indole alkaloids in *V. rosea* have been provided by the use of a number of doubly-labeled precursors.^{247, 252} These results, summarized in Table III, lead to the following conclusions. The

TABLE III. Administration of Doubly-Labeled Geraniol, Nerol, and Mevalonate to *V. Rosea*: % Retention of ³H Relative to ¹⁴C

Precursor	Loganin	Ajmalicine	Serpentine	Perivine	Catharanthine	Vindoline
1- ³ H ₂ ,2- ¹⁴ C-Geraniol	45	44	43	49	48	47
2- ³ H,2- ¹⁴ C-Geraniol	95	<5	<5	<5	<5	<5
2- ³ H,2- ¹⁴ C-Nerol	101	<5	<5	<5	<5	<5
Sodium 4- ³ H, 2- ¹⁴ C-(3 <i>R</i> ,4 <i>R</i>)-(±)-mevalonate	109	46	—	—	56	57
	98	47	49	50	42	47
Sodium 4- ³ H, 2- ¹⁴ C-(4 <i>S</i>)-(±)-mevalonate	10 ± 5	<5	<5	<5	<5	<5

feeding of 1-³H₂-geraniol resulted in about 50% retention of its activity on conversion to loganin; the oxidation of C-1 of geraniol to the aldehyde state therefore appears to be stereospecific. The resulting C-1 labeled loganin retains its activity throughout the transformations leading to the three alkaloid groups; therefore, if stemmadenine is in fact an intermediate leading to the *Aspidosperma* and *Iboga*-type alkaloids, then the loss of a proton from the starred carbon of stemmadenine (*vide supra*) in the formation of the hypothetical acrylic ester **95** must be stereospecific. With 2-³H-geraniol, no important loss of activity occurs during the formation of loganin, but almost complete loss takes place in the steps leading to the three alkaloid types. Thus, if saturation of the 2,3-double-bond of geraniol is a stage in its conversion to loganin, both the reduction and the subsequent loss of a proton from C-2 on formation of the five-membered ring must be stereospecific. The incorporation of 4-³H, 2-¹⁴C-(3*R*,4*R*)-(±)-mevalonic acid provides further information. The 4*R* form of this compound is known to be converted *in vivo* to all *trans*-isoprenoids with unchanged ³H/¹⁴C ratios.¹⁹⁹ In accord

with this expectation, complete retention of tritium is observed in the biosynthesis of loganin from this labeled mevalonate, while complete loss of tritium occurs with the 4*S* compound. About 50% retention of the tritium of loganin obtained from the 4*R* mevalonate occurs in the stages leading to each of the three alkaloid types. Since the tritium at C-2 of loganin has been shown to be lost during these steps, it follows that the tritium at C-7 of loganin must have been retained. Thus, the configuration at C-7 of loganin determines the stereochemistry of the corresponding center of ajmalicine, and presumably of the other *Corynanthe-Strychnos* alkaloids as well; contrariwise, the stereochemical correspondence between C-2 of loganin and C-20 of ajmalicine is only coincidental since the proton is lost from that position of loganin in the biosynthesis. Finally, the suggestion that swertiamarin (**106**)

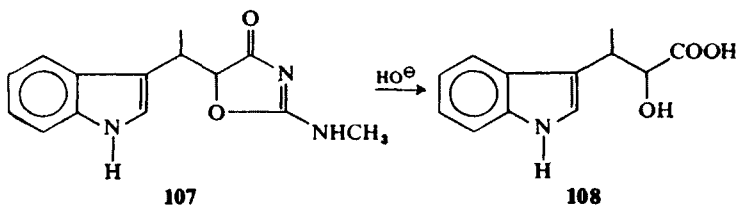
**106**

is a precursor for the indole alkaloids²⁵⁵ is incompatible with these findings.

IV. Addenda

A. Indolmycin

Floss and coworkers²⁵⁶ have investigated the biosynthesis of indolmycin (**107**), an antibiotic produced by a strain of *Streptomyces griseus*. 1'-¹⁴C-L-Tryptophan was specifically incorporated (1.5–7.5%, three feedings) into the antibiotic in the expected manner, while Me-¹⁴C-L-methionine served as a specific source of both the *N*-methyl and *C*-methyl groups present in the molecule (1.3–8.7% incorporation, three feedings). The biosynthesis thus apparently proceeds by *C*-methylation of the tryptophan side chain. Guanidino-¹⁴C-L-arginine was specifically incorporated (1.0–5.0%, three feedings)

**107****108**

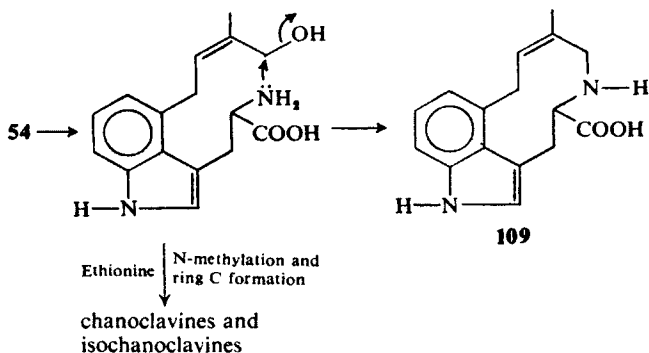
into the extra carbon atom of the oxazolinone ring, and the intermediacy of urea as a precursor excluded by the low incorporation observed for ^{14}C -urea.

Some insight into the sequence of steps in the biosynthesis was gained from hydrolysis of labeled indolmycin, obtained by feeding ^3H - and ^{14}C -tryptophan, to indolmycenic acid (**108**). The two labeled forms of **108** were efficiently incorporated (^3H 7.5%, ^{14}C 12.0%) into indolmycin, suggesting that C-methylation precedes the formation of the oxazolinone ring.

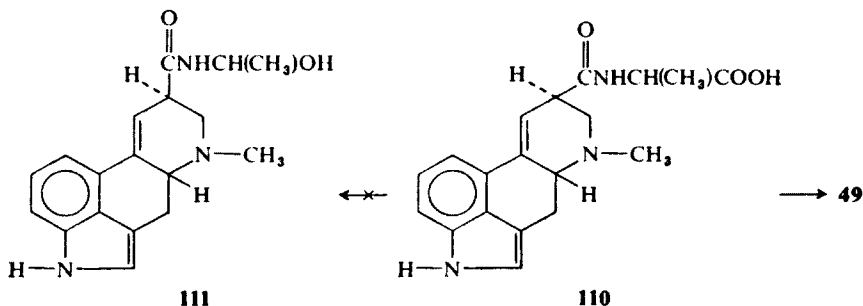
B. Ergot Alkaloids

Additional support for the intermediacy of 4-dimethylallyltryptophan (**54**) in ergot alkaloid biosynthesis has been forthcoming. Reasoning that hydroxylation of one of the dimethylallyl methyl groups must be a step immediately succeeding the formation of **54**, Robbers and Floss²⁶⁷ fed isopentenyl pyrophosphate and $1'\text{-}^{14}\text{C}$ -L-tryptophan to a *Claviceps* culture under anaerobic conditions. The formation of radioactive 4-dimethylallyltryptophan was demonstrated by isotopic dilution.

The same authors have also studied the effect of ethionine on the metabolism of the *Claviceps* fungus. In the presence of this methionine antagonist, a new alkaloid, clavicipitic acid, accumulates.²⁵⁸ This acid, which was assigned the constitution **109**, is also present in lesser amounts in untreated cultures and so represents a natural metabolite of the ergot fungus. The structure of clavicipitic acid provides some interesting clues to the stages in ergot alkaloid biosynthesis which lie between 4-dimethylallyltryptophan and the chanoclavines. In agreement with an earlier proposal¹⁹⁶ (Scheme 8 above), it suggests that hydroxylation of the terminus of the dimethylallyl side chain precedes the formation of Ring C since the genesis of **109** is most easily imagined as occurring through a hydroxylated intermediate.

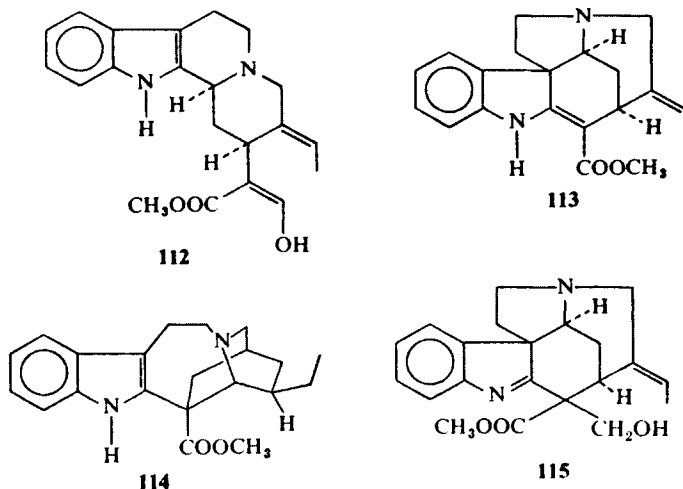


Some evidence has recently been deduced concerning the biosynthesis of the amide-type ergot alkaloids. D-Lysergyl-L-alanine (**110**), labeled with ^{14}C at the 2-position of alanine, has been prepared and fed to *Claviceps paspali*.²⁵⁹ Specific incorporation (1.77%) into ergometrine (**49**) was observed, while very little activity appeared in lysergic acid α -hydroxyethylamide (**111**).



C. Monoterpene-Derived Indole Alkaloids

Recent work has illuminated some of the later, ill-lit stages in the biosynthesis of these alkaloids. Battersby and Hall²⁶⁰ have demonstrated the ability of geissoschizine (**112**) to serve as a precursor for the *Corynanthe*, *Aspidosperma*, and *Iboga* classes of alkaloids in mature *Vinca rosea* plants. Satisfactory incorporations into ajmalicine (**71**), serpentine (**66**), vindoline (**61**), and catharanthine (**60**) were observed. In addition, **112** was shown to be incorporated into akuammicine (**113**), an alkaloid with the *Strychnos* skeleton. The likelihood that geissoschizine is a natural precursor was increased



by its detection in *V. rosea* on isotopic dilution following the administration of 5-³H-loganin, and by its isolation from a large-scale extraction of *Vinca* plants.

Similar observations have been reported by Scott's group, who studied²⁶¹ germinating *V. rosea* seedlings. Geissoschizine was detected in the alkaloidal fractions obtained from the seedlings after 28 to 40 hr of germination, and, on being subsequently administered in labeled form to the seedlings, **112** was incorporated into akuammicine (**113**) and coronaridine, **114**.

Another important link in the biosynthetic chain has been discovered in the study of germinating *Vinca* seedlings. Scott and Qureshi²⁶² have isolated an alkaloid, called preakuammicine, to which they assign the structure **115**, that of the elusive C₁₀-*Strychnos* prototype. This substance retains all ten of the original geraniol-derived carbon atoms, and may be presumed to lie at the branch point leading either to the C₉-*Strychnos* alkaloids by loss of a single carbon or to the *Aspidosperma* and *Iboga* bases by a series of rearrangements (see Scheme 16 above).

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CHAPTER IV

Alkyl, Alkenyl and Alkynyl Indoles

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I. Alkyl, Aryl, and Aralkyl Indoles

A. Preparation

The synthesis of the indole nucleus by classical methods has been discussed in Part I, Chapter 2. The preparations discussed herein will be those particularly applicable to the synthesis of alkyl-, aryl- and aralkyl indoles.

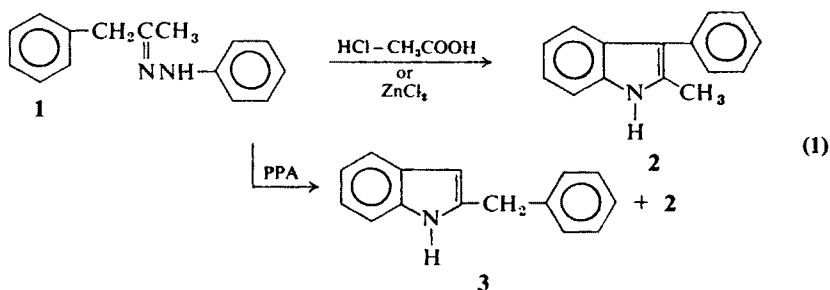
1. The Fischer Indole Synthesis

Since its discovery in 1883, the Fischer indole synthesis¹⁻⁶⁷ has remained the most versatile indole synthesis. Plancher and Bonavia³ have given the following rules governing the course of the reaction:

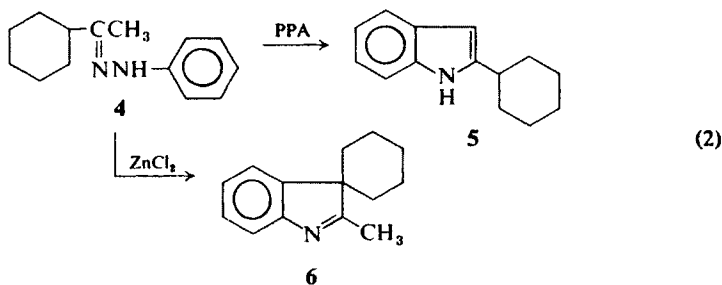
Ketone phenylhydrazones containing the group $\text{NHN}=\text{CCH}_3\text{CHR}_2$ yield only the corresponding indolenine. Those with the grouping $\text{NHN}=\text{C}(\text{CH}_2\text{R})\text{CH}_2\text{R}$ give both the indole and the indolenine. If the group $\text{NHN}=\text{C}(\text{CH}_3)\text{CH}_2\text{R}$ is present, two indoles are produced with condensation by means of the CH_2 group preponderant.

These rules were formulated from experiments conducted with zinc chloride as the catalyst. Subsequent work has shown that the direction of ring closure with unsymmetrical methyl ketone phenylhydrazones is dependent on the

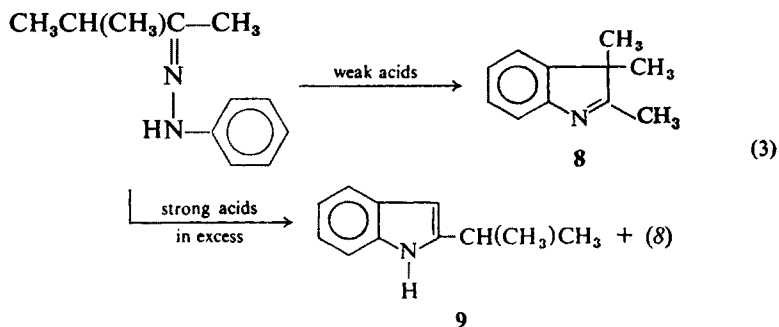
nature and amount of the acid catalyst.⁶⁴⁻⁶⁶ Treatment of phenylacetone phenylhydrazone (**1**) with hydrochloric acid-acetic acid or zinc chloride gave 2-methyl-3-phenylindole (**2**) while reaction with polyphosphoric acid (PPA) gave 2-benzylindole (**3**) as the major product.^{65, 66}



Similarly, the use of PPA with cyclohexylmethyl ketone phenylhydrazone (**4**) gave **5** and zinc chloride gave the indolenine **6**.⁵⁵



It has recently been shown that the use of weak acid catalysts ($-H_0$ less than 3.38) or equimolar amounts of strong acids with isopropylmethyl ketone phenylhydrazone (**7**) gave cyclization at the tertiary carbon atom while an excess of strong acid (H_2SO_4 , PPA) produced a preponderance of cyclization at the methyl carbon atom.⁶⁴

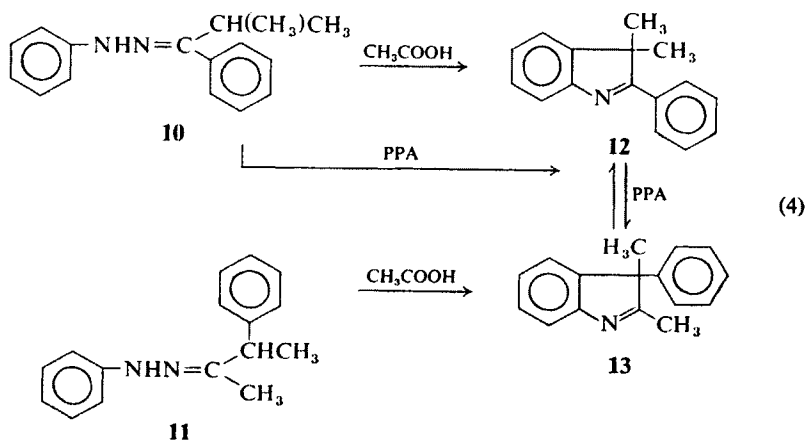


These effects have been rationalized on the basis of the size, strength, and amount of the acid catalyst as they effect the mechanism of the reaction.⁶⁴⁻⁶⁶

The direction of indolization of unsymmetrical alkyl ketone phenylhydrazones (not methyl) has not been extensively studied. The expected mixture of isomeric indoles has been isolated in some cases while apparently homogeneous products have been produced in others.⁶⁷⁻⁷¹

Indolization of *m*-alkyl phenylhydrazones generally leads to mixtures with the 6-substituted indole predominating over the 4-isomer.^{63, 72}

Although phenylacetaldehyde phenylhydrazone gives the expected 3-phenylindole on treatment with alcoholic hydrochloric acid, the use of zinc chloride gives 2-phenylindole. Furthermore, isobutyrophenone phenylhydrazone (**10**) or 3-phenyl-2-butanone phenylhydrazone (**11**) produced the expected products (**12** and **13**) with acetic acid but gave an equilibrium mixture of **12** and **13** with PPA.^{28, 35} Equilibration of **12** and **13** with PPA was demonstrated.³⁵



Several other similar rearrangements during Fischer cyclizations have been reported,^{28, 45-47} and have been rationalized on the basis of Wagner-Meerwein rearrangements.²⁸ Migrations must occur in order for indoles to be formed from 2,6-disubstituted phenylhydrazones, and this fact has been used as an aid in elucidating the mechanism of the Fischer reaction.^{33, 39, 44}

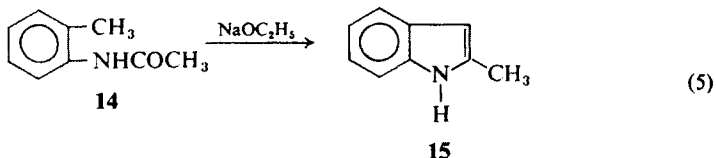
An anomalous reaction has been reported to occur when cuprous chloride is used as the catalyst.^{16, 58}

A reaction analogous to the Fischer synthesis has been reported in which hydrazobenzene reacts with acetone to give 1-phenyl-2-methylindole.⁷³

The synthesis of alkylindoles has often been accomplished by cyclization of phenylhydrazones to produce indole carboxylic acids, followed by decarboxylation.^{10, 18, 22, 26}

2. The Madelung Synthesis

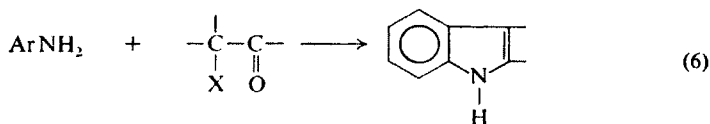
A very useful synthesis of alkyl indoles has been reported by Madelung. It involves the treatment of an *o*-alkyl acylanilide (**14**) with a strong base.^{74, 1}



Numerous variations on the theme have been employed,⁷⁵⁻⁸⁸ and the reaction in the case of alkyl indoles is often more successful than the Fischer synthesis.⁸⁴

3. The Bishler Synthesis

Another general method for the synthesis of alkyl indoles makes use of the reaction of arylamines with α -halogenated ketones, α -hydroxyketones, or their derivatives (Eq.6).⁸⁹⁻¹⁰⁴ The reaction is acid catalyzed and may be



X = O, Cl, Br, OH, pyridinium bromide, etc.

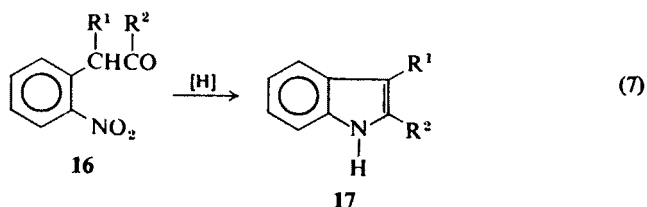
performed starting with the aminoketone, aminoacetal,¹⁰⁵ or ketals.¹⁰⁶

Reactions related to the Bishler synthesis have been reported which involve the acid-catalyzed reaction of aromatic amines with allylic halides¹⁰⁷⁻¹¹³ or with epoxides.¹¹⁴⁻¹²³ Rearrangements have sometimes been reported to occur during these types of reactions.¹¹⁴

4. The Reissert Synthesis

When an *o*-nitrobenzylketone, ketone derivative, or precursor is reduced, an indole **17** is produced.^{124, 125} This reaction has often been used in conjunction with decarboxylation,¹²⁴⁻¹²⁸ since *o*-nitrotoluenes react easily with ethyl oxalate to give *o*-nitrophenylpyruvic acids which yield the easily

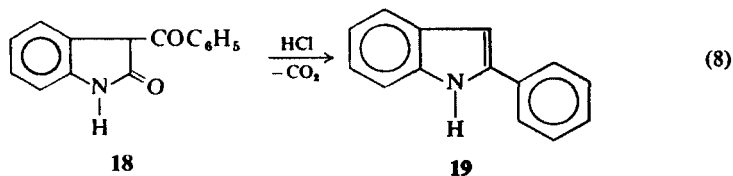
decarboxylated indole-2-carboxylic acids on reduction. *O*, β -Dinitrostyrenes have been employed in this type of synthesis.¹²⁹



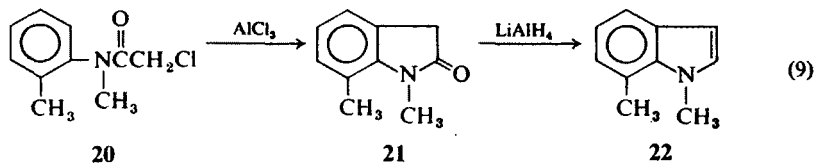
A related synthesis involves the reaction of β -alkyl-*o*-nitrostyrenes with triethyl phosphite to give 2-alkylindoles.^{130, 131}

5. From Oxindoles and Isatins

The rearrangement shown in Eq. (8) has been used for the manufacture of 2-phenylindole (19).¹³²



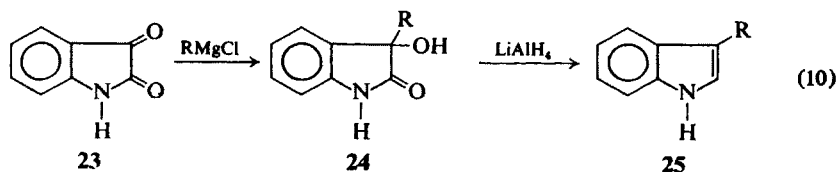
The reduction of oxindoles has been utilized as a synthesis of alkyl indoles. The sequence 20 $\rightarrow$ 21 $\rightarrow$ 22 is illustrative.¹³³ Lithium aluminum hy-



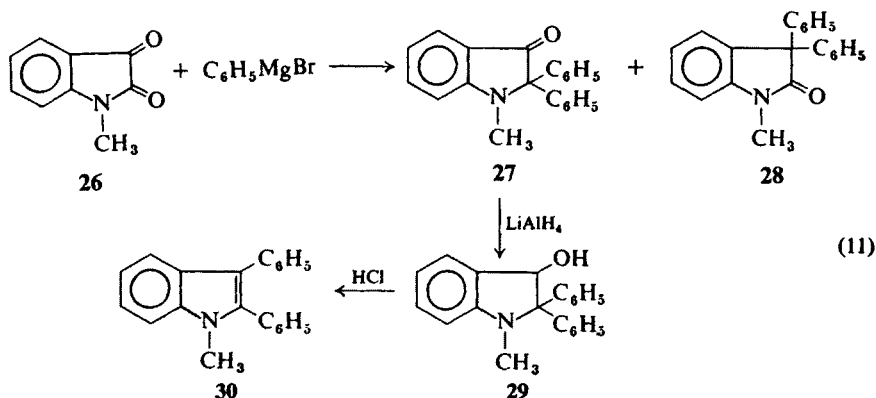
dride,^{133, 134} boron trihydride,¹³⁵ and sodium-propanol¹³⁶ have been used for this reduction. Indolines can also be produced in this reduction,^{137, 138} which can form indoles on dehydrogenation. Catalytic hydrogenation or acetate treatment of 3-acyloxindole oximes also leads to indoles,¹³⁹ and treatment of 3-benzoyloxindole with phosphorus pentasulfide followed by desulfurization with Raney nickel has produced 3-benzylindole.¹⁴⁰

Isatins have also been the starting points for indole syntheses. Reaction of Grignard reagents with isatin gave 3-substituted dioxindoles (24) which gave

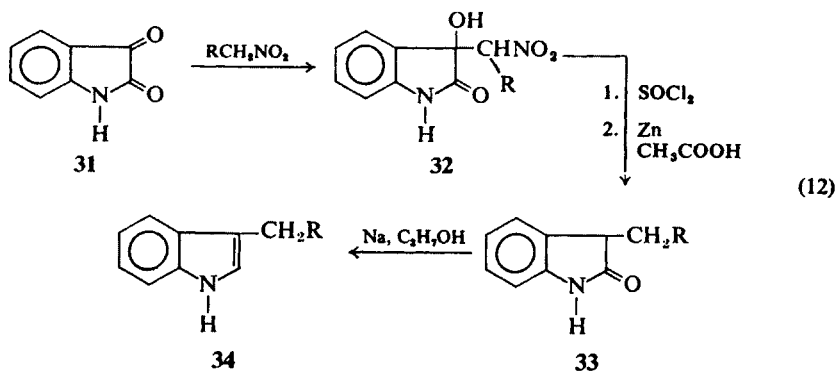
3-substituted indoles on reduction with lithium aluminum hydride.¹⁴¹ Sodium-propanol has also been used for this type of reduction.¹⁴²



With *N*-methylisatin, an excess of phenyl magnesium bromide gave *N*-methyl-2,2-diphenylindoxyl (27) and *N*-methyl-3,3-diphenyloxindole (28).



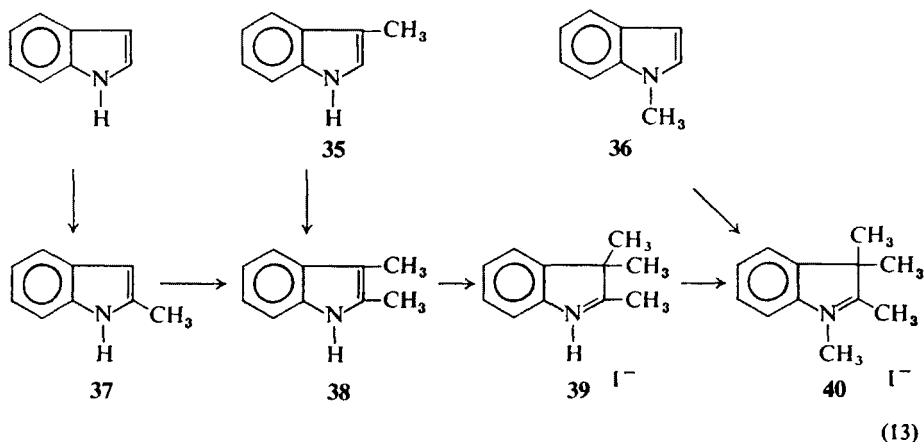
Reduction of 27 with lithium aluminum hydride gave 2,2-diphenyl-3-hydroxy-1-methylindoline (29) which produced 2,3-diphenylindole (30) on treatment with hydrochloric acid.¹⁴³ A similar synthesis (Eq. 12) utilizes nitroalkanes.¹⁴⁴



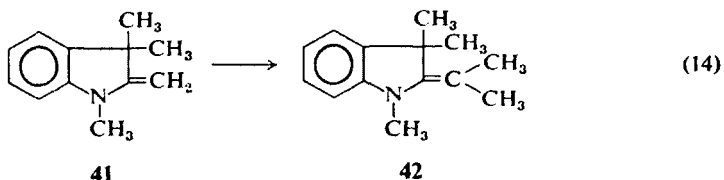
Reduction of *N*-methylisatin, *N*-methyldioxindole, *N*-formylindoxyl, or *N*-methyl- β -isatoxime with lithium aluminum hydride gave 1-methylindole and dimethylindigo.¹⁴⁵

6. By Alkylation

The somewhat complex reaction of methyl iodide with indoles has been elucidated largely through the efforts of Brunner¹⁴⁶ and of Plancher.¹⁴⁷ Starting with indole, 1-methylindole, 2-methylindole, or 3-methylindole, the changes shown in Eq. (13) are affected.



Treatment of **40** with alkalis gives **41** which may be further alkylated to give **42**. On heating, compound **40** loses methyl iodide reversibly to give 1,2,3-trimethylindole.



It has been established that alkylation of the indole system occurs in the pyrrole nucleus and generally at the 3- and 1-positions, although alkylation at the 2-position has been reported.¹⁴⁸⁻¹⁵²

The alkylation of indole sodium salt has been considered to involve preponderant attack at the 1-position.¹⁵³⁻¹⁵⁶ It has now been shown that reaction at the less electronegative 3-position increases the higher the S_N1 character of the alkylating agent and the greater the interaction of the cation with the ambident indole anion.¹⁴⁸ Alkylation at the 1-position still predominates however. Elimination of HBr from the alkyl halide and 1,3-dialkylation are competing reactions in the case of alkylating indole anions.¹⁴⁸

The most used method for forming indole anions is treatment with sodium or sodamide in liquid ammonia,^{145, 153-162} but sodium hydride in hexametaphosphor¹⁶³ or tetrahydrofuran,¹⁴⁸ sodium hydroxide in dimethylformamide,¹⁶⁴ and sodium amide in toluene¹⁶⁵ have been utilized. Alkylating agents may be halides,^{153, 156, 157, 159-161, 164} sulfates,^{161, 163, 166} or toluene sulfonates.¹⁶⁷ Arylation with bromobenzene requires a copper bromide catalyst.¹⁶⁸ Reaction of *N*-benzylindoles with sodium-liquid ammonia leads to debenzylation.¹⁶⁹ Treatment of indole with sodium carbonate and benzyl toluenesulfonate in toluene yields 3-benzylindole, probably by alkylation of indole rather than its anion.¹⁵⁶ Triphenylmethyl chloride with indoles gave 3-triphenylmethyl derivatives.¹⁷⁰

The alkylation of indolylmagnesium halides leads to 3-substituted derivatives^{155, 171-173} with few exceptions. This includes 3-alkylindolylmagnesium halides which give indolenines.

Lithiation of 1-methylindole with butyllithium followed by alkylation with methyl toluenesulfonate yields 1,2-dimethylindole.¹⁷⁴

Indole and various indole derivatives unsubstituted at the 3-position have been alkylated in the 3-position by means of heating with alkoxides or alcohols and base.^{176, 177} Contradictory results have been obtained with other alkylating agents.¹⁷⁸ 3-Acetylindole and 3-acetyl-2-methylindole exchange the acetyl groups for alkyl when heated with alcohols and alkoxides.¹⁷⁹

Indole and its simple derivatives are alkylated by acid-catalyzed reaction with alcohols.¹⁸⁰

Reactions of indoles with free radicals have not been extensively studied. It has been reported that treatment of indoles with *t*-butylperoxide in toluene gave 1-benzylindole and 3-benzylindole. Further reaction gave 1,3- and 2,3-dibenzylindole, α -(1-indolyl)bibenzyl, and other products.¹⁸¹

7-Ethylindoles have been produced by reactions of indole derivatives with ethylene catalyzed by aluminum anilide.^{182, 183}

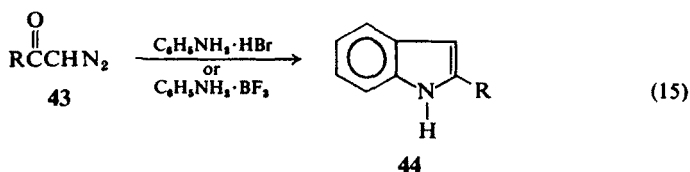
Gramine methiodides are alkylated on the methylene group by Grignard reagents with the loss of trimethylamine.¹⁸⁴ Similar alkylations of indole side chains do not appear to have been much studied.^{185, 186}

7. By Dehydrogenation

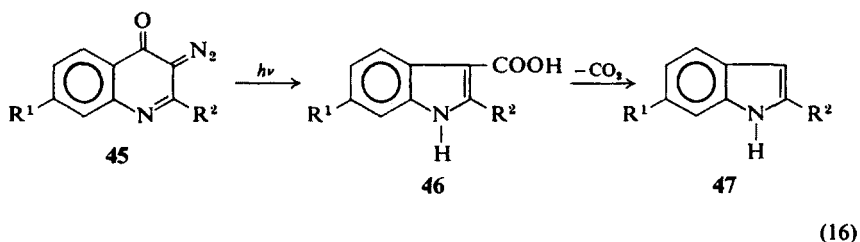
Dehydrogenation of indolines,^{187, 188} or of *o*-alkylanilines,¹⁸⁹⁻¹⁹¹ has given alkyl indoles. Catalysts used for this purpose have been Raney nickel,^{188, 190} platinum,¹⁸⁹ paladium,¹⁸⁷ selenium,^{191, 192} manganese dioxide,¹⁹³ and silver sulfate.¹⁹⁴

8. From Azo and Azido Compounds

Alkyl or aryl indoles have been produced by reaction of diazoketones with anilinium salts¹⁹⁵ (Eq. 15).



Another synthesis utilizes the light-induced decomposition of diazoquinolones **45**.¹⁹⁶



Pyrolysis of α - and β -methyl and α -phenyl styryl azides gave 3-methylindole, 2-methylindole, and 3-phenylindole.¹⁹⁷ 2-Alkylazidobenzenes produced indolines which were dehydrogenated to alkylindoles.¹⁹⁷ Reduction of β,β -diphenylethylene azobenzene with zinc and hydrochloric acid gave 2,3-diphenylindole.¹⁹⁸

Photolysis of 3-azoindolinenes in the presence of cycloalkenes and cycloalkanes has produced indoles.¹⁹⁹

9. By Reduction of Substituents

Since indole ketones and aldehydes are easily synthesized, their reduction constitutes a useful synthesis of alkyl indoles. Reducing agents for this purpose have been lithium aluminum hydride,²⁰⁰⁻²⁰⁴ hydrazine and sodium hydroxide,^{205, 206} lithium borohydride,²⁰⁷ sodium borohydride,²⁰⁸ and diborane.²⁰⁹ Alcohols and diindolylmethanes have also been produced with the borohydrides. Lithium aluminum hydride reduction of 1-acetylkatole gave skatole.²¹⁰

It has been suggested that when preparing 1-methyl indoles by reduction of 3-acylindoles, it is best to acylate, reduce, and then methylate since reduction of 1-methyl-3-acylindoles gives polymeric material.²¹¹ Hydrogenolysis of indole alcohols,^{204, 212} hydroxylamines,²¹³ amines,^{214, 215} and quaternary salts²¹⁶ has produced alkylindoles.

10. By Rearrangement of 3,3-Dialkylindolenines

Alkylation of 3-alkylindoles gives 3,3-dialkylindolenines which may be rearranged to 2,3-dialkylindoles.^{217, 218} In general, with methyl, higher alkyl indolenine, the higher alkyl group migrates to the 2-position.²¹⁷

Treatment of 3-*t*-butyl-2,3-dimethylindolenine with hydrochloric acid gave 2,3-dimethylindole.²¹⁹

11. Miscellaneous Syntheses

Alkyl-, aralkyl-, or arylindoles have been produced in the following reactions but the methods are not, in general, of preparative value: Treatment of an amidine with potassium hydroxide²²⁰ or arylamines²¹¹; heating sultams with copper^{222–224}; copper acetylides with *o*-iodoanilines^{225–228}; reduction of cinnolines^{229–232}; desulfurization of indole sulfides^{233, 234}; reduction of isatogens²³⁵; pyrolysis of β -hydroxyethylanilines^{236–238}; decarboxylation of 3-indole acetic acid²³⁹; an aniline with epichlorohydrin to give a tetrahydro-3-quinolinol followed by treatment with alkaline sodium periodate²⁴⁰; rearrangement of quinoline²⁴¹; reaction of *N*-methylaniline or *N*-methyl anthranilic acid with glycolic aldehyde²⁴²; treatment of the adduct of dimethyl diazodicarboxylate and diphenylethylene with hydrazine followed by reduction²⁴³; pyrolysis of 1a*H*-oxazirino[2,3-*a*]quinolines.²⁴⁴

12. From Natural Sources

Alkylindoles have been isolated from a variety of natural sources both as such and via degradative procedures. Skatole (3-methylindole) especially is widely distributed in nature and has been isolated from lilies,²⁴⁵ compost,²⁴⁶ tobacco smoke,²⁴⁷ tea,²⁴⁸ fetid cultures,²⁴⁹ rumen fluid,²⁵⁰ sapropel deposits,²⁵¹ *lens culinaris*,²⁵² small intestines,²⁵³ *Tachigalia myrmecophila*,²⁵⁴ beef,²⁵⁵ urine,²⁵⁶ tissue,²⁵⁷ cabbage sprouts,²⁵⁸ milk,²⁵⁹ and pork.²⁶⁰ A variety of indoles have been isolated from tobacco smoke,^{247, 261–265} mushrooms,²⁶⁶ urine,^{267, 273} melanine derivatives,²⁷⁴ various plants,²⁷⁵ *Escherichia coli*,²⁷⁶ and

butter.²⁷⁷ Examples of alkaloids which yield indoles on degradation are echinulin,²⁷⁸⁻²⁸¹ quebrachanine,^{282, 283} aspidospermine,²⁸⁴ spermostrychnine,²⁸⁵ lysergic acid,²⁸⁶ and pereinine.²⁸⁷

B. Properties

A number of the physical and spectral properties of alkylindoles have been studied. Table I lists references to some of this work along with some of the specific compounds and topics studied. Table II lists references to chromatographic studies of indoles.

C. Reactions

1. Protonation

The protonation of the indole nucleus has been of interest both from the synthetic and theoretical points of view. One reason for this interest is that many reactions of indoles are acid catalyzed. Two problems are of interest in connection with the protonation of indoles—first, the position of protonation; second, the basicity of indoles and the effect of substituents on the basicity.^{306, 356, 357}

Every position of the pyrrole ring of indoles has been suggested as the sight of protonation. Ultraviolet and nuclear magnetic resonance spectral studies have indicated that the principal conjugate acid of an indole in strong aqueous acids is the 3-protonated indolenine form.⁴⁸ Deuterium exchange experiments show that exchange occurs generally at the 1- and 3-positions but in some cases exchange at the 2-position can occur. Solid salts of indoles appear to consist of 1- or 3-protonated indoles or mixtures of both depending on the indole, the acid and the method of isolation. Solubility is probably a factor of importance in these cases. In the conjugate acid of an indole, deuterium exchange at the 2-position takes place by protonation at a rate similar to that at the 3-position, whereas exchange at the 1-position takes place by proton loss competitive with the 3-position.

The pK_a 's of the alkylindoles studied vary from +0.30 to -4.55. Alkyl substituents in the 3-position generally decrease the basicity while substitution at the 1-position increases basicity and substitution at the 2-position leads to an even greater increase. 1,3-Disubstitution appears to lead to increased basicity. The pK_a 's of some alkylindoles are listed in Table III.³⁵⁷

Hyperconjugative effects appear to be of great importance in determining the basicity of indoles. An alkyl group on the 1- or 2-position would be effective in stabilizing the positive charge of the 3-protonated conjugate acid.

TABLE I. Physical Properties and Spectra of Indoles

	Ref.	Compounds	Special topics
ir	288-301	<i>c, d, e</i>	400-700 cm ⁻¹ <i>g</i> Indolines NH stretching
uv	230, 296, 297 302-312, 356	<i>a, c, d, e, f</i> 1,3-Diphenyl- 2-methyl 3-Phenyl	Protonation
nmr	298, 313-322	<i>b, c, d, f</i> 7-Methyl 3-Ethyl	Complexes Long range coupling <i>g</i> NH
Mass	323, 324		
esr	325		Charge trans- fer complexes Oxidations
epr	326	<i>c, d</i>	
Polarography	327	<i>a, c</i>	
Emission	328, 329	<i>b</i>	<i>g</i>
Chemiluminescence	329-334	<i>a, d, f</i> 1,2-Dimethyl 5,6-Dimethyl	<i>g</i>
Fluorescence	335-337	<i>b, c, e</i>	<i>g</i>
Phosphorescence	338	<i>a</i>	77°K
Radioluminescence	339	<i>e</i>	
Dipole moment	340	<i>f</i>	
Theory	297, 341		Quantum mechanics

^a Fischer base: 2-methylene-1,3,3-trimethylindole.^b 1-Methylindole.^c 2-Methylindole.^d 3-Methylindole.^e 2-Phenylindole.^f 2,3-Dimethylindole.^g Solvent effects.

TABLE II. Chromatographic Behavior of Indoles

Type of chromatography	Ref.
Paper	342-351
Thin layer	352-354
Gas-liquid	355

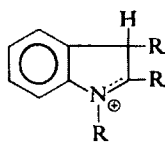
TABLE III. pK_a 's of Alkyl Indoles

Indole	pK
1,2-Dimethyl	+0.30
2,5-Dimethyl	+0.26
2-Methyl	-0.28
2-Ethyl	-0.41
1,2,3-Trimethyl	-0.66
2,3-Dimethyl	-1.49
1-Ethyl	-2.30
1-Methyl	-2.32
1,3-Diethyl	-2.2
1,3-Dimethyl	-3.3
5-Methyl	-3.3
Indole	-3.5
3-Ethyl	-4.25
3-Methyl	-4.55

On the other hand, substitution on the 3-position reduces by one the number of hydrogens available for hyperconjugative stabilization of the positive charge at the 2-position of the conjugate acid and also stabilizes the parent base relative to the conjugate acid.

Indoles do not correlate with any of the established acidity functions and appear to fall into three groups: those unsubstituted in the hetero ring, those 1,3-disubstituted, and any other variation of alkyl substitution in the hetero ring. An acidity function, H_1 , has been developed for use with indoles.³⁵⁷

Protonation of 2,3-diphenylindole appears to lead to mixtures of 3-protonated indolenine and 1-protonated indolium forms.³⁵⁸ Retention of the stilbene-type conjugation in the latter form may explain its increased stability.

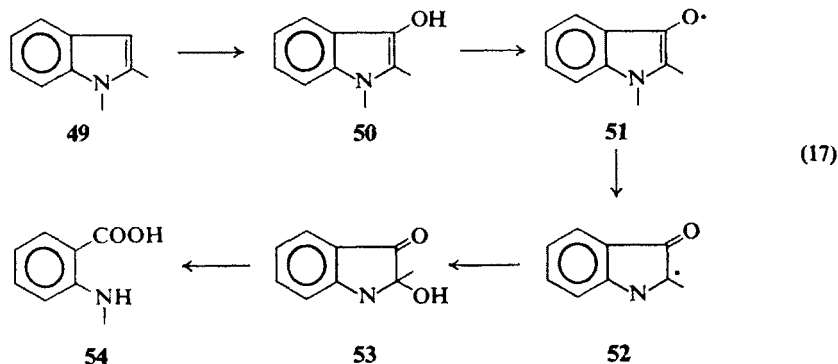


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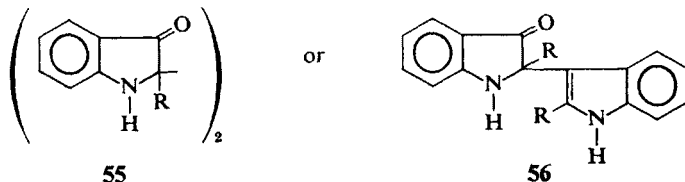
2. Oxidation

The oxidation of alkylindoles can lead to a variety of products depending on the nature of the oxidizing agent and the structure of the indole. In general, with 1 or 2 alkyl substitution the reaction proceeds schematically

as in Eq. (17). The radical intermediate may **152**, add to another molecule of alkylindole to give oxydimers (**55** or **56**).³⁵⁹⁻³⁶⁴ These dimers have been isolated in the case of oxidation with hydrogen peroxide,³⁶²⁻³⁶⁵ oxygen,³⁶³ air,^{359,360}



peracetic acid,³⁶¹ and potassium nitrosodisulfonate.^{365, 366} With 3-alkylindoles, oxidation gives the anthranilic acid or *o*-ketoaniline derivative. This reaction may proceed via the 2,3-glycol and occurs with hydrogen peroxide-peracids³⁶⁷ or chromium trioxide.³⁶⁸ Further oxidation of 1-, 2-, or 3-alkylindoles with hydrogen peroxide-peracids^{365, 369-375} or potassium



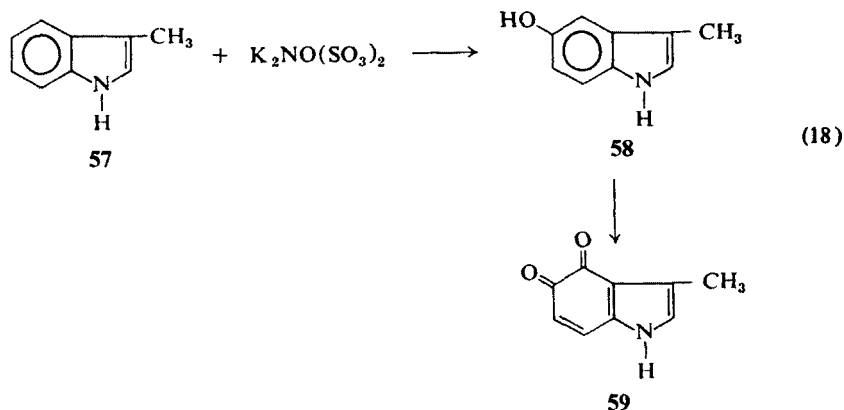
permanganate³⁷⁶ gives *N*-acylanthranilic acids. With potassium permanganate or perbenzoic acid, oxidation of side chains can occur.^{376, 377} Dioxindoles have been isolated³⁷⁸ from oxidation of indoles.

The ozonization of indoles leads to isolable ozonides^{376, 379-383} involving the 2,3-double bond which give anthranilic acids or *o*-ketoanilines on decomposition.

Autoxidation of alkylindoles gives 3-hydroperoxides,^{383, 384} or indoleninyl-hydroperoxides in the case of 3-alkylindoles^{385, 386} Decomposition of the hydroperoxides may give dioxindoles,³⁸⁶ *o*-ketoanilines,^{385, 386} or side-chain oxidation³⁸⁶ to acylindoles.^{378, 384} Side-chain oxidation to acylindoles may also be effected with lead tetraacetate.³⁷⁸

Oxidation of skatole with *N*-bromosuccinimide^{378, 388} or potassium hydrosulfite³⁸⁹ gives 3-methyloxindole. With potassium nitrosodisulfonate skatole,^{390, 391} 2-phenylindole and 2,3-dimethylindole³⁹¹ give oxidation at the 5-position followed by quinone (**59**) formation. Skatole with potassium

persulfate gives 4-, 5-, 6-, and 7-skatolyl sulfates.³⁹² Simulated enzymic oxidation of skatole with ferric salts and ascorbic acid gives 3-methyloxindole, *o*-aminoacetophenone, *N*-formyl-*o*-aminoacetophenone, and 4-, 5-, 6-, and



7-hydroxyskatoles.^{393, 394} Oxidation of indoles with ferric chloride gave complex dyes.³⁹⁵ The light-catalyzed action of oxygen and ammonia on 2-phenylindole gives 2-phenyl-4(1H)-quinazolinone.³⁹⁶

3. Reduction

The reduction of indoles with zinc or tin and hydrochloric acid,³⁹⁷ electrolytic reduction,³⁹⁸ or catalytic hydrogenation³⁹⁹⁻⁴⁰¹ gives indolines. Further hydrogenation gives octahydroindole derivatives,^{399, 401} and destructive hydrogenation can yield aromatic amines.^{402, 403}

Reduction of 1-methylindole with sodium and ethanol in liquid ammonia gives 1-methylindoline and 4,7-dihydro-1-methylindole. Similar reduction of 1-methylindoline gave a conjugated diene.⁴⁰⁴

4. Color Reactions

Numerous color reactions have been developed which are useful in characterizing indoles.⁴⁰⁵⁻⁴¹⁹ Of particular interest is the Ehrlich reaction which is useful in determining the orientation of substitution on the pyrrole ring.⁴²⁰⁻⁴²⁴

5. Rearrangements

Several rearrangements of alkylindoles have been discussed in connection with the Fischer indole synthesis. In addition to these, 3-benzyl and 3-methylindole have been reported to rearrange to the corresponding 2-isomers under

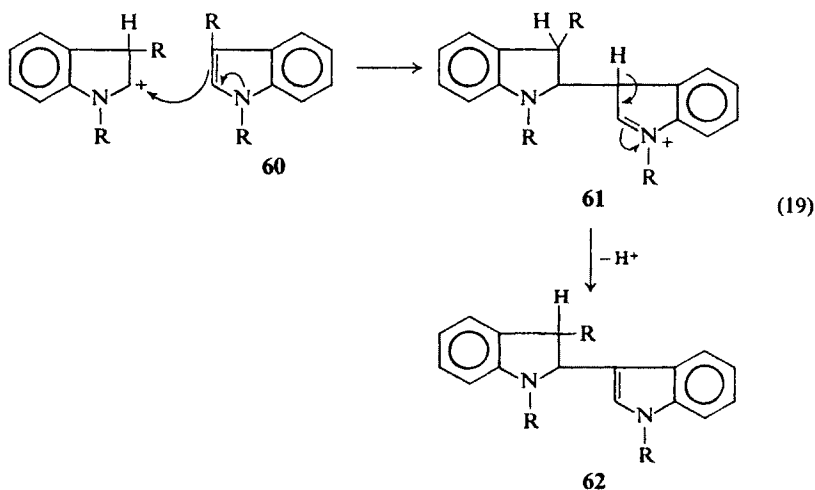
the influence of sodium chloride–aluminum chloride,⁴²⁵ and treatment of 2- or 3-*t*-butylindoles with hydrogen bromide gives dealkylation with the formation of *t*-butylbromides.^{426, 427} Other rearrangements have been reported.^{29, 428–431}

6. Complex Formation

Indoles form molecular complexes with a variety of agents.⁴³²

7. Indole Polymers

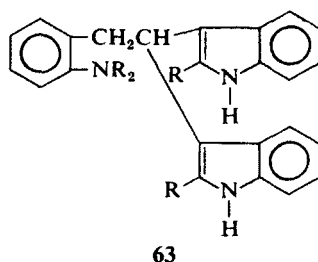
Indoles unsubstituted in the 3-position yield dimeric and trimeric derivatives on treatment with strong acids.^{433–439} The mechanism of dimerization appears to involve the attack of a free indole base on a protonated form (Eq. 19). Since only the protonated component is required to have an open 2-position,



the possibility of mixed dimers exists in which the unprotonated component is substituted in the 2-position. In fact, since 2-methylindole is more nucleophilic than indole, hydrogen chloride treatment of an equimolar ether solution of indole and 2-methylindole gave indole:2-methylindole dimer hydrochloride in quantitative yield.⁴³⁴ A variety of other mixed indole dimers has been prepared.⁴³⁴

Indole dimers may be dehydrogenated to the fully unsaturated derivatives.^{324, 436, 440}

Indole trimers have been shown to have a ring-opened structure (63).⁴³⁴

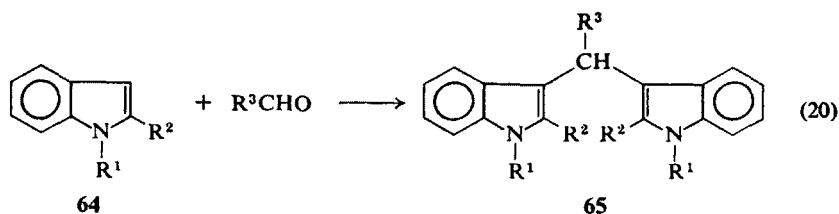


8. Sulfonation

Sulfonation of skatole with pyridine-sulfur trioxide complex gives 3-methylindole-2-sulfonic acid while 2-methylindole is not sulfonated.⁴⁴¹

9. Reaction with Aldehydes and Ketones

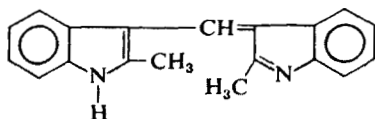
Indoles yield diindolylmethanes (65) on reaction with aldehydes.⁴⁴²⁻⁴⁴⁴



The diindolylmethane derivatives from formaldehyde ($R^3 = H$) have been extensively studied, have been prepared by a number of alternate methods, and are formed as side products in several reactions.⁴⁴⁵⁻⁴⁵² Oxidation of the diindolylmethanes yields dyes known as rosindoles. Glyoxal gives products formulated as tetraindolythylenes when condensed with indoles.⁴⁵³

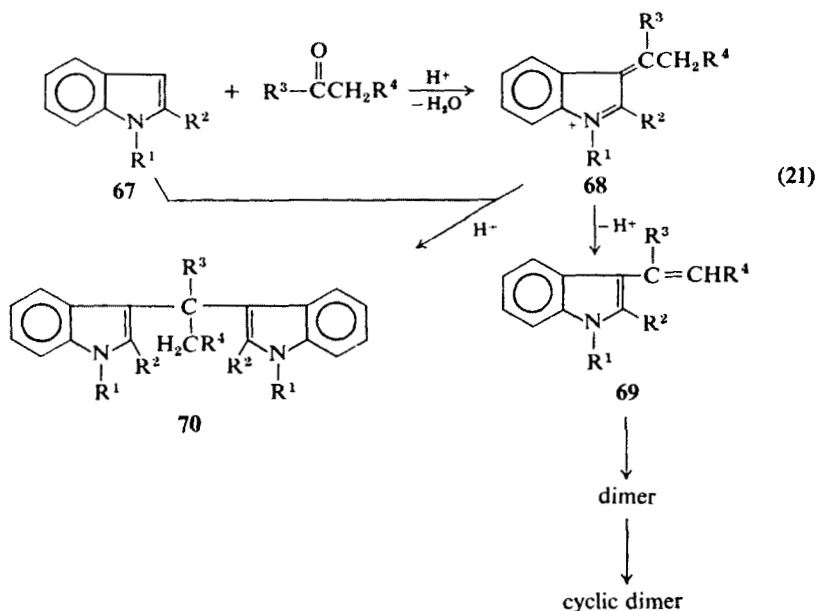
2-Methylindole-3-aldehyde on treatment with sulfuric acid yields an orange-yellow dye,⁴⁵⁴ which is also obtained by reaction of 2-methylindole and formic acid in the presence of sulfuric acid. The same compound can be prepared by reaction of 2-methylindole with 2-methylindole-3-aldehyde. The product is regarded as having Structure 66 and can be prepared through the action of 2-methylindolemagnesium bromide on iodoform or carbon tetrachloride.⁴⁵⁵ 2-Methylindole condenses with formic acid in the presence of hydrochloric acid to give tri-(2-methyl-3-indyl) methane.¹

Ketones and indoles can form a variety of products depending on the nature and concentration of the indole and the ketone and the acidity of the



66

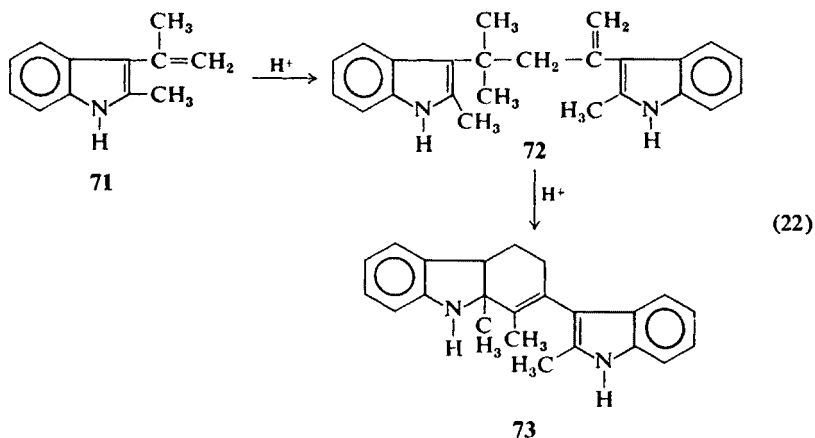
reaction medium.⁴⁵⁶⁻⁴⁶¹ The reaction of indoles with unsubstituted 3-positions appears to take the course represented by Eq. (21).



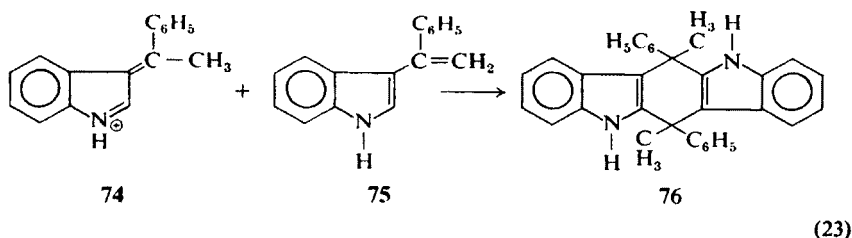
The following generalizations have been made in regard to condensation of indoles with methyl ketones⁴⁶⁰: In refluxing acetic acid, 3,3'-alkylindene-bisindoles from acetone or acetophenone and indoles form with decreasing ease 1-methylindole > 5-methylindole > indole > 1-methylindole > 1,2-dimethylindole.

Bisindole formation requires low enough acidity so that a significant concentration of free indole is present. The rate of acid-catalyzed formation of 1:1 condensation products must not substantially exceed the rate of bisindole formation from them, otherwise the products will be derived from

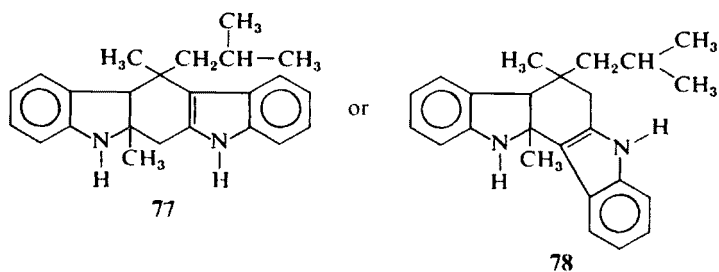
dimerization of the 1:1 condensation products. For example, the reaction of acetone and 2-methylindole in refluxing acetic acid gave 2,2'-dimethyl-3,3'-isopropylidenebisindole.⁴⁵⁷ Indole behaves similarly.⁴⁶¹ In hydrochloric acid-ethanol, **73**⁴⁵⁷ was the product.



Indoles with open 2-positions can yield indolo[2,3-b]carbazoles. For example indole with acetophenone gave **76**. All authentic reports of the



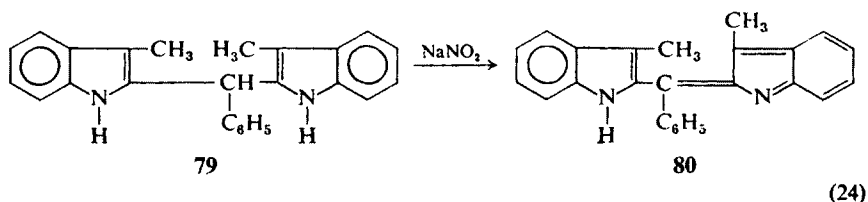
formation of bisindoles from ketones have involved methyl ketones and even with them the scope of bisindole formation is limited.⁴⁶⁰



The product from 2-methylindole and methyl isobutyl ketone is a 2:1 condensation product and appears to have Structures **77** or, less likely, **78**.⁴⁶²

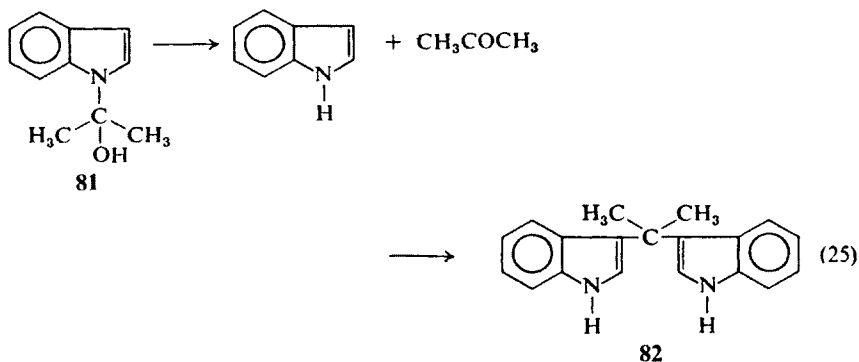
Reactions of indoles with 1,4-diketones and with cyclic ketones have been reported.⁴⁶³

2,2'-Bisindole formation can also occur with 3-substituted indoles if the 2-position is unsubstituted. Skatole with benzaldehyde and sulfuric acid gave



3,3'-dimethyl-2,2'-benzilidenebisindole.^{464, 465} The latter can be oxidized with sodium nitrite to form **80**.⁴⁶⁴ The formation of 2,2'-bisindoles has been reported to proceed via reaction at the 3-position followed by migration.⁴⁶⁶ Skatole with ethyl orthoformate gave 2,2',2''-triskatylmethane.⁴⁶⁷ Treatment of the latter with hydrochloric acid, neutralization, and acidification with perchloric acid gives the purple dye 2,2'-diskatylmethene perchlorate.⁴⁶⁷ A similar compound is produced from skatole-2-aldehyde and skatole in the presence of sulfuric acid.⁴⁶⁸ 3,3',3''-Triindolylmethanes are prepared by reaction of 3-indole aldehydes with indoles.⁴⁶⁹

Indole Grignard reagents yield bisindoles, **82**, with aldehydes.⁴⁷⁰⁻⁴⁷³



Indole magnesium iodide on treatment with acetone is reported to initially yield an *N*-hydroxypropyl derivative which decomposes to indole and acetone which ultimately yield the 3,3'-bisindole **82**.⁴⁷⁴

D. Uses and Biological Activity

2-Phenylindole has found use as a rat repellent,⁴⁷⁵ as a polyvinyl chloride resin stabilizer,⁴⁷⁶⁻⁴⁸¹ and as a styrene polymerization catalyst.⁴⁸² 2-Methylindole is reported to be a polymerization regulator⁴⁸³ and is useful in photosensitive compositions.⁴⁸⁴ Other indoles,⁴⁸⁵ such as dimethylindole,⁴⁸⁶ 2-methyl-3H-indole,⁴⁸⁷ 3-methylindole,⁴⁸⁸ 3-methyl-5-phenylindole,⁴⁸⁸ 1-methyl-2-phenylindole,⁴⁸⁸ and *N*-vinylindole,^{489, 490} have found use in photography. Skatole has been reported to promote the dimerization of butadiene,⁴⁹¹ 2,3-diphenylindole is used as an optical bleaching agent for nylon,⁴⁹² and 1,2,3-triphenylindole is a plastic scintillator.⁴⁹³

Numerous indole derivatives have been used as intermediates in the preparation of dyes.⁴⁹⁴⁻⁵⁰³

Skatole has been found to have biological action as an antidiuretic, stimulant, hypertensive,⁵⁰⁴ muscle relaxant,⁵⁰⁵ respiration inhibitor,⁵⁰⁶ heart stimulant,⁵⁰⁷ and tuberculostat.⁵⁰⁸ Furthermore, skatole inhibits lysozyme,⁵⁰⁹ binds to serum albumin,⁵¹⁰⁻⁵¹² is absorbed in the colon,⁵¹³ catalyses the decomposition of cystine,⁵¹⁴ gives pleomorphism in *Escherichia coli* and *Proteus vulgaris*,⁵¹⁵ inhibits respiration in cancer cells,⁵¹⁶ and is a plant growth regulator.⁵¹⁷⁻⁵²⁵

2-Methylindole, 2,3-dimethylindole, 2,3-diphenylindole, and 2,3-ditolylindole are active as growth stimulants for farm animals,⁵²⁶ 2-phenylindole is active in liver response tests⁵²⁷ and 7-methylindole inhibits tryptophan hydrolase.⁵²⁸ Furthermore, indoles have been reported to suppress the orientation reflex⁵²⁹; to have antitumor activity⁵³⁰; to exhibit neutospore crassa tryptophan synthetase⁵³¹; to effect muscular contractility⁵³²; to be serotonin antagonists^{533, 534}; and to inhibit insulinase,^{535, 536} α -chymotrypsin,⁵³⁷ and azo dye destruction by rat liver homogenates,⁵³⁸ and to be growth promoting agents in sweet corn.⁵³⁹

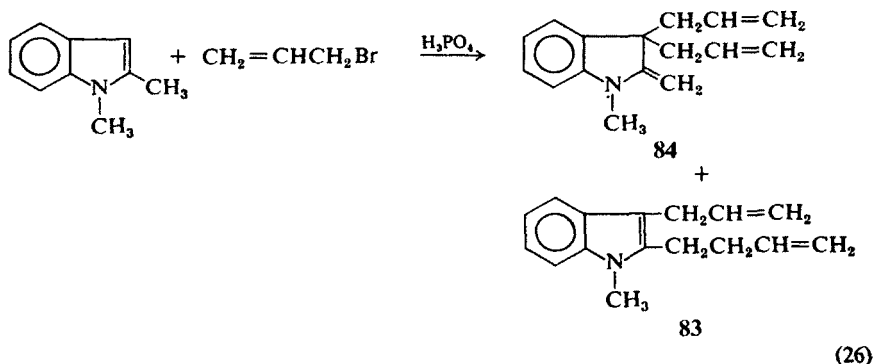
II. Alkenyl and Alkynyl Indoles

A. Preparation

1. Alkylation

Treatment of indole Grignard reagents with allyl or propargyl^{540, 541} halides gives the corresponding 3-allyl or propargylindoles. The reaction of allyl bromide with 1,2-dimethylindole in the presence of phosphoric acid gave

1-methyl-2-(3-butenyl)-3-allylindole (**83**) and 1-methyl-3,3-diallyl-2-methyleindoline (**84**).⁵⁴²



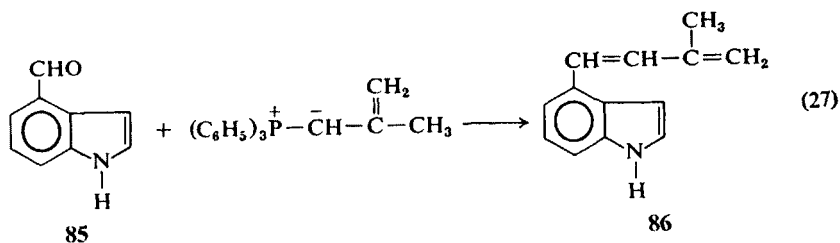
Acetylene reacts with indoles in the presence of potassium hydroxide to give *N*-vinylindole.⁵⁴³⁻⁵⁴⁶

2. By Eliminations

Hoffman-type eliminations from indole amine oxides^{547, 548} or quaternary salts^{549, 550} has given 2- or 3-alkenylindoles. The simplest member of the series, 3-vinylindole, has been prepared in this manner.⁵⁴⁷ The dehydration of indole alcohols has given vinyl indoles.^{480, 551}

3. The Wittig Reaction

4-Indolylisoprene (**86**) has been prepared by the use of the Wittig reaction (Eq. 27).⁵⁵² This synthesis should have general applicability.



4. Indoles with Ketones

Under certain conditions, indoles yield 3-vinylindoles on reaction with aldehydes, ketones, or ketone derivatives.^{456, 460, 463, 553, 554}

B. Reactions

1. *Reduction*

Catalytic hydrogenation of alkenylindoles gives alkylindoles. Palladium^{545, 553, 554} and nickel^{544, 547, 554} have been used.

2. *Oxidation*

Oxidation of 3-allylindole with osmium tetroxide gave the corresponding glycol which gave 3-indolealdehyde on treatment with sodium periodate.⁵⁵⁶

3. *Miscellaneous Reactions*

Treatment of *N*-vinylindole with sulfuric acid gave acetaldehyde and indole.⁵⁵⁷ The polymerization of *N*-vinylindole has been studied.^{544, 545, 558}

III. Alkyl, Aralkyl, and Aryl Indolines

A. Preparations (see also reduction of indoles and oxindoles)

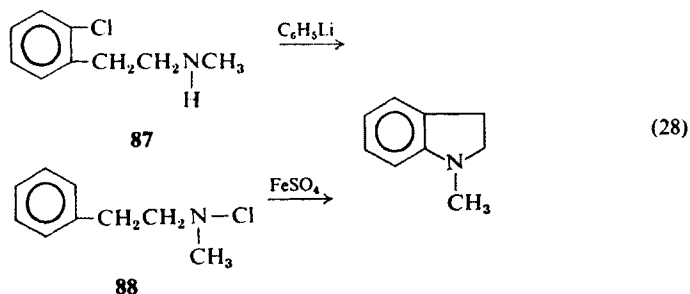
1. *By Reduction*

Indoline derivatives may be obtained from the corresponding indoles by reduction with zinc or tin and hydrochloric acid, through electrolytic reduction,^{559, 560} or with sodium and ethanol.⁵⁶¹ Catalytic hydrogenation with platinum, nickel, nickel salts, copper, or copper salts has produced indolines.¹ The hydrogenation may proceed past the dihydro stage to yield octahydroindoles, aniline derivatives,⁵⁶²⁻⁵⁶⁵ or aminocyclohexanes.⁵⁶⁵

Reduction of oxindoles with lithium aluminum hydride⁵⁶⁶ and Wolf-Kishner reduction of indoxyls⁵⁶⁷ yields indolines. The action of tin and hydrochloric acid on 1,5-diacetylindoline gave 5-ethylindoline,⁵⁶⁸ and the lithium aluminum hydride reduction of the zinc chloride complex of 3,3-dimethylindolenine gave 3,3-dimethylindoline.⁵⁶⁹

2. By Cyclizations

Treatment of *N*-methyl- β -(*o*-chlorophenyl)ethylamine with phenyl lithium^{570, 571} and reaction of *N*-methyl-2-phenylethyl-*N*-chloroamine with ferrous sulfate⁵⁷² gave *N*-methylindoline (Eq. 28).

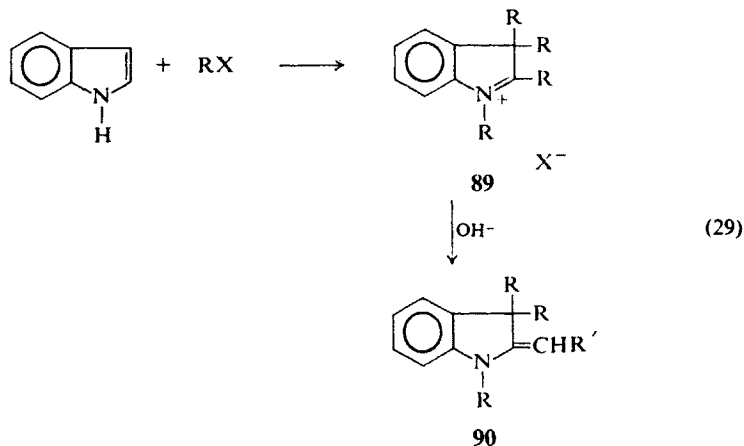


The deoxygenation of *o*-butyl nitrobenzene with triethyl phosphate gave 2-ethylindoline, perhaps via a nitrene intermediate.⁵⁷³ Pyrolysis of *o*-alkyl azidobenzenes has also given indolines.^{574, 575}

2,2-Dimethylindoline results from dehydration of *o*-isopropylamino-benzyl alcohol.⁵⁷⁶ 3,3-Dimethylindoline has also been described.^{569, 577}

3. 2-Methyleneindolines

Exhaustive alkylation of indoles gives indoleninium salts (**89**) which yield 2-methyleneindolines (**90**) on treatment with base.^{1, 578, 579} Treatment with



hydrogen halide regenerates the salt. Rearrangement of alkyl groups has been reported to occur when indoleninium salts are heated. An isopropyl or ethyl group in the 2-position exchanges with a methyl group in the 3-position.⁵⁸⁰

The phenylhydrazone of methyl isopropyl ketone gives the 2-methyleneindoline analog without an *N*-methyl group when treated under Fischer synthesis conditions.¹

1-Allyl-3,3-dimethyl-2-methyleneindoline undergoes an allylic rearrangement to form 3,3-dimethyl-2-(3-butenyl)-indolenine when heated at 200°C.⁵⁸¹

B. Reactions

The indolines are typical secondary aromatic amines and undergo reactions typical of this class.

1. Alkylation

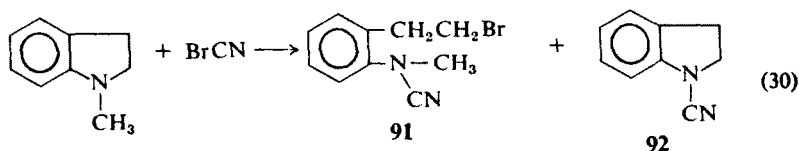
N-Alkylated indolines are produced when indolines are treated with alkyl halides in the presence of alkali metal carbonates.^{582, 583}

Phenylacetaldehyde and indoline gave *N*-styrylindoline.⁵⁸⁴

The reaction of indoline salts with nucleophiles has been studied.⁵⁸⁵

2. Dealkylation and Ring Opening

N-Methylindoline yields indoline on treatment with hydrogen iodide and phosphorus,⁵⁸⁶ and 2-methylindoline gives *o*-amino-*n*-propylbenzene. Cyanogen bromide converts *N*-methylindoline into **91** and **92**.⁵⁸⁷



3. Miscellaneous Reactions

2-Methylindoline has been the subject of numerous studies.^{1, 588} Oxidation of 2-methyleneindolines with potassium permanganate or chromium trioxide gives oxindoles,¹ and alkylation occurs on the 2-methylene group.¹

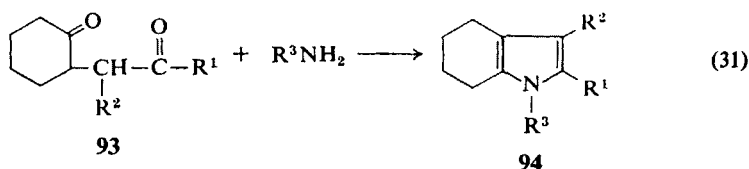
Dehydrogenation of indolines yields indoles.

IV. Tetra-, Hexa-, and Octahydroindole Derivatives

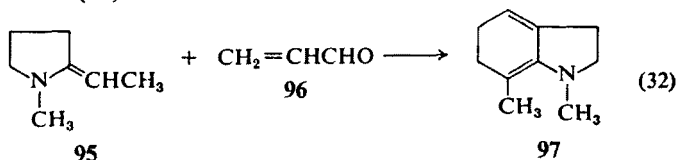
A. Preparation.

1. By Cyclization

The 4,5,6,7-tetrahydroindoles have generally been prepared by reaction of a 2-ketocyclohexanone (**93**) with an amine.^{589, 590} Preparation of 1,7-dimethyl-

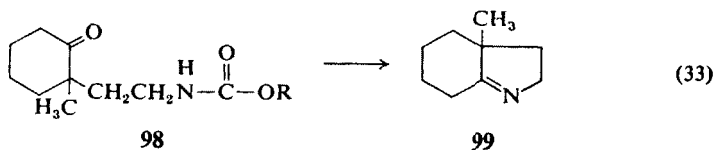


2,3,5,6-tetrahydroindole (**97**) has been accomplished by reaction of *N*-methyl-2-ethylidene pyrrolidine (**95**) with acrolein.^{591, 592}

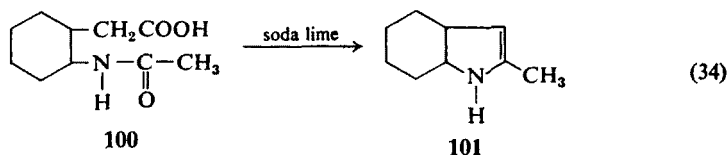


Similar reactions of vinyl ketones with Δ^2 -pyrrolines gave 2,3,4,5-tetrahydroindoles.⁵⁹³

3-*Methyl- Δ 1,7-hexahydroindole* (**99**) resulted by cyclization of a 2-(β -aminoethyl)cyclohexanone derivative **98**,⁵⁹⁴ and distillation of *trans*-2-acetamidocyclohexanecarboxylic acid (**100**) over soda lime gave *trans*-2-methyl-



3*a*,4,5,6,7,7*a*-hexahydroindole (**101**).⁵⁹⁵ The 2-phenyl derivative was also prepared by the latter method.⁵⁹⁵



Treatment of 2-(2-bromoethyl)-4,5-dimethyl cyclohexylamine hydrobromide with sodium hydroxide gave 5,6-dimethyloctahydroindole.⁵⁹⁶

2. By Reduction

Hydrogenation of indoles (see Section I.C.3) or partially hydrogenated derivatives^{591, 594, 595} gave octahydroindoles as does lithium aluminum hydride reduction of hexahydrooxindoles.⁵⁹⁷⁻⁵⁹⁹ Formic acid has been used to rearrange 1,5-dimethyl-4-oxo-2,3,4,5,6,7-hexahydroindole to 1,7-dimethyl-2,3,4,5,6,7-hexahydroindole.⁵⁹¹

Reduction of indole with Raney nickel in the presence of methanol gives methyloctahydroindole.⁶⁰⁰

B. Reactions

Partially hydrogenated indoles may be dehydrogenated to indoles.⁵⁹¹

1. Alkylation

2-Phenyl-4,5,6,7-tetrahydroindole may be *N*-alkylated with alkyl halides.⁶⁰¹ *N*-Methylation of octahydroindoles has been accomplished with formaldehyde⁶⁰²⁻⁶⁰⁴ and formic acid.

2. Miscellaneous Reactions

Lithium aluminum hydride reduction of *N*-acyl octahydroindoles gives *N*-alkyl octahydroindoles.^{603, 604}

With phenyllithium, $\Delta^1(7a)$ -hexahydroindole gave 7a-phenyl octahydroindole.⁶⁰³⁻⁶⁰⁵

The pyrolysis of **102** was anomalous, giving **103**.⁶⁰⁶

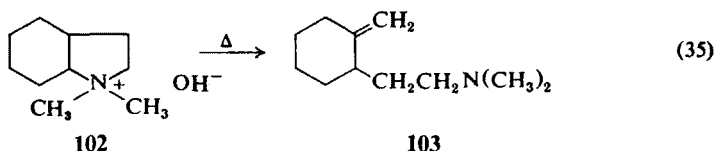


TABLE IV. Alkylindoles

Compound	mp (°C)	bp (°C/mm)	n_D^{22}	mp picrate	Ref.
1-Methyl		109.12	1.6082 ^{18,5}	149	22, 135, 156, 159, 76, 165
2-Methyl	56–159				5, 138, 78, 15, 17, 22, 32 51, 58
3-Methyl	95.5			174	22, 23, 32, 50, 57, 141
4-Methyl		131/14		189–190	22, 390
5-Methyl	59.5			159–160	22, 60, 240
6-Methyl	58–59		1.5824 ²⁵	160–161	196, 22, 221, 241
7-Methyl	82	83–86/0.3		175.5–176.0	22, 87, 221, 236
1,2-Dimethyl	57–59	105/104		125	76, 97, 109, 159, 174, 164
1,3-Dimethyl		103–105/2	1.5896	142–143	17, 76, 97, 134, 224
1,6-Dimethyl				132	593
1,7-Dimethyl	76.5–77.5	122.3/9		151–152	133, 591, 592, 593
2,3-Dimethyl	103–104	150–165/12			217, 79, 97, 109, 110, 5, 9, 12, 17, 19, 23, 25, 43, 50, 56, 105
2,5-Dimethyl	115–116				78, 51, 84, 109, 376, 113
2,6-Dimethyl					105
2,7-Dimethyl	33–35	112–116/1		154–156	78, 84, 109, 376, 113, 105,
3,4-Dimethyl					286
3,5-Dimethyl					17, 389
3,6-Dimethyl					241
4,7-Dimethyl	98–100				18
1-Ethyl		107–108/7		101–102	188, 545
2-Ethyl	44–45				78, 187, 233
3-Ethyl	42	145–155/13–14		120–121	56, 50, 17, 114, 204, 201, 215, 547
7-Ethyl		142/12	1.6050 ²⁵		189
1,2,3-Trimethyl		117–120/6	1.5701	148–149	17, 76, 97, 153, 166, 205, 216
1,5,7-Trimethyl	81.2				53
2,3,5-Trimethyl	118–119				13, 114, 382
2,3,6-Trimethyl	117–118				63, 382

TABLE IV (Contd.)

Compound	mp (°C)	bp (°C/mm)	n_D^{22}	mp picrate	Ref.
2,3,7-Trimethyl	86-87	105-106/2		155-157	109, 114, 122
2,5,6-Trimethyl	124			152	86, 376
2,5,7-Trimethyl		104-106/0.4	1.5506		78, 84, 316, 376
3,5,7-Trimethyl	69-70			176-178	316
5,6,7-Trimethyl					129
1-Ethyl-2-methyl		80-90/0.8		96-97	97
1-Ethyl-3-methyl		84-86/0.5		106-108	97, 102
2-Ethyl-1-methyl	29.5-30				233
2-Ethyl-3-methyl	65-66				217
2-Ethyl-5-methyl	78-84				54, 75, 59, 105
2-Ethyl-6-methyl					105
2-Ethyl-7-methyl					105
3-Ethyl-1-methyl		74-76/0.35	1.5808	97-98	211
3-Ethyl-2-methyl		138-145/12.5			8, 122, 217
7-Ethyl-2-methyl	33, 145/10			144	79, 182
1-Propyl					188
1-Isopropyl					148
2-Propyl	33-34	119-120/1		144-145.5	8, 118, 195, 226
2-Isopropyl	73.5			120	78, 118
3-Propyl		153-154/15		110-111	144, 171, 433
3-Isopropyl	29				437, 148
2,3-Trimethylene					50, 61, 56
2,3,5,7-Tetramethyl	68-70	138/16		158-159	316
1,3-Dimethyl-2-ethyl		93-95/0.5		70-91	97, 185
2,3-Dimethyl-6-ethyl	72.5-73.5				206
2,3-Dimethyl-7-ethyl		155/10		131	182
2,5-Dimethyl-3-ethyl	65-66	130-132/4		143-145	115, 123, 13
2,7-Dimethyl-3-ethyl		123-126/3	1.5848		115, 123
2-Methyl-3-propyl		131-132/1.1		145-147	109, 365
2-Methyl-3-isopropyl		120/0.8			108, 217
3-Methyl-1-isopropyl					102
3-Methyl-2-propyl					217

TABLE IV (Contd.)

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp picrate	Ref.
3-Methyl-2-isopropyl		140–145/2			386, 217
1,3-Diethyl					148
2,3-Diethyl	65–66	118–120/2	1.4335	147–150	120, 122, 203, 384, 217
2-Butyl	36–37			110–111	78, 226
2-Isobutyl	40–41				98, 555
2- <i>t</i> -Butyl	77			134–135	40, 78, 374, 316, 426
3-Isobutyl	31–32				200
3- <i>t</i> -Butyl	67	166–169/9		109	141, 316, 426, 437
2,3-Tetramethy- ene	118				50, 61
4-Ethyl-1,2,3-trimethyl	40.5–41			44–46	205
5-Ethyl-1,2,3-trimethyl		139–141/7		120–121	205
6-Ethyl-1,2,3-trimethyl		110–113/5		119.5–120	206
7-Ethyl-1,2,3-trimethyl	42.5–43.5	115–120/3		118–120	205, 206
7-Ethyl-2,3,5-trimethyl	112–114	162/10		168–169	182
2,3-Diethyl-1-methyl		160/0.01	1.5724 ²⁷		203
2,7-Diethyl-3-methyl		158/10			182
1,2-Dimethyl-3-propyl		85–88/0.02			542
2,5-Dimethyl-3-propyl	59	155/4		128	13, 109
2,5-Dimethyl-3-isopropyl	79	152/5		155	13
1-Ethyl-2-propyl					226
1-Isobutyl-2-methyl					503
1-Butyl-3-methyl		100/0.1			102, 149
2-Butyl-3-methyl		140/0.2			149
2- <i>t</i> -Butyl-3-methyl		120–123/0.1		148–150	427
2- <i>t</i> -Butyl-5-methyl	104–105			146	78
3-Butyl-2-methyl		124–127/1	1.5671		119
3- <i>t</i> -Butyl-2-methyl	48	135–136/0.5		160–161	427

TABLE IV (Contd.)

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp picrate	Ref.
1-(1'-Methyl)- butyl					148
3-(1'-Methyl)- butyl					148
1-Isoamyl					148
1- <i>t</i> -Amyl					148
2-Amyl	47-48			110-111	78
2-Isoamyl	61-62			119-120	78
2- <i>t</i> -Amyl		165-168/8		95-96	78
3-Isoamyl					148
3- <i>t</i> -Amyl					148
6-Amyl	53-55				127
2-(1,1-Dimethyl- propyl)		120-125/0.1		97	377
2,3-Pentamethyl- ene	142				56, 50, 60, 61
2- <i>r</i> -Butyl-3,5- dimethyl		130/0.1			427
2- <i>r</i> -Butyl-5,7-di- methyl	62			147	40, 78
2-Hexyl		175-177/15		92-93	78
7-Methyl-2,3- tetramethylene	97				61
1-Isopentyl-3- methyl		170/0.1			148, 149
2- <i>r</i> -Amyl-5- methyl		170-172/15		112-113	78
1,3-Dipropyl					148
1,3-Diisopropyl					148
2- <i>r</i> -Butyl-3,5,7- trimethyl	62	135/0.1		174-175	427
3-(1-Methylheptyl)		148-153/0.3	1.5329 ²⁵		176
3-(2-Ethylhexyl)		138-142/0.5	1.5422 ²⁵		176
2- <i>r</i> -Amyl-5,7-di- methyl				118-119	78
3-(2-Octyl)		150/0.1			217
2-Butyl-1-methyl- 3-propyl		115-118/0.02			542
3-Hexyl-2-methyl		202/15	1.5675	125	29
2- <i>r</i> -Amyl-2,5,7- trimethyl					426
3-Octyl	33-34	125-127/0.2			176
5,7-Di- <i>r</i> -butyl- 2-methyl	78-79				78
2-Nonyl	61-62			89-90	78

TABLE IV (Contd.)

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp picrate	Ref.
1,3-Diisoamyl					148
1,3-Di-(1'-methyl)butyl					148
1-Amyl-2,3-pentamethylene					108
3-Decyl-2-methyl		239/15	1.5425	114	29
3-(2-Butyloctyl)		179/0.3	1.5214 ²⁵		176
2- <i>t</i> -Amyl-5,7-di- <i>t</i> -butyl	55–57	175–185/0.2			78
2-Methyl-3-tetradecyl	37	276/15		112	29
2- <i>t</i> -Amyl-5,7-diisoamyl					40, 42, 281
3-Hexadecyl-2-methyl	47	284–286/15		110	29
2-Heptadecyl					442
2-Cyclopentyl	84–85	75/0.003			99
2-Cyclohexyl	42			101–102	78
3-Cyclohexyl	92–92.5				176
1-Cyclohexyl-2-methyl					496
3-Cyclohexyl-methyl	72–72.5	140–149/0.1			176
3-Cyclohexyl-2-methyl				180–181	199

TABLE V. Alkenylindoles

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp picrate	Ref.
1-Vinyl	29-30	71-72/1	1.6300		544, 545
3-Vinyl	76-82				547
1-Methyl-3-vinyl			1.5944 ^{25,6}		348
2-Methyl-1-vinyl		105/2			543
1-Allyl		114-116/6		79-79.5	155
3-Allyl		94-95/0.03	1.5998	104.5-106	171
1,3-Dimethyl-2-vinyl	10-19				185
1-Allyl-3-methyl		110/0.5			149
2-Allyl-3-methyl					217
2-Isobutenyl	102-103				555
1-Allyl-2,3-dimethyl		159-160/16		86	153
1-(4-Indolyl)-1-pentene				146-147	552
4-Dimethylallyl	22-23				552
4-Indolylisoprene					552
1,3-Diallyl					148
1,2-Dimethyl-3-(1-methylenebenzyl)					551
3-Allyl-2-(3-butenyl)-1-methyl		130-135/0.05			542
2-(1,1-Dimethylallyl)-5,7-(3-methyl-2-butenyl)					278
2-(1-Cyclopenten-1-yl)-3-methyl	250				463
3-(2 or 3-Cyclopenten-1-yl)-2-phenyl	163-164				199
2-(1-Cyclohexen-10-yl)-3-methyl	215				463
3-(2-Cyclohexen-1-yl)	161-162				199
3-Cyclooctenyl	138-140				199
3-(1',2'-Diphenylethylene)-2-methyl	163-164				456
2-(2,3,3-Tri-methyl-cyclopenten-1-yl)					47
3-(2-Propynyl)		125.5-126/1.4			540, 541

TABLE VI. Aralkylindoles

Compound	mp (°C)	bp (°C/mm)	mp picrate	Ref.
1-Benzyl	44	172-175/1.2	80-82	155, 156, 163, 181
2-Benzyl				46
3-Benzyl	96-98	180-183/1.3	109-111	140, 156, 141, 176, 181
1-Benzyl-2-methyl	59-60			447
2-Benzyl-1-methyl	60		97	139
2-Benzyl-3-methyl	90-91		140-142	217
2-Benzyl-5-methyl				46
3-Benzyl-1-methyl	58-59		120-121	142
3-Benzyl-2-methyl	119-120			176, 379, 585
1-Benzyl-2,3- dimethyl	59-60	110-115/1.5	98-99	153, 185
3-Benzyl-1,2-di- methyl	56.8-57			585
3-Benzyl-2,5-di- methyl	114-116			379
1-Benzyl-3-ethyl				57
1-Benzyl-3- cyclopentyl				57
1-Benzyl-3-cyclo- hexyl				57
1-Benzyl-3-(3- methylcyclohexyl)				57
1-(2-Phenylethyl)		150-155/6.5		151
2-(2-Phenylethyl)	123-124	160-170/0.1		160
3-(1-Phenylethyl)	76.5-77			176
3-(2-Phenylethyl)	119-120		143-144	136
3-(3-Phenylpropyl)				176
1-Benzyl-2,3-di- ethyl				234
2-Benzyl-1-methyl- 3-phenyl	122			296
4,5-Dibenzyl-2- methyl				369
2- <i>p</i> -tolyl	217			4, 30
3- <i>p</i> -tolyl	95-95.5			176
2- <i>p</i> -Ethylphenyl)	196			30
2-(<i>p</i> -Propylphenyl)	196			30
2-(<i>p</i> -Cyclopentylphenyl)	236			24
2- <i>p</i> -Cyclohexyl- phenyl	206	310-315/20		21
1-(1-Indolyl)- bibenzyl				181

TABLE VI (Contd.)

Compound	mp (°C)	bp (°C/mm)	mp picrate	Ref.
1,3-Dibenzyl				148, 181
2,3-Dibenzyl				181
2,3-Ditolyl				526
3-Diphenylmethyl	127-128			176
3-Triphenylmethyl				170
1-Methyl-3-tri- phenylmethyl				170
2-Methyl-3-tri- phenylmethyl				170
2-Benzyl-3-phenyl				46, 378

TABLE VII. Arylindoles

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp, picrate	Ref.
1-Phenyl		179-180/11	1.6555		168
2-Phenyl	187-188				116, 5, 220, 228, 231, 14, 17, 27, 34, 38
3-Phenyl	87-88			107-109	50, 232, 230, 243, 141
6-Phenyl	160-161				196
7-Phenyl	124-125				55
1-Methyl-2-phenyl	107-108			83-84	5, 38, 160, 373, 488, 166
1-Methyl-3-phenyl	62-63				97
1-Methyl-6-phenyl					593
1-Methyl-7-phenyl				107-108	397
2-Methyl-3-phenyl	78-79	196-200/3		139-140	46, 382, 296, 430
2-Methyl-7-phenyl	104-104.5				55
3-Methyl-2-phenyl	89-90	194-195/3		144-145	5, 430, 6, 195, 82, 161
3-Methyl-5-phenyl					488
3-Methyl-7-phenyl	80-81	160-180/3			55
4-Methyl-2-phenyl	185				104
5-Methyl-2-phenyl	134				104
7-Methyl-2-phenyl	118				104
1,2-Dimethyl-3-phenyl	113.5-115	130-135/0.1		199-201	26, 28
1,3-Dimethyl-2-phenyl	69	172-175/2		117	76, 97, 161
2,3-Dimethyl-7-phenyl	82-83				55
2,5-Dimethyl-3-phenyl					46
3,5-Dimethyl-2-phenyl	122				161
3,6-Dimethyl-2-phenyl	142				161
4,7-Dimethyl-2-phenyl	65.5-66.5				33, 39
5,7-Dimethyl-2-phenyl	96				101
1-Ethyl-2-phenyl					226
3-Ethyl-2-phenyl					17
7-Ethyl-2-phenyl	58.5-60			136.7	182
2-Phenyl-1,3,5-tri- methyl		182.4/2		104	161
2-Phenyl-1,3,6-tri- methyl		183.5/2		103	161
2-Phenyl-4,5,7-tri- methyl					44

TABLE VII (Contd.)

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp, picrate	Ref.
2-Phenyl-1-propyl		175-176/2.5	1.6320		160
1-Butyl-2-phenyl		165-175/1.5			471
3,2'-Methylene-2-phenyl					50
3-Cyclohexyl-2-phenyl	158-159				199
1,3-Diphenyl	103-104	200-230/3			95
2,3-Diphenyl	125-125.5	184-208/0.065			37, 48, 229, 106, 95
2,7-Diphenyl	116-117				55
1,3-Diphenyl-2-methyl					310
2,3-Diphenyl-1-methyl	137-138			160-161.5	92, 95, 143
2,3-Diphenyl-4-methyl					10
2,3-Diphenyl-5-methyl	150-151				92, 63, 382, 229, 95
2,3-Diphenyl-6-methyl	104	240-260/7			10, 63, 229, 92
2,3-Diphenyl-7-methyl	128				95, 229
2,7-Diphenyl-3-methyl	86-87				55
3,7-Diphenyl-3-methyl	124-125				55
4,6-Dimethyl-2,3-diphenyl	193				229
4,7-Dimethyl-2,3-diphenyl	130			132	92
5,7-Dimethyl-2,3-diphenyl	149			157-158	92
6,7-Dimethyl-2,3-diphenyl	144			162-163	92
2,3-Diphenyl-1-ethyl					92
2,3-Diphenyl-7-ethyl					103
1,2,3-Triphenyl					95, 493
2,3,7-Triphenyl	215-216				55
2-(1-Naphthyl)	140-141				195
2-Methyl-3-(1-naphthyl)	147-149				379
3-Methyl-2-(2-naphthyl)					195
2-(4-Biphenyl)	300-300.5				5, 195
2-(4-Biphenyl)-3-methyl	162-163.5				195
2-(4-Biphenyl)-1-ethyl	133.5-135				195
3-(4-Biphenyl)-1-ethyl	111.5-112				195
2-(2-Indolyl)tri-phenylene	225				7
4'-(2-Indolyl)- <i>p</i> -terphenyl	386				62

TABLE VII (Contd.)

	mp (°C)	bp (°C/mm)	n_D^{20}	mp picrate	Ref.
2,3-Diphenyl- β -naphthyl					95
1,4-Di(2-indolyl)-benzene	> 360				195
4,4'-Di(2-indolyl)-biphenyl	482-484				62
1,5-Di(2-indolyl)-naphthalene	312				62
3,6-Di(2-indolyl)-acenaphthene	276				62
2,7-Di(2-indolyl)-fluorene	423-424				62
2-(2-Furyl)	122-123				30
2,3-Difuryl	> 285				91
5-(3-Indolylmethyl)-tetrazole	179-180			131-132	612
3-Indolylthiazolo-[5,4- <i>d</i>]thiazole	> 400				611
3-(Indol-3-yl)-5-phenyl-2-pyrazoline	192				610

TABLE VIII. Indolenines

Compound	mp (°C)	bp (°C/mm)	mp picrate	Ref.
3,3-Dimethyl	214–215			56, 569, 149
2,3,3-Trimethyl		113/21	158	50, 153, 327
3-Ethyl-3-methyl	163–164		148	217
1,2,3,3-Tetramethyl- sulfate				299
3,3-Diethyl		120–125/2	105–106	217
3-Methyl-3-propyl		100/0.1		149, 217
3-Methyl-3-isopropyl	75		160–161	217
3-Allyl-3-methyl				149, 217
2,3-Dimethyl-3-iso- propyl		100–110/11	173–174.5	153
3,4-Butyl-2,3-dimethyl	42.5–43.5	120–122/6.5	129	219
3-Allyl-2,3-dimethyl		128–132/12	156–157	153
2-(3-Butenyl)-3,3- dimethyl				581
3-Benzyl-3-methyl	61			217
2,3-Dimethyl-3-phenyl				35, 429
3,3-Dimethyl-2-phenyl		141–145/1.5		5, 28, 35
1-Benzyl-2,3-dimethyl	48–49		138–141	153
3-Benzyl-2,3-dimethyl	48–49		141–142	219, 561
2-Phenyl-3,3-tetra- methylene		164–167/1	175	28
3,3-Dibenzyl				148
3-(1-Cyclohexen-1-yl)- 2-phenyl	154–156			199

TABLE IX. Indolines

Compound	mp (°C)	bp (°C/mm)	n_D^{22}	mp picrate	Ref.
1-Methyl		95–96/6		166–168	135, 570, 571, 572, 583, 607
3-Methyl					574
1,2-Dimethyl		227–228			109
1,3-Dimethyl		103–104/1		131–133	463
1,7-Dimethyl					133
2,2-Dimethyl		90–92/13	1.5518	151–153	567
2,3-Dimethyl		74/2	1.5513		109, 110
2,5-Dimethyl		239–240			109
2,7-Dimethyl		240–245	1.563 ²²		109
3,3-Dimethyl					149, 569
1-Ethyl		99–102/8	1.5603	101–112	583
2-Ethyl					573, 575
3-Ethyl					547
5-Ethyl		110–111/7	1.5724		568
1,3,3-Trimethyl		100/15		130	132
2,3,7-Trimethyl		238–242			109
1-Ethyl-3-methyl					238
1-Isopropyl		112–115/10	1.5585	165–166	583, 529
3-Methyl-3-propyl				164	149
1-Butyl		128–132/12	1.5429	167–168	583, 529
2-Methylene-1,3,3-trimethyl		105–108/10		147–148	578
2-Methylene-1,3,3-trimethyl		111/12			56
3,3-Dimethyl-1-ethyl-2-methylene					500
1-Allyl-3,3-dimethyl-2-methylene					581
3,3-Diallyl-2-methylene-1-methyl		100–101/0.05			542
3,3-Dimethyl-2-methylene-1-phenyl		100–102/0.1			31, 579
1-Benzyl	21.5–22	173–175/8		158–160	137, 583, 529
1-Benzyl-2-methyl		181–182/19			582
3-Benzyl-2,3-dimethyl	80–82			177–179	561
1-Styryl	81–82				151, 584
1-Methyl-7-phenyl				180–181	397
7-Phenyl	68–70				138
3,3-Diphenyl					566
2-(2-Naphthyl)	96–97				20

TABLE X. Tetra-hexa- and octahydroindoles

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp, picrate	Ref.
4,7-Dihydro-1-methyl		102–106/15	1.5490 ¹⁸		404
1,4-Dihydro-3-phenyl					230
1-Methyl-4,5,6,7- tetrahydro		128–129/24			590
1,6-Dimethyl-2,3,4,5- tetrahydro					593
1,7-Dimethyl-2,3,5,6- tetrahydro		176/14			591
2-Ethyl-1-methyl- 4,5,6,7-tetrahydro		71–72/2			590
2-Butyl-1-methyl- 4,5,6,7-tetrahydro		95–96/2			590
2-Benzyl-1-methyl- 4,5,6,7-tetrahydro		145–146/2			590
1-Benzyl-2-phenyl- 4,5,6,7-tetrahydro	72–73				601
3,6-Dimethyl-1-phenyl- 4,5,6,7-tetrahydro		112–115/0.1			222, 608
2-Ethyl-1-phenyl- 4,5,6,7-tetrahydro		107–108/0.02			223
1-Butyl-2-phenyl- 4,5,6,7-tetrahydro		151–152/2	1.5829		601
1-Phenyl-4,5,6,7- tetrahydro	104–105				590
1-Ethyl-2-phenyl- 4,5,6,7-tetrahydro		127–128/2	1.6015		601
1,3-Diphenyl-2-methyl- 4,5,6,7-tetrahydro	77–79				589
2-Methyl-3a,4,5,6,7,7a- hexahydro		126–129/110		126–127	595
1,7-Dimethyl-2,3,4,5,6,7- hexahydro		72–73/11		174.5–175.5	591
9-Methyl- $\Delta^{1(8)}$ - hexahydro	87.5/20				594
2-Phenyl-3a,4,5,6,7,7a- hexahydro	83–84			183–184	595
1-Methyloctahydro		55/9	1.4749	203–205	191, 597
<i>cis</i> -1-Methyloctahydro		57/9			607
Methiodide	208				607
<i>trans</i> -1-Methyloctahydro		54.5/8			607
Methiodide	229				607
2-Methyloctahydro		100/50	171–172		595
9-Methyloctahydro				228–230	
Methiodide	321–323				594
1,7-Dimethyloctahydro					592
1,9-Dimethyloctahydro					594

TABLE X (Contd.)

Compound	mp (°C)	bp (°C/mm)	n_D^{20}	mp picrat	Ref.
5,6-Dimethyloctahydro			1.4804	178-179	596
1-Benzyl-octahydro		152-153/9	1.5369		597
1-Methyl-7-phenyl- octahydro					602
7-Methyl-7-phenyl- octahydro- hydrochloride	345-347				598
1-Methyl-7a-phenyl- octahydro		115-120/12			603
1-Ethyl-7a-phenyl-octa- hydro		105-107			603
1-Methyl-9-phenyl-octa- hydrohydrochloride	246				604
1-Phenyl-octahydro	53-54				599
2-Phenyl-octahydro		146-148/9.5			595
5-Phenyl-octahydro		107-108/115			604
7-Phenyl-octahydro					602
7a-Phenyl-octahydro		101-105/0.11			603, 605
1-Methyl-9-phenyl- octahydro hydrochloride	246				609
1-Methyl-9- <i>p</i> - tolyl-octahydro hydrochloride	238				604

TABLE XI. Cycloarylindoles and Indolenines

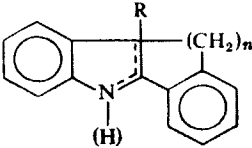
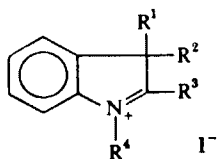
					
<i>n</i>	R	mp (°C)	bp (°C/mm)	mp, picrate	Ref.
1	H	225-227			309
2	H	161			309
3	H	91-92			309
1	C ₂ H ₅		150.5/1	165-167	36
2	CH ₃	98-98.5		167-168	36
3	CH ₃	105-106		183-184	36
4	CH ₃	145-147		119-120	36

TABLE XII. Indolenium Iodides



Compound	mp (°C)	Ref.
1,2,3,3-Tetramethyl		11
3-Ethyl-1,2,3-trimethyl		11
3-Isopropyl-1,2,3-trimethyl		11
3-Isobutyl-1,2,3-trimethyl		11
3-Phenyl-1,2,3-trimethyl		28
2-Phenyl-1,3,3-trimethyl	202-203	28
1-Methyl-2-phenyl-3,3-tetramethylene	186.5-188	28

TABLE XIII. Indole Dimers

Component 1	Component 2	Form	mp (°C)	Ref.
Indole	Indole			435
1-Methylindole	1-Methylindole			440
3-Methylindole	3-Methylindole			434, 436
3-Methylindole	3-Methylindole	Oxalate	184-185	434
Indole	2-Methylindole	Hydrochloride	133-135	434
3-Methylindole	2-Methylindole		214-215	438
Indole	1,2-Dimethylindole		134-135	434
Indole	1,2-Dimethylindole	Hydrochloride	149-151	434
1,3-Dimethylindole	1,3-Dimethylindole		124-125.5	434
1,3-Dimethylindole	1,3-Dimethylindole	Hydrochloride	113-117	434
3-Propylindole	3-Propylindole	Hydrochloride	160-162	437
1-Methylindole	1-Methylindole	Oxidized form	132-133	440
3-Methylindole	3-Methylindole	Oxidized form	162-163	436

TABLE XIV. Diindolylmethanes

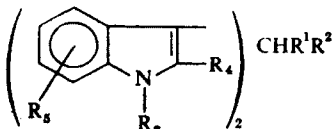
						
R ₁	R ₂	R ₃	R ₄	R ₅	mp (°C)	Ref.
					164	186, 443, 444
		CH ₃			105-109	207
			CH ₃		235-238	449, 458
		CH ₃	CH ₃		161.5-162.5	208
			C ₆ H ₅		184-185	446, 450
		CH ₃	C ₆ H ₅		185-186	160, 450
		C ₆ H ₅ CH ₂	CH ₃		143-144	447
					164-165	211, 443, 444
CH ₃			CH ₃			554
CH ₃				6-CH ₃	157	444
CH ₃	CH ₃				163	444, 460, 463, 553
CH ₃		CH ₃				211
CH ₃	CH ₃	CH ₃			153-155	459
CH ₃	CH ₃		CH ₃		185-197	457
CH ₃	CH ₃			5-CH ₃	185-186	46
CH ₃	CH ₃	CH ₃	CH ₃		195-197	457
C ₄ H ₇					155	444
C ₁₇ H ₃₅						442
CH ₃ CH:CH					130	443
C ₆ H ₅ CH ₂	CH ₃		CH ₃		269-271	456
C ₆ H ₅					125	443
C ₆ H ₅			CH ₃		245	443
CH ₃	C ₆ H ₅				191-193	460
CH ₃	C ₆ H ₅	CH ₃			212-218	460
CH ₃		CH ₃	C ₆ H ₅		212-215	554
CH ₃	C ₆ H ₅		CH ₃		237-239	460
C ₂ H ₅		CH ₃	C ₆ H ₅			471
1-C ₁₀ H ₇					252	443
C ₆ H ₅ CH:CH					99	443
2-Thienyl					149-156	473

TABLE XV. Diindolylalkanes

Compound	mp (°C)	bp (°C/mm)	Ref.
1,3-Di(1-indolyl)propane		195/0.1	158
1,4-Di(1-indolyl)butane	88		158
1,4-Di(3-indolyl)butane		254/0.5	177
1,4-Di(1,2-dimethyl-3-indolyl)butane	174–176		463
1,5-Di(1-indolyl)pentane	81	230/0.05	158
1,6-Di(1-indolyl)hexane	84		158
2,5-Di(1,2-dimethyl-3-indolyl)hexane	157–160		463
1,4-Di(3-indolyl)cyclohexane	218–220		177
1,10-Di(1-indolyl)decane	67		158
α,α' -Di(1-indolyl)- <i>p</i> -xylene	111.5		158
1,2-Di(2,3-dihydro-2-methyl-1-indolyl)-ethane	93–94		582
1,3-Di(2,3-dihydro-2-methyl-1-indolyl)-propane	133–135		582
1,4-Di(2,3-dihydro-2-methyl-1-indolyl)-butane	160		582
1,6-Di(2-phenyl-4,5,6,7-tetrahydro-1-indolyl)hexane	114–115		601

TABLE XVI. Diindolylalkenes

Compound	mp (°C)	Ref.
1,1-Di(2-methyl-3-indolyl)ethylene	201–203	554
1,1-Di(1-methyl-2-phenyl-3-indolyl)-ethylene	193–194	554
1,1-Di(1,2-diphenyl-3-indolyl)ethylene	217–219.5	554
1-(3-Indolyl)-1-[3(2 <i>H</i> -indoliden)]ethane	232–234	553
1,4-Di(1,2-dimethyl-3-indolyl)butadiene	292–294	463
2,5-Di(1,2-dimethyl-3-indolyl)hexa-2,4-diene	242	463
1,4-Di(2-methyl-3-indolyl)cyclohexa-1,3-diene	261	463
α -(2-Methyl-3-indolyl)- α -(2-methyl-3-indoleninylidene)toluene	247	554
α -(2-Phenyl-3-indolyl)- α -(2-phenyl-3-indoleninylidene)toluene	320–325	554
1,3-Di(2-methyl-3-indolyl)-1,3-diphenyl-1-butene	224–230	457
3,3'-Diindolylhexacyclotrimethin bromide	252	463
2,2'-Dimethyl-3,3'-diindolylhexacyclotrimethine bromide	257	463
3,3'-Diindolylpentacyclotrimethine bromide	300	463
2,2'-Dimethyl-3,3'-diindolylpentacyclotrimethine bromide	330	463

TABLE XVII. Indole Trimers

R ¹	R ²	mp (°C)	Ref.
H	H	250	469
CH ₃	H	265	469
H	CH ₃	297	469
CH ₃	CH ₃	320	469

TABLE XVIII. Miscellaneous Indole Dimers and Trimers

Compound	mp (°C)	Ref.
1-Skatylindole	76–80	186
1-Skatylskatole	139–140	186
5-Skatylindoline	148	186
5-Skatylindole	142–143	186
2,2'-Dimethyl-3,3'-diindole	226–228	41
2,2'-Diskatylmethene perchlorate		467
3,3'-Diindolylmethene sulfate		445
3,3'-Dimethyl-2,2'-benzilidenebisindole	162	443, 464, 465
2,2',2''-Triskatylmethane	320–321	467
2,2',2''-Triskatylmethene perchlorate		467
3-(3'-Indolylmethyl)-3-methylindoline	132–134	209
1,3-Dimethyl-3-(1'-methylindolyl-3'-methyl)-indoline	66	209
2,3-Dimethyl-3-(2'-methylindolyl-3'-methyl)-indoline	85	209

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CHAPTER V

Haloindoles and Organometallic Derivatives of Indoles

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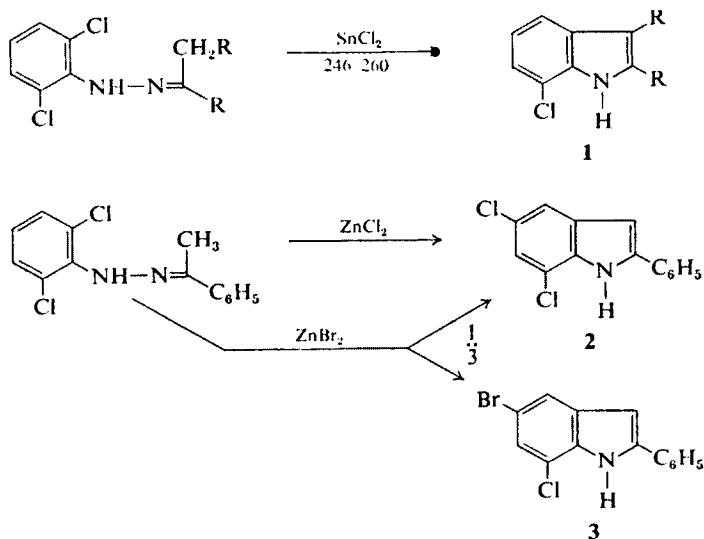
I. Ring Halogenated Indoles

Halogenation of simple indoles with a variety of agents leads to products substituted on the pyrrole ring. The first halogen enters the 3-position if this is available. If the 3-position is blocked, substitution occurs preferentially at the 2- or at the 5- and/or 6-position of the benzene ring depending upon the presence of other substituents. Halogenation in aqueous solution with reagents such as *N*-bromosuccinimide and *N*-chlorosuccinimide usually leads to oxindoles or to haloindoles. Since the bromination of indoles has been extensively studied, bromination methods will be discussed in some detail under the section on bromoindoles. The discussion of other halogenation methods will not be as extensive in their respective sections of this chapter unless the nature of the reaction or the products differ from those observed in bromination.

Benzene-ring-substituted haloindoles are usually prepared via standard indole ring syntheses such as the Fischer indole synthesis and the Reissert synthesis.^{56, 61, 62, 94} But these methods are not without their difficulties. The Fischer indole synthesis gives a mixture of products when applied to *m*-chlorophenylhydrazones. Cyclization of the *m*-chlorophenylhydrazone of acetone with zinc chloride yielded a mixture of 4-chloro- and 6-chloro-2-methylindole.¹⁴⁴ In this case the isomers could be separated because of different solubility properties in benzene-ligroin. Carlin has found that the Fischer indole synthesis can lead to a variety of products when applied to certain halophenylhydrazones.^{63, 85, 89} Indolization of 2,6-dichlorophenylhydrazones with stannous chloride yields 7-chloroindoles (**1**).⁶³ If zinc chloride is used as the cyclizing agent, a rearrangement takes place and 5,7-dichloroindoles (**2**) are obtained.⁸⁵

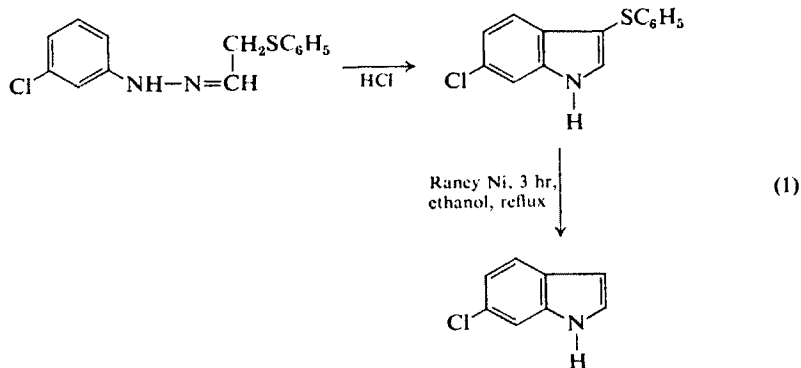
Treatment of the 2,6-dichlorophenylhydrazone of acetophenone with zinc bromide yields a mixture of the dichloroindole **2** and a bromochloroindole **3** (Scheme 1). Thus, the mechanism of these reactions must involve a halogenation of either one of the indolization intermediates or of a monohaloindole which could be formed initially.

Many indole ring syntheses involve reduction of a nitro group as the last step; the indole ring being formed in the course of the reaction. Haloindoles



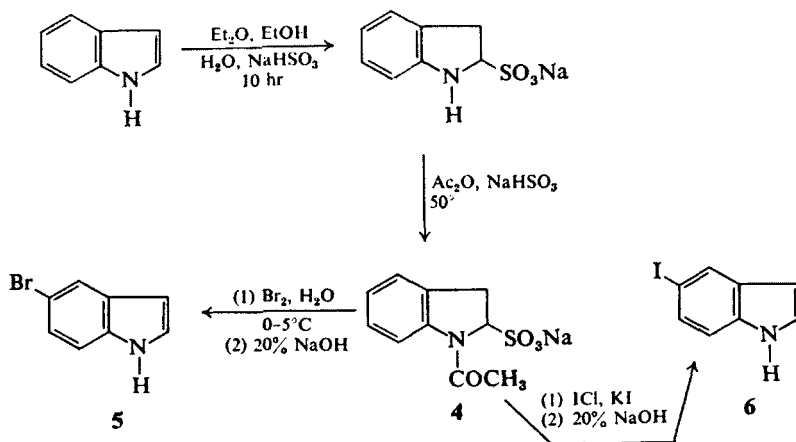
Scheme 1

can be prepared using this method since the reducing conditions (iron or zinc in acetic acid) do not remove the halogen.^{5, 144} Chloroindoles are also stable to Raney nickel as is illustrated by the unusual synthesis²⁰ in Eq. (1).



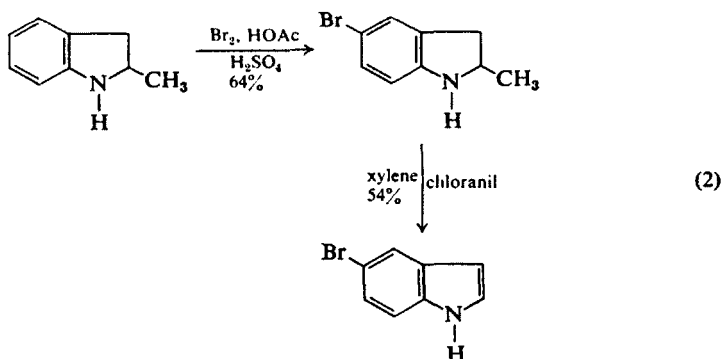
An elegant synthesis of 5-halo indoles has recently been developed by Thesing and coworkers.^{17, 15} Sodium 1-acetylindoline 2-sulfonate (**4**) was prepared by reaction of indole with sodium bisulfite followed by acetylation. This salt was brominated and iodinated at the 5-position. Alkaline hydrolysis then regenerated the indole nucleus and gave 5-bromoindole (**5**) and 5-iodoindole (**6**). A chlorination procedure failed since a mixture of polychlorinated indoles was obtained when the sulfonate **4** was treated with chlorine followed by alkaline hydrolysis.

A related method for the synthesis of benzene-substituted indoles involves halogenation of indolines followed by dehydrogenation. Indolines brominate



Scheme 2

at the 5-position and the resulting bromoindolines can be dehydrogenated to bromoindoles with chloroanil in refluxing xylene²⁸ (Eq. 2).

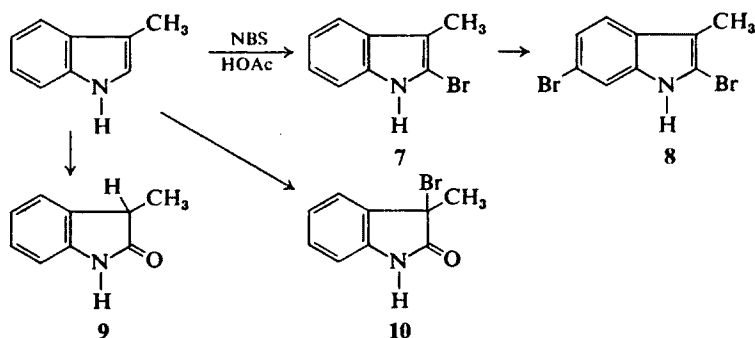


Indoline has been converted to 5-chloro and 5-fluoroindole by a similar procedure.⁷⁵ Nitration of indoline in a mixture of acetic anhydride and nitric acid gave a 1-acetyl-5-nitro derivative. This was converted to the corresponding haloindoles by a process that involved a Sandmeyer reaction and chloroanil dehydrogenation. When indoline was nitrated in concentrated sulfuric acid, 6-nitroindoline was obtained.⁷⁵ A similar series of steps was utilized to convert this into 6-chloro and 6-fluoroindole.

A. Bromoindoles

Bromination of indoles has been more extensively investigated than any other halogenation reaction. This will be discussed first and in depth because the results are directly applicable to the reaction of indoles with the other halogens.

Bromination of indole with pyridiniumhydrobromide perbromide in pyridine, with trimethylphenylammonium perbromide, or with dioxane-dibromide in dioxane yields 3-bromoindole.^{79, 49, 44, 199} 3-Bromoindole is

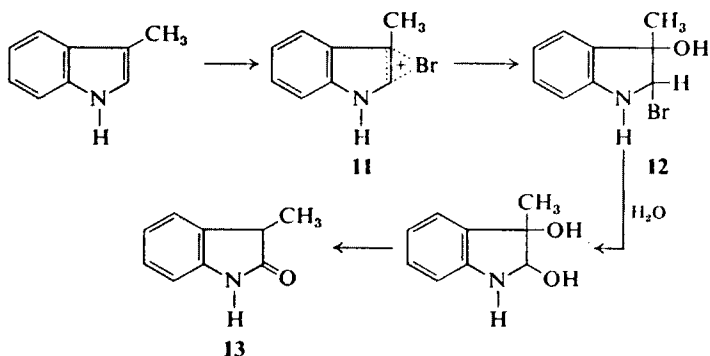


Scheme 3

also obtained by bromination of *N*-benzoylindole with bromine in cold CS_2 or with *N*-bromosuccinimide followed by alkaline hydrolysis.^{112, 125} 2-Bromoindole has not yet been prepared. Oxidation of indolylmagnesium bromides with *p*-nitroperbenzoic acid affords excellent yields of 3-bromoindoles (Section V.A.4).

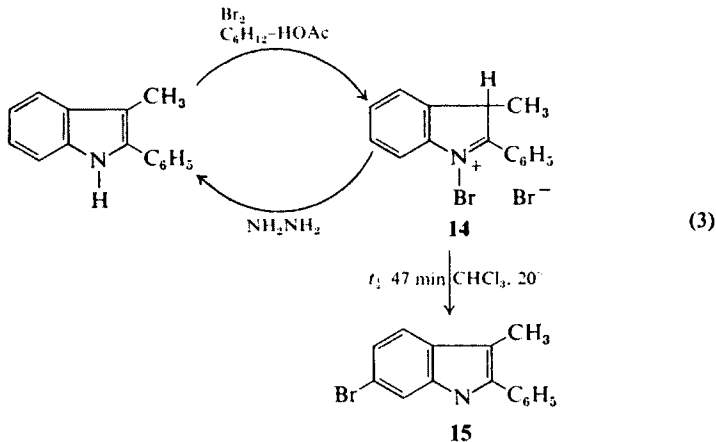
Bromination of skatole with *N*-bromosuccinimide (NBS) in acetic acid yields a 2-bromo derivative (7).³³ Further reaction with NBS or bromination with *N*-bromophthalimide results in the 2,6-dibromo derivative 8.^{92, 33, 142} Bromination in aqueous solvents or in *t*-butanol yields oxindoles (9) or 3-bromooxindoles (10).^{33, 92} Further bromination of the initial oxindole product yields substitution at the 5-position in contrast to the above results with 2-bromoskatole.³³

Green and Witkop have detected an unstable intermediate in the reaction of skatole with 1 equiv of NBS to yield the oxindole (13). This was postulated to be a bromohydrin 12 formed by reaction of a bromonium ion 11 with water. It has the ultraviolet (uv) spectrum of an indolinine and can be trapped by a reaction with piperidine. At pH 9–10 a half-life of 20 min is observed, while at pH 5–6 oxindoles are formed in seconds. The mechanism shown in Scheme 4 explains the results.¹⁶¹



Scheme 4

Addition of 1 mole of bromine to a solution of skatole in ether at -70°C gives a yellow precipitate which is unstable at room temperature.¹²⁰ Treatment of this precipitate with piperidine or aqueous sodium hydroxide yields 60–70% 2-bromo-3-methylindole together with small amounts of 3-methyloxindole. A similar yellow precipitate was obtained in the reaction of 2-phenyl-3-methylindole with bromine in acetic acid.⁹² Further reaction gave 6-bromo-2-phenyl-3-methylindole (15). The yellow precipitate was assigned the perbromide structure 14 (Eq. 3). Both yellow compounds deserve further study.

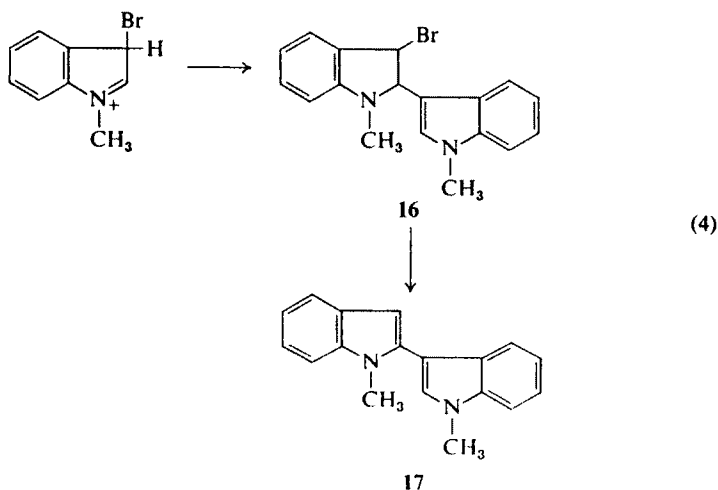


Bromination of 2,3-diphenyl-, 1-acetyl-2,3-diphenyl-,^{116, 117} or 3-methyl-2-phenylindole¹¹⁶ yields the 6-bromo derivatives, although the 4-bromo isomer has not been eliminated as a possibility in these instances. The structure of Bz-brominated indoles is usually determined by preparing the 5-bromo and a mixture of the 4- and 6-bromoindoles by a Fischer indole synthesis from the *p*- and the *m*-bromophenyldiazine, respectively, and comparing the properties of these compounds with those of the bromination product.

Bromination of 2,3-dimethylindole in concentrated sulfuric acid containing some silver sulfate gives the 5-bromo derivative in 75% yield. An authentic sample was prepared from the *p*-bromophenylhydrazone of 2-butanone. In contrast, bromination of 2,3-dimethylindolenine under the same conditions yields a monobromide which is dehydrogenated by chloranil to the 6-bromo-2,3-dimethylindole. The 5- and 6-isomers can be distinguished by infrared bands at 590 cm^{-1} (5-isomer) and 1326 cm^{-1} (6-isomer).¹²⁶

Bromination of 1-acetyl-2,3-dimethylindole, followed by hydrolysis and chloranil treatment, also yields 5-bromo-2,3-dimethylindole.¹²⁶ The structures of the intermediates in this reaction sequence are unknown.

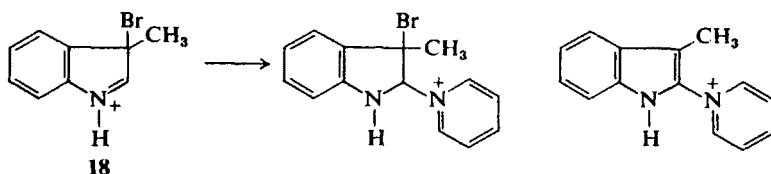
Bromination of indoles occasionally leads to unusual products because bromination intermediates are often trapped by reaction with nucleophiles. Bromination of 1-methylindole, for example, in dioxane yields a dimeric monobromide **16** which is converted by aqueous sodium hydroxide into a diindole (**17**).¹² The mechanism of this reaction probably involves trapping of



the intermediate bromoindolenine (Eq. 4) by reaction with the excess 1-methylindole in a process very reminiscent of the acid-catalyzed dimerization of indole. The same diindole is obtained by treatment of the orange precipitate from the reaction of 1-methylindole with sulfuryl chloride in benzene with 5% aqueous sodium carbonate.¹³

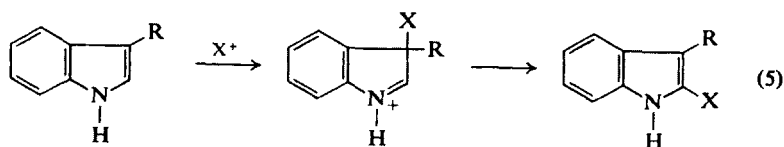
Bromination intermediates such as **18** can also be trapped by reaction with pyridine or piperidine if the reaction is carried out in the presence of these nucleophiles.

Skatole yields a pyridinium indole (Eq. 5) upon treatment with dioxane dibromide in dioxane-pyridine.^{124, 127} Since 2-bromo-3-methylindole undergoes no reaction under these conditions, the product is probably formed as



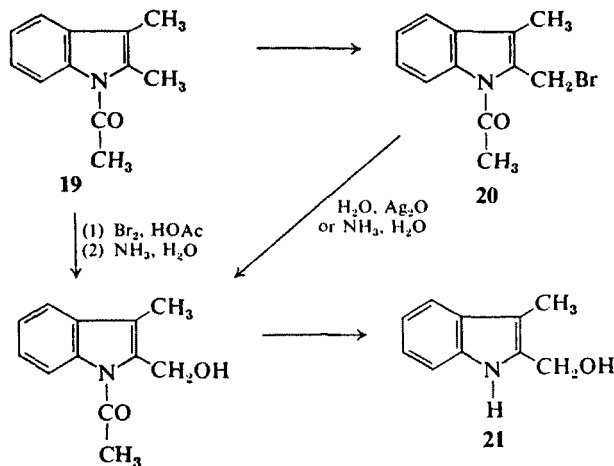
shown by reaction of the intermediate bromoindolenine with pyridine followed by dehydrobromination. This mechanism is similar to that proposed by Hinman and Bauman for the formation of oxindoles in the reaction of NBS with indoles. Similar results are obtained with 3-phenylindole.¹²⁷

Jackson has proposed that all electrophilic substitution reactions on 3-alkylindoles take place initially at the 3-position to give an indolenine which rearranges in a subsequent step to a 2,3-disubstituted indole.¹⁸⁴ The above bromination reactions in the presence of piperidine or pyridine provide additional support for this hypothesis. Thus, it is most likely that 2-halo-3-alkylindoles are formed by the reaction mechanism of Eq. (5).



B. Side-Chain Bromination

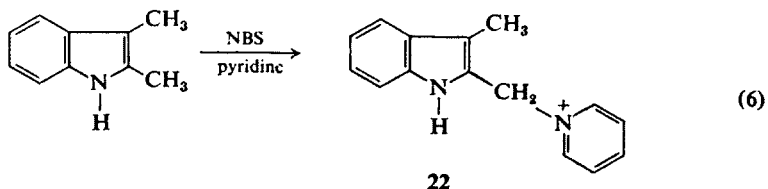
Very few instances in which indoles have been brominated in the side chain are reported. *N*-Acetyl-2,3-dimethylindole (19) reacts with bromine



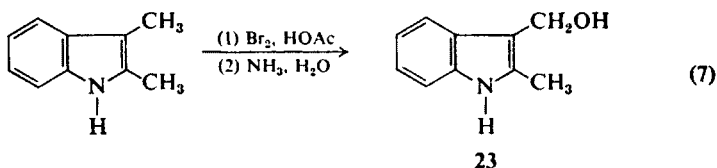
Scheme 5

in a minimum amount of acetic acid to give the 2-bromomethyl derivative **20**. This is easily converted into the corresponding hydroxymethyl derivatives **21** (Scheme 5).¹¹⁶

Bromination of 2,3-dimethylindole with NBS in pyridine yields the pyridinium salt **22**, certainly via 2-bromomethyl-3-methylindole¹²⁸ (Eq. 6).



Dimethylindole, in contrast to its *N*-acetyl derivative and the NBS reaction, reacts¹¹⁶ with bromine in acetic acid at the 3-methyl group to give **23** (Eq. 7) after hydrolysis.

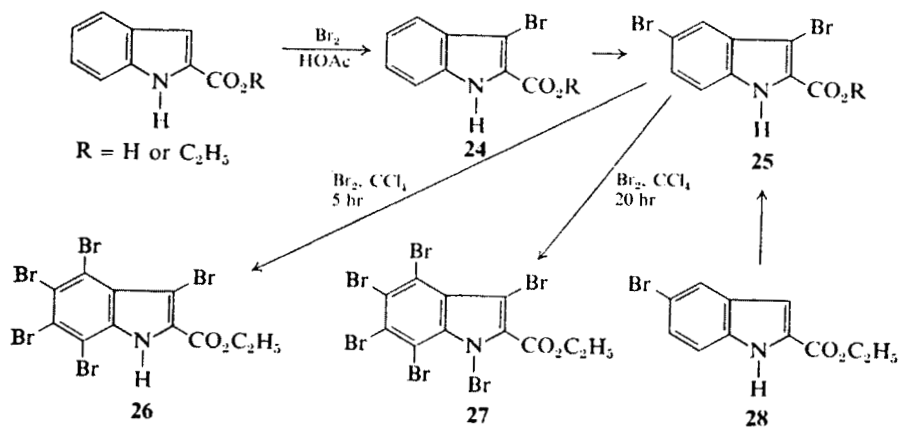


C. Bromination of Functionalized Indoles

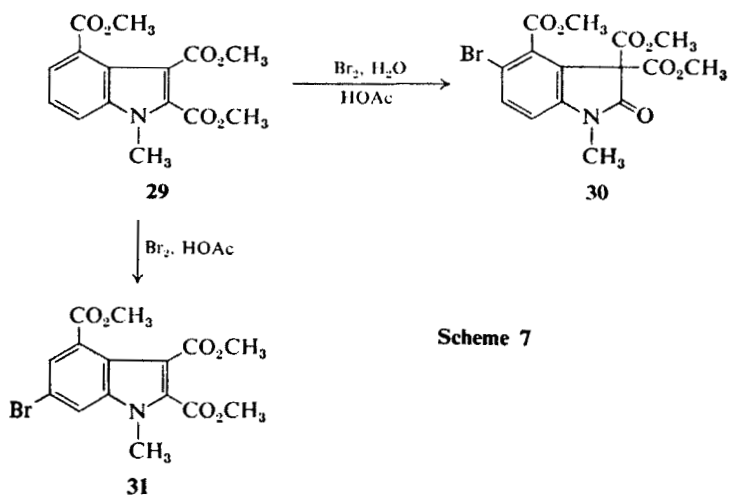
Bromination of ethyl indole 3-carboxylate with bromine in acetic acid yields either the 6-bromo or the 5,6-dibromo derivative depending upon conditions.¹⁰⁹ These compounds can be converted, respectively, to 6-bromoindole and 5,6-dibromoindole by decarboxylation of the acid obtained through basic hydrolysis. Bromination of ethyl indole 2-carboxylate has been stated to yield an inseparable 1:1 mixture of the 5- and 6-bromo isomers. This mixture could be transformed into a still unseparable mixture of 5- and 6-bromoindole.⁸⁰ In contrast, Kunori reports that the first product in the bromination of either ethyl indole 2-carboxylate or the corresponding acid is the 3-bromo derivative **24** (Scheme 6). Further bromination takes place at the 5-position to yield **25**. The ester **25** ($R = C_2H_5$) is also obtained upon direct bromination of **28**. Further bromination of **25** ($R = C_2H_5$) yields **26** and **27**.²⁶

Acheson and Snaith¹⁴⁵ observed the unusual bromination reactions given in Scheme 7. The triester **29** brominates in acetic acid to give the 6-bromo derivative **31**. When the reaction is carried out in acetic acid–water, the oxindole **30** is obtained.

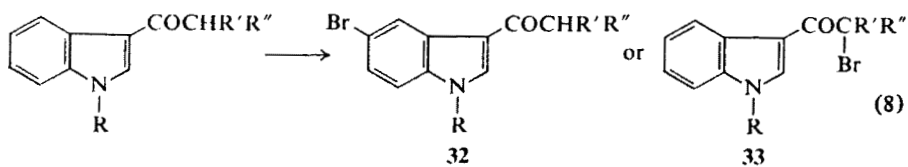
Bromination of 3-acylindoles can take place either at the 5-position or α -to the carbonyl to give **32** or **33** depending upon conditions¹²¹ (Eq. 8).



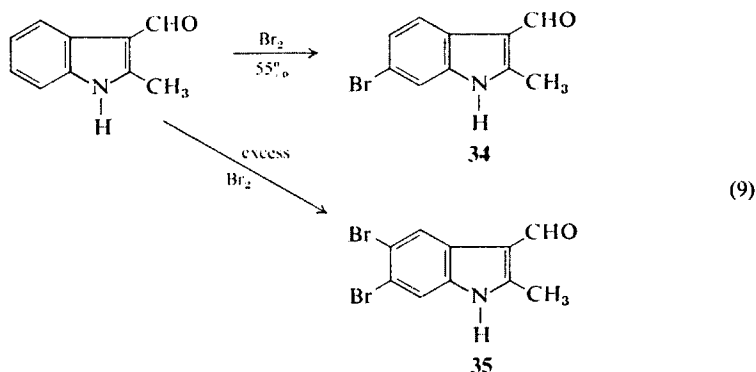
Scheme 6



Scheme 7



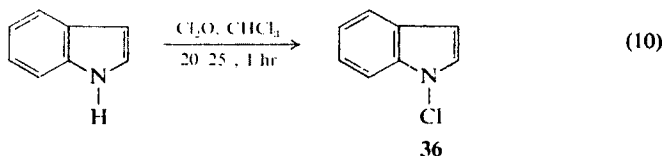
Reaction of 3-acetyl-2-phenylindole with bromine in acetic acid or water or with zinc chloride and bromine yields the 5-bromo derivative in good yield.¹²⁹ Likewise, bromination of ethyl 3-indolylglyoxalate produces a 82% yield of the 5-bromo derivative.¹⁰¹ In contrast, 2-methylindole 3-carboxyaldehyde brominated at the 6-position¹⁰⁴ to give **34**. The dibromide **35** is obtained upon reaction with excess bromine (Eq. 9).



Indole 3-carboxaldehyde was brominated in acetic acid to give a mixture of the 5-bromo (6%) and the 6-bromo derivative (3%). Further bromination of this mixture gives a 5,6-dibromo derivative and 2,3,5,6-tetrabromoindole.¹⁰⁴ The latter compound is certainly formed by a cleavage reaction analogous to the acid- and base-catalyzed cleavages which have been observed earlier.¹³⁰ In this case the electrophilic cleavage is initiated by a bromonium ion instead of a proton.

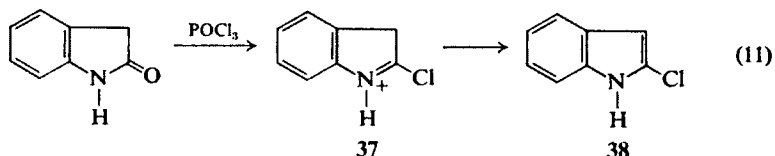
D. Chloroindoles

A preparation of 1-chloroindole (**36**) in 90% yield has been reported (Eq. 10).⁷



Synthesis of 2-chloroindole proceeds by reaction of oxindole with phosphorus oxychloride to give a Vilsmeier salt **37** which is converted to the indole **38** upon treatment with sodium bicarbonate (Eq. 11). This chloroindole was unstable; an analytically pure sample was completely decomposed after standing for 3 days in a sealed vial. *N*-Benzyl-2-chloroindole, prepared in a

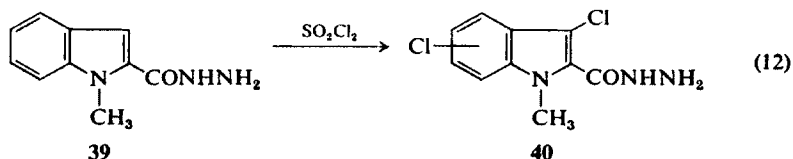
similar fashion from *N*-benzyloxindole, was considerably more stable. This is the only reported preparation of a 2-monosubstituted haloindole.¹³¹



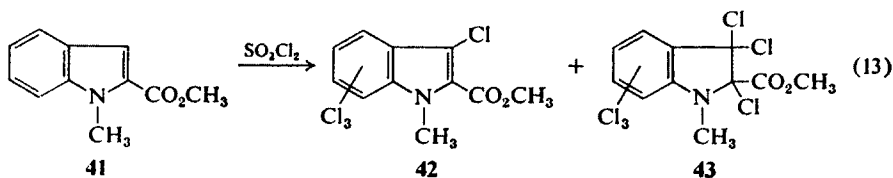
Direct chlorination of indole with sulfuryl chloride yields a mixture of 3-chloroindole and 2,3-dichloroindole.^{132, 131} This dichloroindole has also been prepared by the action of phosphorus pentachloride on either oxindole or dioxindole.¹³³ The reaction of phosphorus pentachloride with oxindole probably proceeds by way of 2-chloroindole which is further chlorinated under the reaction conditions.¹³¹ Chlorination of *N*-benzoylindole in carbon disulfide followed by hydrolysis yields 3-chloroindole.^{112, 83}

Chlorination of 2-methylindole with *N*-chlorosuccinimide in methanol yields 3-chloro-2-methyl indole. Phosphorus pentachloride reacts to give a dichlorophosphoryl indole.¹³¹ A rich harvest of oxindolic products is reaped when skatole is treated with a variety of chlorinating agents.¹³¹

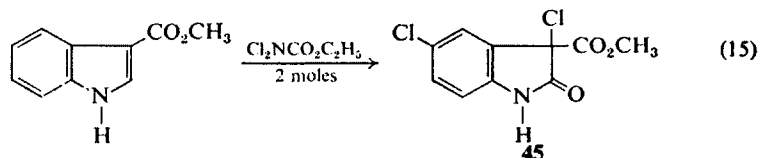
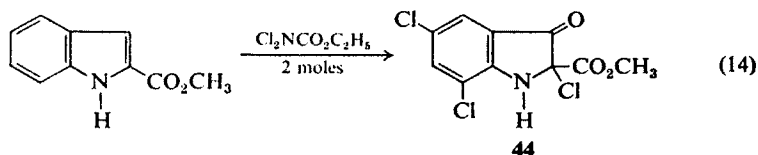
Treatment of 1-methylindole-2-carboxylic acid hydrazide (39) with sulfuryl chloride affords a dichloro derivative¹³⁴ 40 of uncertain structure (Eq. 12).



Reaction of methyl 1-methylindole-2-carboxylate (41) with sulfuryl chloride affords a mixture of a tetrachloro (42) and a hexachloro compound¹³⁴ 43 (Eq. 13).



Indole, indole-2-, and indole-3-carboxylic acid react with *N,N*-dichloro-urethan in acetic acid-water to produce a high yield of 3,3,5-trichloro-oxindole. The 2- and 3-carboxylic esters react to yield the trichloroindolxyl 44 (Eq. 14) and the oxindole 45 (Eq. 15), respectively.¹³⁸



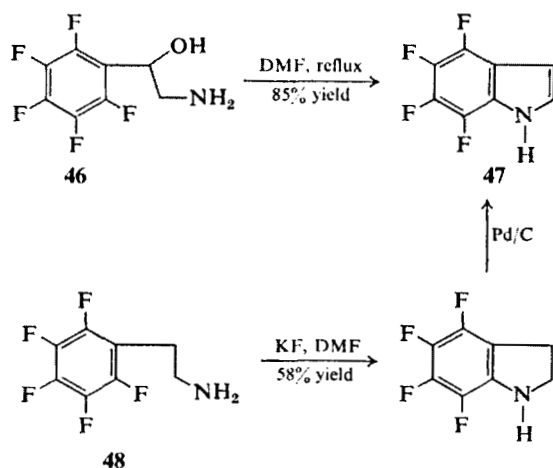
E. Iodoindoles

Iodination of indole with iodine or ICl yields 3-iodoindole.^{99, 49, 113, 114} Indole and iodine form a black 1:1 charge transfer complex with a strong electron spin resonance signal when reacted^{39, 40} in CHCl_3 at -20° . The C-2 and C-3 carbon atoms are probably involved in complex formation. The kinetics of iodination of indole have been studied at different pH's and in the presence of iodide ion. K_{obs} is inversely proportional to the square of the initial iodide concentration and is insensitive to change in pH in the range 7.86–6.50. The results are in agreement with a mechanism involving I^+ as an iodinating agent.¹¹⁹ Indolyl magnesium halides react with diiodoacetylene to give a 83% yield of 3-iodoindole.⁵⁰ A preparation of 2-iodoindole has not yet been reported. Iodination of substituted indoles takes place at the 2-position if the 3-position is substituted.

An acetoxymcury derivative of 2-methylindole has been converted to 3-iodo-2-methylindole (see the discussion of the mercury derivatives of indole). However, the authenticity of other iodoindoles prepared by this procedure is in doubt because of their unusually high melting points. Indigo is formed as a by-product of the iodination of indole with iodine in basic solution.¹¹³

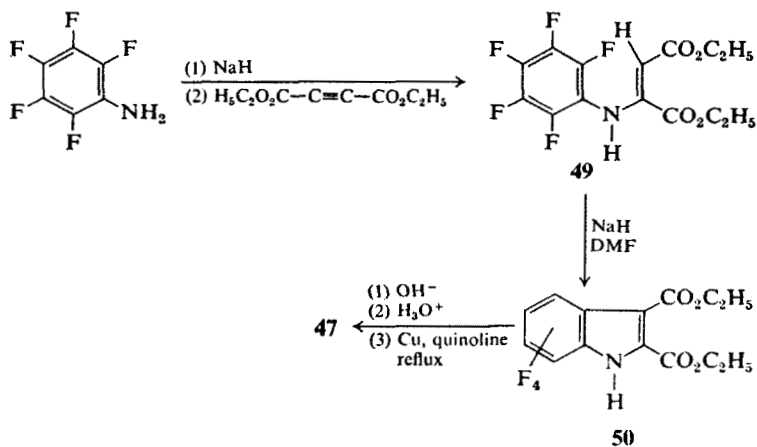
F. Fluoroindoles

Fluorination of 2-methylindole with CoF_3 yielded a mixture of products containing perfluorocyclohexane and perfluoromethylcyclohexane.⁵⁵ All the Bz-substituted monofluoroindoles have been prepared from fluorobenzene derivatives by various indole ring syntheses. No pyrrole-ring-substituted fluoroindoles have yet been prepared. The tetrafluoroindole **47** can be prepared by an interesting ring closure¹¹⁸ from the pentafluorophenylethylamine derivatives **46** and **48** (Scheme 8).



Scheme 8

Tetrafluoroindole **47** is also prepared by addition of pentafluoraniiline to diethyl acetylenedicarboxylate to give **49** followed by cyclization to **50** and then hydrolysis and decarboxylation⁴² (Scheme 9).

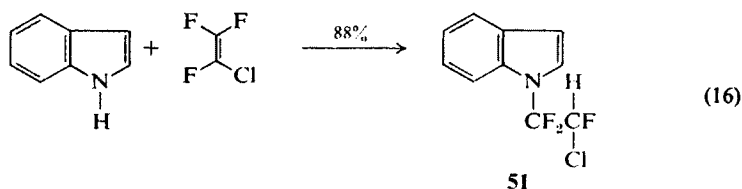


Scheme 9

II. Side-Chain Halogenated Indoles

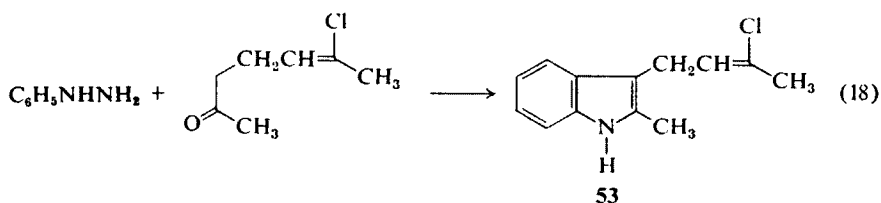
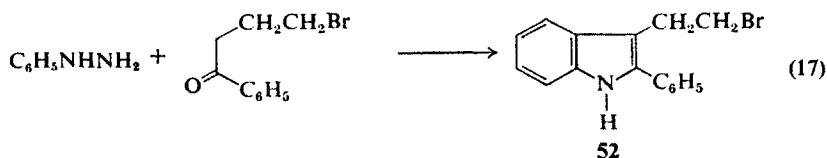
Most preparations of side-chain halogenated indoles involve reaction of the respective hydroxyalkyl indole with a halogenating agent such as phosphorus tribromide or thionyl chloride. A few examples of direct halogenation

of alkylindoles have been reported (see bromination discussion, Section I.B). Indole reacts with certain haloethylenes to afford *N*-haloalkyl indoles.^{84, 71} The reaction (Eq. 16) with 1-chloro-1,2,2-trifluoroethylene to give **51** is



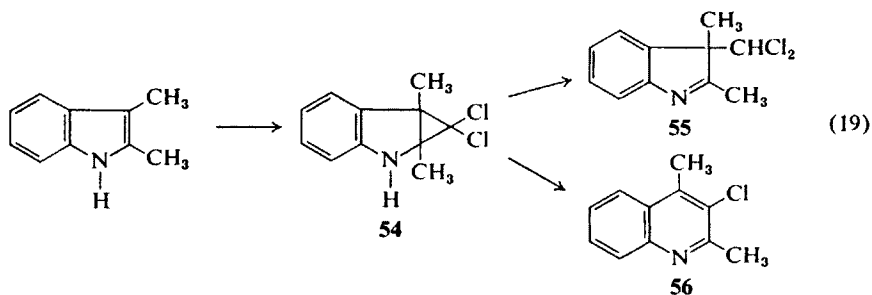
representative. *N*-Vinylindole forms charge transfer complexes with chlorine bromine, and iodine.¹⁰⁵ Addition of bromine in carbon tetrachloride at -10° to *N*-vinylindole produces a product with the composition of *N*-(1,2-dibromoethyl)indole.¹³⁵ Excess bromine yields a tribromoethylindole. Both of these compounds are probably polymeric because they fail to melt at high temperatures. Reaction of chlorine with *N*-vinylindole in carbon tetrachloride at -15° yields a red solid (mp $148-150^{\circ}$) in 85% yield which has been assigned dichlorodimer structure.¹³⁵ Hydrogen halides react with *N*-vinylindole in carbon tetrachloride at -10° to afford *N*-(2-haloethyl)indoles.¹³⁶ The products from these *N*-vinylindole reactions deserve further characterization.

Several haloalkylindoles have been prepared from the appropriate precursor via Fischer indole synthesis.^{137, 11} The preparation of **52**¹³⁷ and **53**¹¹ are examples of this method (Eqs. 17 and 18).



Dimethylindole reacts with sodium ethoxide and chloroform¹²³ or with methyl lithium and chloroform followed by treatment with acetyl chloride¹²² to produce a mixture of dichloromethylindolenine **55** and the chloroquinoline

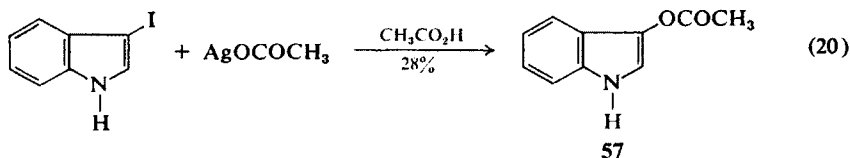
56 (Eq. 19). This reaction has been shown by ^{14}C studies to proceed via the dichlorocyclopropane derivative¹²² **54**.



III. Reactions of Haloindoles

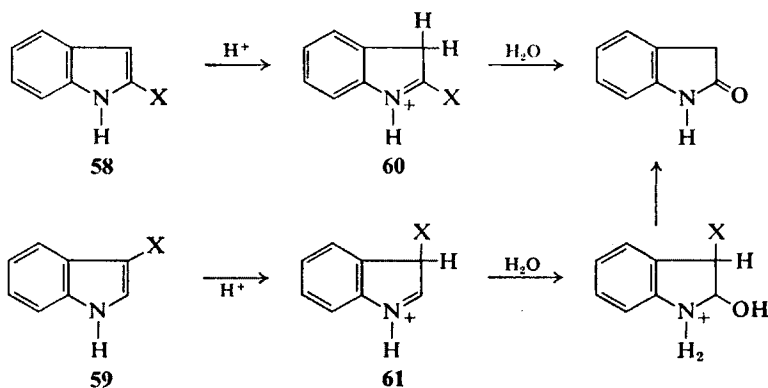
Benzene-ring-substituted haloindoles undergo a variety of displacement reactions. Concentrated ammonia converts 4- or 6-bromoindole-2-carboxylic acid into 4- or 6-aminoindole.³ Cuprous chloride converts bromoindoles into chloroindoles³ and cuprous cyanide converts bromo and iodoindoles into cyanoindoles.^{13, 17, 198}

The only reported substitution reaction with a pyrrole-ring-substituted haloindole is the reaction of 3-iodoindole with silver acetate⁹⁹ to give **57** (Eq. 20).



Oxindoles are formed upon acid hydrolysis of both 2- (**58**) and 3-haloindoles (**59**).^{131, 112, 92, 33} The mechanism of hydrolysis of 2-haloindoles probably involves initial protonation to give a haloindolenine **60** which reacts with water in a subsequent step. This is substantiated by the fact that 2,6-dibromo-3-methylindole is more stable to acidic hydrolysis than 2-bromo-3-methylindole due to the decreased basicity of the indole ring in the dibromide.^{33, 92} The mechanism of hydrolysis of 3-haloindoles probably involved protonation to give an immonium salt **61** which adds water and loses HCl to give oxindole¹³¹ (Scheme 10).

Haloindoles are stable to base hydrolysis. No reaction is obtained upon refluxing 2-bromo-3-methylindole in KOH and ethanol for 24 hr.³³ Likewise, treatment of 3-iodo-2-methylindole with moist silver oxide of alkali metal hydroxides results only in the recovery of the starting material.¹⁰⁷



Scheme 10

IV. Physical and Spectroscopic Properties of Haloindoles

Gas chromatography has been used to separate and identify 4-, 5-, and 6-bromoindole and 4-, 5-, 6-, and 7-chloroindole.²² Isomeric haloindoles are usually not separable easily. For example, the 5- and 6-bromo isomers of indole and of ethylindole 2-carboxylate could not be separated.⁸⁰ On the other hand, 4- and 6-chloro-2-methylindole obtained from a Fischer indolization of the *m*-chlorophenylhydrazone of acetone could be separated because of their different solubility properties in benzene–ligroin.¹⁴⁴

The uv spectra of 3-, 4-, 5-, 6-, and 7-chloroindole^{67, 83}; 3-, 4-, 5-, 6-, and 7-bromoindole; 3-iodo-2-methylindole, and several disubstituted indoles⁸³ have been measured. Introduction of the halogen on the benzene ring did not modify the indole uv spectra. Introduction of the halogen on the benzene ring had varying effects depending on the position and substituent.⁸³ The nuclear magnetic resonance (nmr) spectra can be utilized to distinguish 2- and 3-chloroindole because both the chemical shift and the coupling constant of the remaining carbon bound proton on the pyrrole ring are distinctive.¹³¹ The nmr spectrum of 3-bromoindole has been measured.⁷⁸

The *pK*'s of indole and several substituted indoles have been measured.¹⁹⁷ A fluorine or bromine substituent at the 4- or 5-position lowers the *pK* of the indole 0.6–0.8 *pK* units.

V. Organometallic Derivatives of Indoles

A. The Indole Grignard Reagent

Ten years after the discovery of alkylmagnesium halides by Grignard, Oddo¹⁷¹ found that indole and ethylmagnesium iodide reacted in diethyl

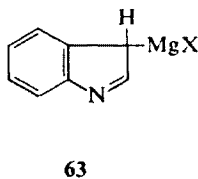
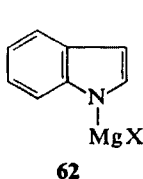
ether with the evolution of ethane to produce the indole Grignard reagent (indolylmagnesium iodide). This Grignard reagent undergoes many of the reactions characteristic of simple alkylmagnesium halides, such as carbonation, alkylation, and acylation. The products formed are substituted predominantly at the 3-position of the indole ring, although 1-substituted, 2-substituted, and 1,3-disubstituted products are often obtained. This selectivity in substitution reactions has led to the widespread use of the indole Grignard reagent in the synthesis of naturally occurring and pharmacologically important substances.¹⁷²

A comprehensive review of the chemistry of indole Grignard reagents by Heacock and Kasperek has recently appeared.¹⁷³ Two earlier abridged reviews of the chemistry of the indole Grignard reagent^{174, 175} and a listing of all the compounds prepared by reactions of the indole Grignard reagent prior to 1948¹⁷⁶ are available.

Indole Grignard reagents are prepared by the addition of a solution of the appropriate indole in diethyl ether or tetrahydrofuran (THF) to a preformed solution of 1 equiv of an alkyl magnesium halide (usually ethyl or methyl magnesium iodide). The extent of the reaction can be determined by measuring the volume of alkane that is evolved although it is generally assumed that the reaction proceeds to completion. At concentrations above 0.2 *M*, indolylmagnesium iodide is not soluble in diethylether and forms a viscous mass on the bottom of the reaction flask.¹⁶⁷ This Grignard reagent can be precipitated from ether solution as a pyridine complex.¹⁷¹ Other solvents have been employed. Usually the Grignard reagent is prepared in diethyl ether, a higher boiling solvent (such as anisole) is added, and the ether removed by distillation. This enables reactions to be carried out at higher temperatures. Indolyl magnesium iodide was reacted with a heterocyclic halide at high temperature in the absence of any solvent in at least one case.¹⁷²

1. Structure

The indole Grignard reagent has been variously formulated as a N-MgX (62) and a C-MgX species (63).^{179, 174, 180} Recent nmr investigations of the indole Grignard reagent have helped to clarify these structures.^{168, 177, 178, 196}

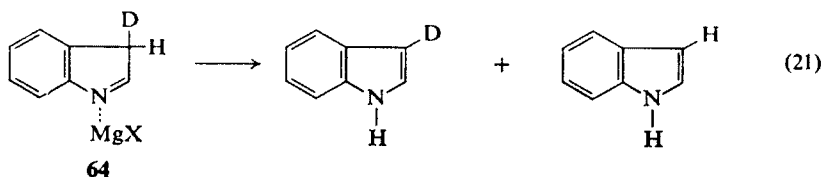


Upon formation of the Grignard reagent of indole and 2,5-dimethylindole in THF, Sebastian¹⁶⁸ observed that the 2- and 7-protons were shifted downfield while the 3-, 4-, 5-, and 6-protons were shifted upfield. The C-MgX formulation for the Grignard reagent was clearly excluded by these nmr investigations. In THF the Grignard reagent was concluded to contain a N—Mg bond with a high degree of ionic character.^{177, 168} The nmr shifts were explained on the basis of the charge differences between indole and its anion and to anisotropy effects arising from the lone pair of electrons in the nitrogen sp^2 orbital of the indolyl anion.^{168, 196} Infrared studies by Foti and Ruff support the N—Mg formulation.¹⁸³

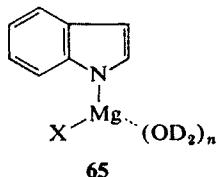
The high degree of similarity between the nmr spectra of the indole Grignard reagent and indolylsodium supported the earlier suggestion that the Grignard reagent was an essentially ionic resonance hybrid.^{181, 182} However, nmr exchange experiments indicated that indolylmagnesium bromide did not exchange with indole while the alkali metal salts rapidly exchanged.¹⁶⁸ Powers and coworkers have concluded on the basis of a study of the protonation behavior of the indole Grignard reagent and alkali metal derivatives of indole that the indole Grignard reagent must have considerably more covalent character (or must be a much tighter ion pair) in ether than the alkali metal salts.¹⁶⁷ In THF, a stronger base than ether, increased dissociation of the N—Mg bond occurs, with the result that the Grignard reagent behaves more like an alkali metal salt.

2. Protonation

The mechanism of protonation of the indole Grignard reagent as well as the alkali metal derivatives of indole has been studied by Powers and coworkers.¹⁶⁷ The indole Grignard reagents protonates either predominantly on nitrogen or on carbon, depending primarily on concentration and solvent effects. Addition of D_2O to indolylmagnesium iodide or water to the Grignard reagent of 3-deuteroindole yields an indolenine complex **64** which decomposes to a mixture of indole and 3-deuteroindole (Eq. 21). Before complete destruction of this complex, hydrogen exchange at the 3-position can occur. This is postulated to involve reformation of the indole Grignard reagent from the indolenine magnesium complex **64**.



The concentration of added D_2O has a profound effect on the amount of 3-protonation of the indole Grignard reagent in ether.¹⁶⁷ The results were explained by postulating that a Grignard- $(D_2O)_n$ complex **65** is initially



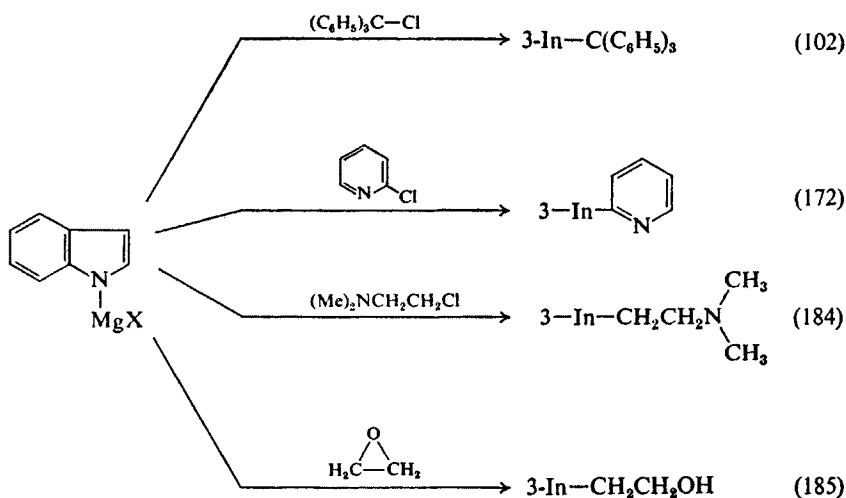
formed and that protonation occurs in a subsequent step. When large amounts of D_2O were available, increased polarity of the reaction medium and the large number of D_2O molecules in the coordination sphere of Mg caused dissociation to a largely ionic indole anion which protonated on nitrogen as do the alkali metal derivatives of indole. Addition of intermediate amounts of D_2O yielded carbon protonation. This was explained by the fact that D_2O had only partially replaced ether in the coordination sphere of magnesium so that a covalent complex was retained which protonated primarily at the least hindered site, the 3-carbon. Addition of small amounts of D_2O yielded a complex which was stable under the reaction conditions and underwent *N*-protonation during the workup procedure. Addition of D_2O to the indole Grignard reagent in THF yielded nitrogen protonation irrespective of the concentration of D_2O . The Grignard reagent in THF was postulated to be more ionic in THF due to the increased basicity of THF (compared to ether) which filled the coordination sphere of the magnesium atom.

3. Alkylation

The methylation of indolylmagnesium iodide in THF with methyl iodide has been recently studied by Sebastian.¹⁶⁸ He found that 3-methylindole was the only product obtained in significant amounts when the reaction was carried out in THF or toluene. This is in contrast to earlier reports in the literature that a mixture of 1-methyl-, 3-methyl-, and 1,3-dimethylindole were obtained from this reaction.^{173, 174} The alkylation of the indole Grignard reagent with isoamyl bromide and allyl bromide has been studied recently by Casnati and Pochini.²⁰² In hexamethylphosphoric triamide (HMPT) the major product is the *N*-alkylindole. Carbon alkylation predominates in solvents such as THF, acetonitrile, and acetonitrile-HMPT. Alkylation of 3-alkylindole Grignard reagents yields 3,3-dialkylindolenines.^{173, 174} Occasionally other products are obtained. Reaction of the Grignard reagent of skatole with allyl iodide yields a mixture of 1-allyl-3-methylindole, 2-allyl-3-methylindole, and 3-allyl-3-methylindolenine, the indolenine being the major

product.¹⁵³ However, when the alkylating agent is 3,3-dimethylallyl bromide or crotyl bromide, only 1- and 2-allylic products are obtained. Nitroethylene reacts with 3-methylindolyl magnesium iodide to yield only a 1-(2-nitroethyl) derivative.⁸⁹

In general, the indole Grignard reagent has been found to react with a wide variety of alkylating agents to produce 3-substituted indoles in excellent yield. This selectivity has found wide application in the synthesis of indoles containing a variety of functional groups and of natural products. The examples given in Scheme 11 illustrate some of the applications.



Scheme 11

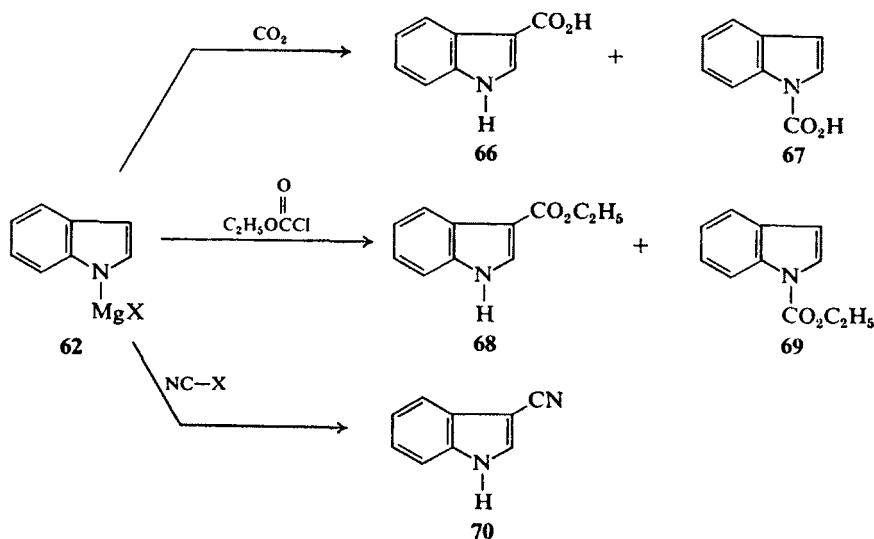
4. Other Reactions

Indole Grignard reagents react with a variety of compounds to yield indole containing diverse functional groups. This section will not attempt to discuss all the reactions that have been reported for the indole Grignard reagent but will attempt to give the reader an impression of the diversity of compounds that can be prepared. For further examples the reader is referred to the comprehensive review of indole Grignard reagent reactions¹⁷³ or to the chapter which deals with indoles containing specific functional groupings.

Indolylmagnesium iodide (**62**; $\text{X} = \text{I}$) reacts with CO_2 to give a mixture of the 3-substituted (**66**) and the 1-substituted indole carboxylic acid (**67**) in approximately equivalent amounts.¹⁸⁶ The reaction of ethyl chloroformate with the indole Grignard reagent follows a similar course; the 3-substituted

(68) and 1-substituted products (69) are obtained in nearly equivalent amounts along with a small amount of disubstituted product.¹⁸⁷ Other acyl indoles can be prepared by reaction of the Grignard reagent with the appropriate acyl halide, anhydride, or ester. In many cases excellent yields of 3-substituted products are obtained.

It would appear that 3-acylindoles are obtained in excellent yields by reaction of Grignard reagents with acyl halides while the reaction with esters often produces only 1-substituted indoles. Cyanogen halides react with indolyl magnesium halides to afford 3-cyanoindoles (70) (Scheme 12).



Scheme 12

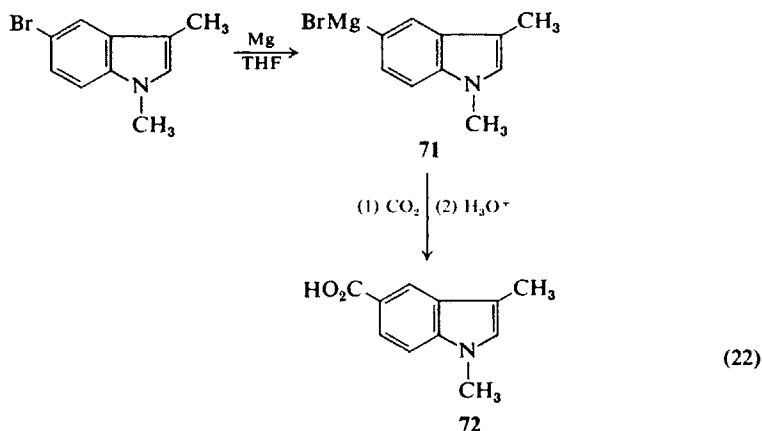
Nitriles themselves are usually unreactive and this allows the preparation of compounds such as 3-indolylacetonitrile by the reaction of the Grignard reagent with a haloacetonitrile. In a few cases nitriles have been reacted to produce indolyl ketones.¹⁷² Indolyl magnesium bromide reacts with phenyl isocyanate and phenyl isothiocyanate to afford only the 1-substituted urea or thiourea.¹⁸⁹

Carbonyl compounds react with the indole Grignard reagent to yield a variety of products. The major reaction product from aldehydes and ketones are diindolylmethanes. However, numerous other products have been reported. Benzaldehyde yields 3-benzoylindole, diindolylphenylmethane, and several as yet unidentified products.¹⁸⁸ Reaction of indolylmagnesium bromide with 2-pyridinecarboxaldehyde yields the corresponding carbinol. Ketones yield either the carbinol or the diindolylmethane depending upon conditions.

Oxidation of indolylmagnesium bromide with *p*-nitroperbenzoic acid affords an excellent yield of 3-bromoindole.^{6, 199} 2-Bromo-3-methylindole and 3-bromo-2-methylindole can be similarly obtained from skatole and 2-methylindole. Diiodoacetylene iodinate the indole Grignard reagent, and 3-iodoindole is obtained in 83% yield.⁵⁰ Indolylmagnesium bromide reacts with sulfur and a variety of sulfur compounds to produce diindolylsulfide.^{180, 173}

5. Benzene Ring Indolyl Grignard Reagents

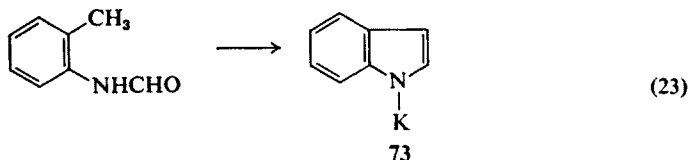
Only two examples have been reported where indole Grignard reagents have been prepared from the corresponding halide. In both instances the indole nitrogen was substituted. Plieninger and his coworkers reacted 1-benzyl-4-bromoindole with methylmagnesium iodide to produce the 4-indolyl Grignard reagent. Treatment of this with carbon dioxide followed by acid hydrolysis yielded 1-benzylindole-4-carboxylic acid.³ Noland and Reich have prepared a Grignard reagent (**71**) from 5-bromo-1,3-dimethylindole.²⁹ Reaction of this with oxygen gave a low yield of 5-hydroxy-1,3-dimethylindole and reaction with carbon dioxide gave the indole 5-carboxylic acid **72** (Eq. 22).



B. Alkali Metal Salts

The lithium, sodium, potassium, and silver salts of indole have been prepared. In addition, the alkali metal salts of many substituted indoles have been described. These salts are typically prepared by addition of the indole to a solution or a suspension of a strong base in solvents such as liquid

ammonia, benzene, dimethylsulfoxide, or other inert organic solvents. The bases that are typically used are *n*-butyllithium,¹⁶⁷ lithium hydride,¹⁶⁸ sodium,^{148, 154, 156, 157} sodium hydride,^{167, 168, 159, 165} sodium amide,^{158, 100, 155, 156, 152, 157} potassium,^{146, 168, 165, 147, 90} potassium amide,¹⁵⁸ and silver amide.¹⁶⁵ The potassium salt of indole (73) can also be prepared by heating *o*-methylformanilide with KOH in a nonpolar solvent while removing the water as formed⁴³ (Eq. 23).



The alkali metal salts of indoles have generally been regarded as having N—metal structures. This has been recently confirmed by nmr studies.¹⁶⁸ Sebastian has prepared and measured the nmr spectra of the lithium, sodium, and potassium salts of indole and 2,5-dimethylindole. The 2- and 7-protons of the indole ring are shifted downfield on salt formation, while the 3-, 4-, 5-, and 6-protons are shifted upfield the spectra of all the indole salts are very similar. The N—H proton of indole undergoes rapid exchange with indolyl-sodium, indolyllithium, or indolylpotassium in THF in contrast to the Grignard reagent which does not exchange. This indicates that the alkali metal salts of indole are less associated or have less covalent bonding than the Grignard reagent.

The alkali metal salts of indoles react predominately at nitrogen although there are some exceptions. Hydrolysis of indolylsodium or indolyllithium with deuterium oxide or reaction of the sodium salts of 3-deuteroindole with water yields indole which has undergone 3–8% exchange at the 3-position. This indicates protonation predominates on the nitrogen.¹⁶⁷

Alkylation of the alkali metal salts of indoles yields mixtures of 1-alkyl- and 3-alkylindoles accompanied by small amounts of dialkylated products. Sebastian has studied the reaction of indolyl-metal salts with methyl iodide in THF, diethylether, and toluene and obtained the results listed in Table I.¹⁶⁸

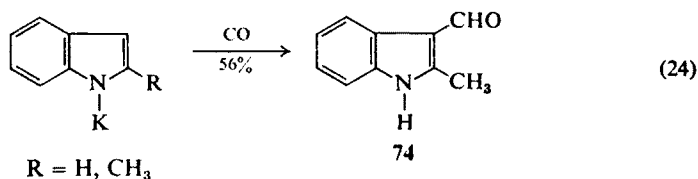
The reaction of indolylsodium with benzyl chloride in polar solvents gives 1-benzylindole.¹⁵⁴ In nonpolar solvents the reaction of indolylsodium with either trityl chloride or benzyl chloride yields the 3-alkylated indole.¹⁰¹ Alkylation of 2,3-dimethylindolylsodium with alkyl halides such as methyl iodide yields mainly 1-alkylated product^{155, 100}; reaction with benzyl chloride or allyl chloride in toluene yields only the 3-alkylated product.¹⁰⁰ The distribution of products upon reaction of indolylsodium with various alkylating agents¹⁴⁸ and a study on the alkylation of the alkali metal salts of indole have been reported.¹⁶⁹

TABLE I.

Cation	Solvent	Relative % methylindole	
		1-Isomer	3-Isomer
Li	THF	56	44
Na	THF	88	12
K	THF	97	3
Na	Ether	65	35
Li	Toluene	13	87
Na	Toluene	40	60
K	Toluene	87	13

The results obtained upon alkylation of the alkali metals salts of indole have been explained on the basis of the degree of dissociation of the metal salt and of the S_N1 character of the alkylating agent.^{168, 169, 148} The dissociated species gave 1-alkylated products (reaction at the most electronegative site; the nitrogen atom) while the associated salts yielded mostly 3-substituted indoles (reaction at the least hindered site; the 3-carbon). Thus, factors that increase the ability of these organometallic indole derivatives to dissociate, such as an increase in solvent polarity, increasing homogeneity of the reaction mixture, and increasing electropositive character of the metal ion, tend to produce more *N*-alkylation.¹⁶⁸ Alkylating agents that are characterized by ready S_N1 reactions (benzyl and allyl halides) yield greater percentage reaction (in some cases predominate) at the less electronegative site (the 3-carbon atom) than normal alkyl halides, all other factors being the same.¹⁴⁸

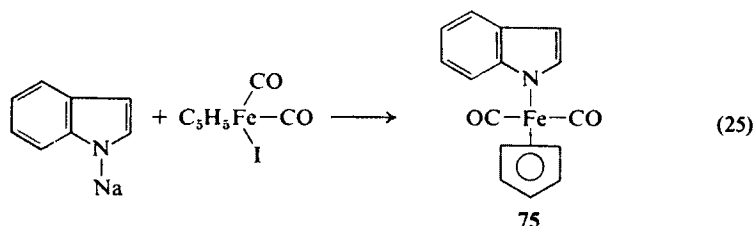
The potassium salt of the indole and of 2-methylindole are carbonylated at the 3-position to give the indole 3-carboxyaldehydes^{60, 90} **74** (Eq. 24). No 1-acylated product was reported.



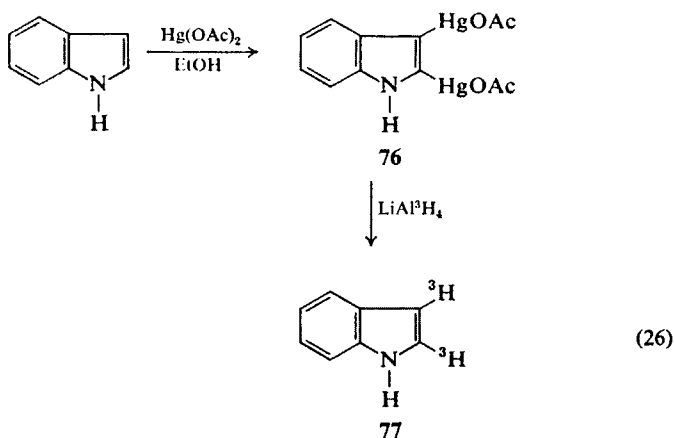
C. Other Organometallic Derivatives of Indole

Numerous metal salts of indoles have been reported, but little evidence for structure and practically no chemistry is available for most of these compounds. Salts of indole with titanium tetrachloride, stannous chloride, and

aluminum chloride have been prepared.¹⁶⁶ Calcium,¹⁶⁵ zinc,¹⁶⁷ phosphorus,¹³¹ and arsenic¹⁷⁰ derivatives of indoles have been reported. The indole Grignard reagent reacts with potassium tetrafluoroborate to give a boron derivative of indole.¹⁶³ The potassium salt of 2-methylindole reacts with pentacarbonyl-bromomanganese to give tricarbonyl- π (2-methylindolyl)manganese,¹⁴⁷ and dicarbonylcyclopentadienyliodoiron undergoes the following reaction with indolylsodium in benzene¹⁴⁶ to give **75** (Eq. 25).

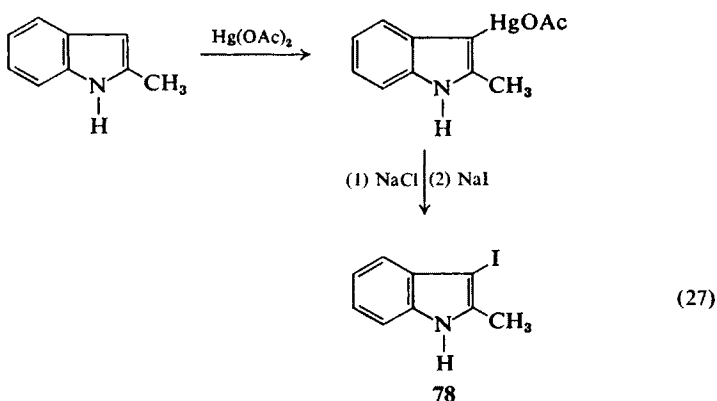


The mercury salts of indole are the only organometallic derivatives beside the Grignard reagent and the alkali metal salts that have had any synthetic utility. Indoles react with mercuric chloride¹⁰⁶ and mercuric acetate^{107, 164, 192} to yield mercury salts. Mingoia¹⁰⁷ discovered that mercuric acetate converts indole into 2,3-diacetoxymercuryindole and skatole, and 2-methylindole into monoacetoxymercury derivatives. Ramachandran and Witkop¹⁹² reinvestigated this reaction and confirmed the earlier observations. The 2,3-diacetoxymercury derivative **76** was obtained by reaction of indole with 2 equiv of mercuric acetate in ethanol. The structure was substantiated by its nmr spectrum and conversion to 2,3-ditritioindole (**77**) upon reduction with lithium aluminum tritide (Eq. 26).



Indole reacted with excess mercuric acetate to yield a 1,2,3-triacetoxy-mercury derivative, while 2,3-dimethylindole, 2,3-diphenylindole, and 1-methyl-2-acetylindole yielded insoluble products. *N*-Acetyltryptophanamide yielded three uncharacterized products and indole 3-propionic acid gave a 1,2-diacetoxymercury derivative. This diacetoxymercury derivative or the one derived from indole could be reconverted to the starting indole by passage through a Dowex 50X8 (H^+ form) or by treatment with hydrogen sulfide or thiolacetic acid in acetic acid.

Mingoia reported that the acetoxymercury derivatives of indoles could be converted into chloromercury derivatives by reaction with sodium chloride, these in turn yielded iodoindoles upon treatment with sodium iodide. The authenticity of most of these iodoindoles is in doubt, however, because of the unusually high melting point of the products except for 3-iodo-2-methylindole (**78**) which has a melting point identical with material prepared by direct iodination¹⁰⁷ (Eq. 27).



An effort by Lawson and Witkop to substantiate some of these reactions was reported to have failed.¹⁹² It would appear that a reinvestigation of the preparative values of these derivatives would be warranted.

VI. Tables of Haloindoles and Indole Organometallic Derivatives

The compounds are listed in the tables in order of increasing number of substituents; the indoles with no substituents appearing first. Within each group, the compounds are listed according to the position of the halogen on the indole ring.

TABLE I. Fluoroindoles

Compound	Starting Material	Yield (%)	mp (°C)	Ref.
4-F	2-Fluoro-6-nitrotoluene	20-25	29	77
			30	56
		—	—	195
5-F	3-Fluorotoluene	29	46-47	37
		46	44	139
	<i>p</i> -Fluorophenylhydrazone of ethyl pyruvate		46	56
	5-Fluoro-2-nitrotoluene ^a		46	88
		—	—	195
	Indoline	13	45-46	75
	<i>p</i> -Fluorophenylhydrazine ^b		46	93
6-F	4-Fluoro-2-nitrotoluene		75	96
	1,4-Difluoro-2-nitrobenzene		58-70	96
	4-Fluoro-2-nitrotoluene		73	18
	4-Fluoro-2-nitrotoluene ^a		75-76	36
	Indoline	27	74.5-75.5	75
	<i>m</i> -Fluorophenylhydrazone of ethyl pyruvate		75, picrate 147-148	56
	4-Fluoro-2-nitrotoluene ^a			56
			73	73
			72	88
			—	195
7-F	<i>o</i> -Fluorophenylhydrazone of ethyl pyruvate		61-62, picrate 154-155	56
5-F-2-CH ₃	<i>p</i> -Fluoroaniline + allyl chloride		112-120 (0.1 mm); 99-101	31
	Propionaldehyde- <i>p</i> -fluorophenylhydrazone ^c	41	102	93
	<i>p</i> -Fluorophenylhydrazone of acetone ^c	43	102	110
5-F-3-CH ₃			86	93
5-F-2,3-diCH ₃	<i>p</i> -Fluorophenylhydrazone of methyl ethyl ketone	60	102-103	93
			98	140
5-F-1-benzyl	5-Fluoroindole		61-62	95
5-F-2,2-di-(4-CH ₃ OC ₆ H ₄) ^b				10
7-F-2,3-di-(4-CH ₃ OC ₆ H ₄) ^b				10
6-CF ₃	2-Chloro-5-trifluoromethyl-nitrobenzene		109-110	103
4,5,6,7-Tetrafluoro-indole	—		92.5-93	42
	—		93-93.5	118

^a The Reissert procedure was used to form the listed indolic product.^b The Fischer indole synthesis was used to form the listed indolic product.^c Cyclization catalyzed by ZnCl₂.

TABLE II. Monochloroindoles

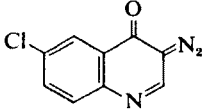
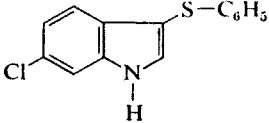
Compound	Starting material	Method of synthesis	Yield (%)	mp (°C)	Ref.
1-Cl	Indole	Cl ₂ O, CHCl ₃ , 20–25°, 1 hr	90	—	7
2-Cl	Oxindole	POCl ₃	—	72–76	131
3-Cl	1-Benzoylindole	—	—	94–95	112
		—	—	95.5–96	83
		—	—	91.5	132
	Tryptophan	<i>Pseudomonas auero Faciens</i>	—	—	201
4-Cl	4-Chloroindole-2- carboxylic acid	Heat 1 hr above mp	—	bp 129–130 (4 mm), picrate 192–193	83
		Heat 1 hr above mp	—	bp 130 (11 mm), picrate 175–176	1
	2-Chloro-6-nitro- toluene	Reissert synthesis	—	bp 143 (10 mm), picrate 171–173	61, 62
		—	—	bp 106–108 (0.6 mm)	59, 94
		—	—	bp 127 (5 mm)	5
	4-Bromoindole	Cuprous chloride	—	Colorless oil	3
5-Cl		Irradiation and decarboxylation	—	69	47
	5-Chloroindole-2- carboxylic acid	—	—	71.5–72.5, picrate 146.5– 147.5	16 83
	Ethyl pyruvate <i>p</i> - chlorophenyl- hydrazone	—	—	71–72, picrate 147	59, 94
6-Cl	Indoline	Chlorination	22	69–70	75
		Raney nickel	—	78	20

TABLE II (Contd.)

Compound	Starting material	Method of synthesis	Yield (%)	mp (°C)	Ref.
6-Cl	6-Bromoindole	Cuprous chloride		78-80	3
	6-Chloroindole-3-carboxylic acid	Heat		90	4
	2-Nitro-4-chlorobenzaldehyde	—		89.0-89.5, picrate 142.5-143.5	19
	4-Chloro-2-nitrotoluene	Reissert synthesis		86-87, picrate 143-144	59, 94
	6-Chloroindole-2-carboxylic acid	—	74	83-86	62
				88.8-89, picrate 142-143	83
	Indoline	—	26	89-90	75
7-Cl	<i>o</i> -Chlorophenylhydrazone of pyruvic acid	—		57-58, picrate 154-155	59, 94
	7-Chloroindole-2-carboxylic acid	—		58-58.5, picrate 156.5-157.5	83

TABLE III. Substituted Monochloroindoles

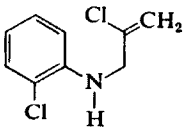
Compound	Starting material	mp (°C)	Ref.
2-Cl-2-methyl	—	113.5, picrate 121–122	83
3-Cl-2-methyl	—	98, picrate 139	83
4-Cl-2-methyl	Acetone <i>m</i> -chlorophenyl- hydrazone	97–98	131
	2-Nitro-6-chlorophenyl acetic acid		144
4-Cl-3-methyl	4-Chloro-3-indolylacetic acid	39, picrate 182	1
5-Cl-2-methyl	<i>p</i> -Chloroaniline + allyl chloride	114–116	31
	<i>p</i> -Chlorophenylhydrazine	117–119	34
			64
5-Cl-7-methyl	<i>p</i> -ClC ₆ H ₄ NHCH ₂ CCl=CH ₂	119	46
6-Cl-2-methyl	—	<i>bp</i> _{0.2} 138	200
	Acetone <i>m</i> -chlorophenyl- hydrazone	—	144
	2-Nitro-4-chlorophenylacetic acid	—	144
7-Cl-2-methyl			46
			
7-Cl-5-methyl	2-Chloro-4-methylaniline		8, 9
5-Cl-2,3-dimethyl	<i>p</i> -Chlorophenylhydrazine	143, picrate 132	52
		144–145	70
	Ethyl methyl ketone <i>p</i> - chlorophenylhydrazine	139–141	38
6-Cl-2,3-dimethyl	Ethyl methyl ketone <i>m</i> - chlorophenyl	166–167	38
7-Cl-2,3-dimethyl	Ethyl methyl ketone <i>o</i> - chlorophenylhydrazine	69–70.5	97
5-Cl-3-ethyl-2-methyl	—	76, picrate 155	52
7-Cl-2,3-tetramethylene	—	56	63
5-Cl-2-methyl-3-propyl	<i>p</i> -chloroaniline + allyl chloride	picrate 135–136	31

TABLE III (Contd.)

Compound	Starting material	mp (°C)	Ref.
5-Cl-2-methyl-3-propyl	—	62, picrate 137	52
5-Cl-2-methyl-3-isopropyl	—	63, picrate 166	52
5-Cl-2-phenyl	<i>p</i> -Chloroaniline	195	25
	Phenacyl- <i>p</i> -chloroaniline	196–197	129
	<i>p</i> -Chloroaniline	191	57
		—	76
6-Cl (or 4-Cl)-2-phenyl	<i>m</i> -Chloroaniline	181–182	141
7-Cl-2-phenyl	<i>o</i> -Chloroaniline	112	63, 76
7-Cl-2(<i>p</i> -chlorophenyl)	—	126	63, 87
2-Cl-1-benzyl	—	73.5–75.5	131
5-Cl-1-benzyl	5-Chloroindole	65–66	95
7-Cl-2(2-naphthyl)	—	111	63
4(6)-Cl-2,3-diphenyl	—	—	98
4-Cl-2,3-diphenyl	Deoxybenzoin <i>p</i> -chloro-phenylhydrazone	168–170	38
5-Cl-2,3-diphenyl	—	128–130	38
	—	—	98
7-Cl-2(<i>p</i> -biphenyl)	—	216.5	63
7-Cl-2,3-diphenyl	Deoxybenzoin <i>o</i> -chloro-phenylhydrazone	96–97	58
7-Cl-4-methyl-2,3-diphenyl	2-Chloro-5-methylaniline + benzoin	128	58
Di(5-chloroindolyl)methane	—	—	143
Di(6-chloroindolyl)methane	—	—	143
Di(5-chloro-2-methyl-indolyl)methane	—	234	53
5-Chloro-2-methyl-indolyl(2-methyl-indolyl)methane	—	180–181	53

TABLE IV. Polychloroindoles

Compound	Starting material	mp (°C)	Ref.
2,3-diCl	Oxindole	103–104	133
	—	103–104, picrate 102–104	83
	Indole	103–104	132
4,6-diCl	4,6-Dichloroindole 2-carboxylic acid	bp 130–132 (4 mm), pic- rate 125–126	83
4,7-diCl	4,7-Dichloroindole 2-carboxylic acid	bp 119–121 (6 mm), pic- rate 127–128	83
5,7-diCl	5,7-Dichloroindole 2-carboxylic acid	58–58.5, picrate 126.5	83
2,3-diCl-CH ₃	2,3-Dichloroindole	58–59	133
5,7-diCl-2-CH ₃	Acetone 2,4-dichlorophenylhydrazone	61	111
		66.5	85
	Acetone 2,6-dichlorophenylhydrazone	66.5	85
4,7-diCl-2,3- (CH ₃) ₂	Methyl ethyl ketone 2,5-dichlorophenyl- hydrazone	90–91	97
5,7-diCl-2,3- (CH ₂) ₄		68	85
4,6-diCl-2-C ₆ H ₅	Acetophenone 3,5-dichlorophenylhydrazone	115	85
4,7-diCl-2-C ₆ H ₅	Acetophenone 2,5-dichlorophenylhydrazone	106	85
5,7-diCl-2-C ₆ H ₅	—	138–139	63
	Acetophenone 2,4-dichlorophenylhydrazone	142	85
	Acetophenone 2,6-dichlorophenylhydrazone	144	55
5,7-diCl-2- (4-ClC ₆ H ₄)		166	85, 87
5,7-diCl-2-(4- C ₆ H ₅ C ₆ H ₄)		214	63, 85

TABLE V. Monobromoindoles

Indole	Starting material	Method of synthesis	Yield (%)	mp (°C)	Ref.
3-Br	1-Benzoylindole	Bromine	77	67	112
		NBS	—	—	125
	Indole	—	—	66-67	83
	Indole	Pyridinium bromide perbromide in pyridine	64	65-66	79
	Indolyl magnesium bromide	Oxidation		65-67	6, 199
	Indole	Dioxane dibromide, 0°			44
		Dioxane dibromide	60	67	49
		Trimethylphenylammonium perbromide	—	66	199
3-Br-1-D	3-Bromoindole	D ₂ O	80	65-66	78
4-Br	6-Bromo-2-nitrotoluene	Several steps		Yellow oil	3
	4-Bromoindole 2-carboxylic acid	Copper bromide, quinoline heat	55	115-118 (3 mm), picrate 184-185	83

5-Br	5-Bromo-2-nitrotoluene Ethyl pyruvate <i>p</i> -bromophenyl- hydrazone Indole	Reisert synthesis	—	85.5-86	91
		—	—	85-86	68
		Via 1-acetylindoline-2-sulfonic acid sodium salt	—	90-91	15
		Bromination and dehydrogenation	—	92-93	28
	Ethyl pyruvate <i>p</i> -bromophenyl- hydrazone	—	—	83	81
	5-Bromoindole 2-carboxylic acid	Copper bromide, quinoline heat	60	90.5-91, picrate 137-138	83
6-Br	4-Bromo-2-nitrotoluene 6-Bromoindole 2-carboxylic acid	Several steps Copper bromide, quinoline heat	— 60	94 93.5-94, picrate 138-139	3 83
7-Br	Ethyl pyruvate <i>o</i> -phenyl- hydrazone 3-Bromo-2-nitrotoluene 7-Bromoindole 2-carboxylic acid	Fischer indole synthesis Reisert synthesis Copper bromide, quinoline heat	— 60	42-43 41.5-42, picrate 150.5-152	80 80 83

TABLE VI. Substituted Bromoindoles

Compound	Starting material	Method of synthesis	Yield (%)	mp (°C)	Ref.
2-Br-3-CH ₃	Skatole Grignard reagent	Oxidation	—	—	6, 199
	Skatole	NBS, acetic acid	45	88-89	33
2-Br-3- <i>n</i> -C ₃ H ₇	Skatole	Bromine, ether	70	88-90	120
3-Br-2-CH ₃	3- <i>n</i> -Propylindole	NBS, acetic acid	25	Oil	33
	2-Methylindolylmagnesium bromide	Oxidation	—	86-87	6, 199
	2-Methylindole	NBS, acetic acid	50	90-91	33
		Dioxane dibromide	—	—	44
3-Br-1,2-(CH ₃) ₂	1,2-Dimethylindole	NBS, acetic acid	—	86-87	49
4-Br-1-CH ₂ C ₆ H ₅	—	—	64	73-74	33
4-Br-1-CH ₂ C ₆ H ₅	4-Bromoindole	Alkylation	—	68	3
4-Br-1-CH ₃	2-Nitro-6-bromophenyl acetic acid	—	60	—	48
4-Br-COCH ₃ -2,3-(C ₆ H ₅) ₂					144
5-Br-1-CH ₃	<i>p</i> -BrC ₆ H ₄ NNH ₂ CH ₃	Fischer indole	—	223-225 42-43	116 13
	5-Bromoindole	Methylation of sodium salt	32	bp 148 (5 mm)	29
	1-Methylindoline	Bromination and dehydration	—	bp 147-148 (4 mm), pic- rate 88.5-90	69
5-Br-2-CH ₃	2-Methylindoline			bp 155-164 (4 mm), pic- rate 97-98	28
	<i>p</i> -Bromophenylhydrazine	Fischer indole	—	93-96	64, 29
			45	104-105	34, 29

5-Br-3-CH ₃	5-Bromoindole	Formylation, reduction	—	93-96	51, 29
5-Br-7-CH ₃	Ethyl pyruvate 2-methyl-4-bromophenylhydrazone	—	—	103-104	93
5-Br-1-CH ₂ C ₆ H ₅	5-Bromoindole	—	—	79.5-80.5	29
5-Br-1,3(CH ₃) ₂	5-Br-3-methyl	Alkylation of the sodium salt	64	b _{0.1} 165	200
5-Br-2,3-(CH ₃) ₂	—	Methylation of sodium salt	66	88-89	95
5-Br-2,3-(CH ₃) ₂	—	—	76	87-88	29
5-Br-2,3-(C ₆ H ₅) ₂	—	—	—	bp 148 (1.5 mm)	29
5-Br-2,3-(C ₆ H ₅) ₂	—	Fischer indole	—	138, picrate	52
5-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	147	70
5-Br-2-CH ₃ -3-C ₂ H ₅	—	—	75	142-143	126
5-Br-2-CH ₃ - <i>n</i> -C ₃ H ₇	—	—	—	138	116
5-Br-2-CH ₃ -3- <i>i</i> -C ₄ H ₇	—	—	—	148	116
6-Br-2-CH ₃	2-Nitro-4-bromophenyl acetic acid	—	N-Acetyl derivative	218	116
6- ⁸² Br-2-C ₆ H ₅	—	—	—	141	52
6-Br-2,3-dimethyl-indole	—	—	—	63, picrate	52
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	116	52
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	53, picrate	52
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	135	52
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	55, picrate	52
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	162	144
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	188	2
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	146	126
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	147	92
6-Br-2-C ₆ H ₅ -3-CH ₃	—	—	—	147	116

TABLE VI (Contd.)

Compound	Starting material	Method of synthesis	Yield (%)	mp (°C)	Ref.
6-Br-2,3-diphenyl- indole	—	1-Benzoyl derivative 1-Acetyl derivative	— —	116-117 174-176 141-142	116, 117 116 116, 117
7-Br-5-CH ₃	Ethyl pyruvate 2-bromo- 4-methylphenylhydrazone	—	—	<i>b_o</i> , 120-125	200
7-Br-2-C ₆ H ₅	—	Fischer indole	38	117-118	86
2,6-diBr-3-CH ₃	2-Br-3-methylindole	NBS, acetic acid	48	99-101	33
	Skatole	N-Bromophthalimide	—	100	92
			—	100-102	142
5,6-diBr	—	—	—	—	109
5,7-diBr-2-C ₆ H ₅	—	Fischer	44	148.5-149.5	86
2,3,5,6-tetraBr	—	—	—	149-151	104
2,6-diBr-3- <i>n</i> -C ₃ H ₇	3- <i>n</i> -Propylindole	NBS, acetic acid	—	Oil	33
Di (4-bromoindolyl)- methane	—	—	—	—	143
Di (5-bromoindolyl)- methane	—	—	—	—	143
Di (6-bromoindolyl)- methane	—	—	—	—	143

TABLE VII. Iodoindoles

Indole	Starting material	Method of synthesis	Yield (%)	mp (°C)	Ref.
3-I	Indole	KI-iodine	—	—	99
	1-Benzoylindole	—	—	72	112
	Indole	ICl-dioxane in pyridine	—	75	49
		Iodine, KOH, or NaHCO ₃	—	72, picrate 90	113
4-I		Iodine-KI in KOH-water	—	72	114
		Reaction of Grignard reagent with IC≡CI	83	72	50
		Peroxidase and 4-iodo-2,6-dimethylamine	7	71-72	82
	2-Iodo-6-nitrotoluene	Reissert synthesis	—	90, picrate 172	54
5-I	5-Iodo-2-nitrotoluene	Reissert synthesis	—	99	41
	5-Nitroindole	Sandmeyer reaction on the <i>N</i> -acetyl derivative	20	99-102	32
	Indole	Via sodium 1-acetylindoline-2-sulfonate	—	99-100	17, 15

TABLE VII (Contd.)

Indole	Starting material	Method of synthesis	Yield(%)	mp (°C)	Ref.
2-I-3-CH ₃ 3-I-2-CH ₃	Skatole 2-Methylindole	Via diacetoxymercuri salt ICI-dioxane in pyridine Iodination with 1,3-diiodo-5,5-dimethylhydantoin	— — 93	197-198 81.5 83-84	107 49 30
		—	—	84, picrate 108-109	83
		—	—	82, picrate 107	113
		Iodine-NaHCO ₃	100	82	115
		Via diacetoxymercuri salt	—	82	107
		Via diaetoxymercuri Salt	—	220	107
2,3-diI 2-(<i>o</i> -Iodophenyl)-3- iodoindole	Indole 2-(<i>o</i> -Iodophenyl)indole	ICI	76	127	35
Di(5-iodoindolyl)- methane	—	—	—	—	143

TABLE VIII. Indoles Substituted with Two Different Halogens

Compound	Starting material	mp (°C)	Ref.
5-Br-7-Cl-2-C ₆ H ₅	Acetophenone 4-bromo-2-chlorophenyl-hydrazone	139–139.5	86
5-Cl-7-Br-2-C ₆ H ₅	Acetophenone 2-bromo-4-chlorophenyl-hydrazone	143–143.5	86

TABLE IX. Haloindolines

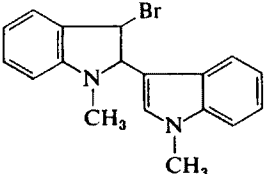
Compound	Starting material	mp (°C)	Ref.
5-F-2-methyl	<i>p</i> -Fluoroaniline and allyl chloride	—	31
5-Br	Indoline	—	28
5-Br-1-CH ₃	1-Methylindoline	Picrate 151–152.5	69
	5-Benzamido-1-methylindoline	Picrate 147–148	69
5-Br-2-CH ₃	2-Methylindoline	—	28
6-Br-2,3-(CH ₃) ₂	2,3-Dimethylindoline	—	126
	—	235–240	12

TABLE X. Haloindolenines

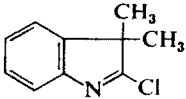
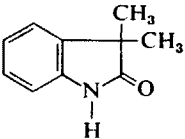
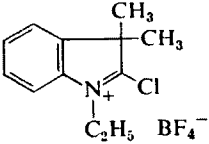
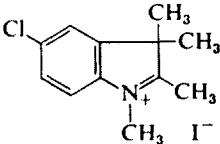
Compound	Starting material	Ref.
	 and POCl ₃ or PCl ₅	65, 74, 27
		65
		70

TABLE XI. Side-Chain Halogenated Indoles and Indolenines

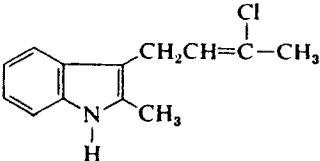
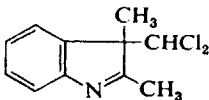
Compound	mp (°C)	Ref.
2-Bromomethyl-1-acetyl-3-methylindole	92-94	116
1-(1,1,2-Trifluoro-2-chloroethyl)indole	bp 78-79 (2 mm)	84, 71
1-(1,1,2,2-Tetrafluoroethyl)indole	bp 83 (10 mm)	71
3-(2-Chloroethyl)indole	80, bp 140 (3 mm)	45
3-(2-Chloroethyl)-2-(<i>p</i> -chlorophenyl)indole	—	137
3-(2-Chloroethyl)-2-(<i>p</i> -bromophenyl)indole	—	137
3-(2-Bromoethyl)indole	98-99	108
	98.5-99	72
3-(2-Bromoethyl)-2-methylindole	58	66
	—	108
3-(2-Bromo-1-methylethyl)-1-benzyl-2-methylindole	89	23
3-(2-Bromopropyl)indole	—	24
3-(3-Bromopropyl)indole	Oil	14
3-(3-Bromopropyl)-2-phenylindole	—	137
	57-58	11
	—	122, 123

TABLE XII. Indole Grignard Reagents^a (N—MgX)

Starting indole	Ref.
Indole	—
2-Methylindole	151, 150, 149
3-Methylindole	152, 151, 150, 149, 89
2,3-Dimethylindole	150, 155
3-Allylindole	152
2-Phenylindole	160
2-Benzylindole	160
2-Methyl-3-benzylindole	150, 151
3-Bromoindole	112
4,5,6,7-Tetrafluoroindole	118
5,6-Dimethoxyindole	89
5-Methoxy-2-phenylindole	160
5-Benzoyloxyindole	89
2-(3-Indolyl)ethylamine	151, 150, 149
2-(2-Methyl-3-indolyl)ethylamine	151, 150, 149

^a This table should not be considered comprehensive since Grignard reagents of indoles are often used in synthetic sequences and are then not subsequently indexed in *Chemical Abstracts*.

TABLE XIII. Miscellaneous Magnesium Derivatives and Grignard Reagents

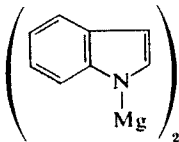
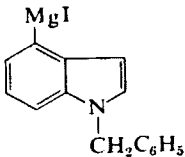
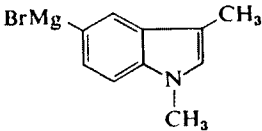
Compound	Starting material	Ref.
	Indole plus Mg in liquid ammonia	165
	Bromo compound plus methyl magnesium iodide	3
	Bromo compound plus Mg in THF	29

TABLE XIV. Alkali Metal Salts of Indoles

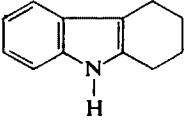
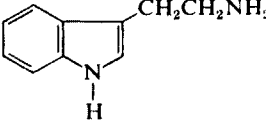
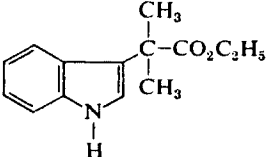
Starting indole	Base and solvent	Ref.
	<i>A. Lithium Salts</i>	
Indole	Butyllithium, ether-hexane	167
	Lithium hydride, THF	168
	<i>B. Sodium Salts</i>	
Indole	Sodium in $\text{NH}_3(\text{l})$	148, 154, 156, 157
	Sodium amide in $\text{NH}_3(\text{l})$	158, 152
	Sodium hydride in DMSO-benzene	167
	Sodium hydride	159, 165, 168
2-Methylindole	—	157
3-Methylindole	—	148
2,3-Dimethylindole	Sodium amide in $\text{NH}_3(\text{l})$	100, 155
4-Bromoindole	—	154
	Sodium amide in $\text{NH}_3(\text{l})$	156
	Sodium amide in $\text{NH}_3(\text{l})$	157
	—	157
	<i>C. Potassium Salts</i>	
Indole	Potassium in THF	146, 168
	Potassium or potassium amide in $\text{NH}_3(\text{l})$	165, 158
2-Methylindole	Potassium in benzene	147, 90
3-Methylindole	—	90
2-Phenylindole	—	90
2-(<i>p</i> -Tolyl)indole	—	90
2-(<i>p</i> -Methoxyphenyl)indole	—	90
	<i>D. Silver Salts</i>	
Indole	Silver amide in $\text{NH}_3(\text{l})$	165

TABLE XV. Group II Metal Derivatives of Indoles (Except Mg Derivatives)

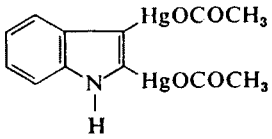
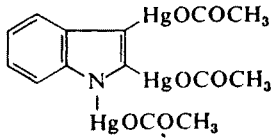
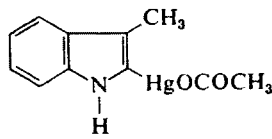
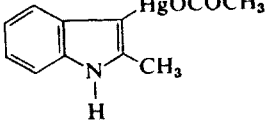
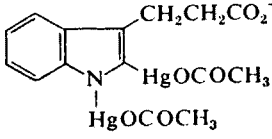
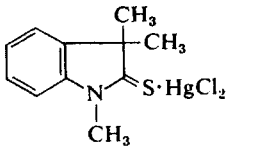
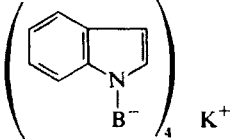
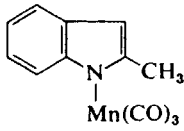
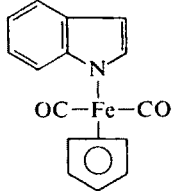
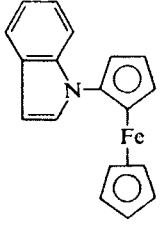
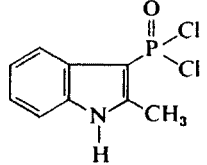
Starting indole	Base and solvent	Ref.
<i>A. Calcium Salts</i>		
Indole	Calcium in $\text{NH}_3(\text{l})$	165
<i>B. Zinc Salts</i>		
Indole	Grignard reagent + zinc chloride	167
<i>C. Mercury Salts</i>		
	—	107, 164, 192
	—	192
	—	107
	—	107
	Hg^{2+}	192
	—	193

TABLE XVI. Miscellaneous Organometallic
Derivatives of Indole

	Ref.
	163
$(C_8H_7N)AlBr_3$	166
$(C_8H_7N)_2TiCl_4$	166
$(C_8H_7N)_2SnCl_4$	166
	147
	146
	162
	131
$(3\text{-Indolyl})_3P$	191
$(1\text{-Indolyl})_3P$	191
$(3\text{-Indolyl})_3PO$	191

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CHAPTER VI

Chemistry of Indoles Carrying Basic Functions

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I. Introduction

The tremendous advances in indole chemistry during the last 15 years are illustrated by the fact that in Sumpter and Miller's monograph on indoles (published in 1954 in this series) the theme of the present chapter covers only 2 pages. The amount of competent work published in recent years in this field has necessitated a strictly systematic presentation. Having the option to arrange the subject either by types of reaction or types of structures, the second possibility was chosen (an exception is Section I on indole Mannich bases). Furthermore, it seemed appropriate for the sake of clarity to make a certain selection from the abundance of publications. Care was therefore taken to cover all the methods by referring to the original papers if possible and to supplement them by a few representative newer applications. Some of our own unpublished results have been included in the discussion. Structural modifications of the basic group by well-known methods, e.g., alkylation, acylation, reduction of amides and azomethines, are not covered in this treatise, unless they contribute substantially to the knowledge of indole chemistry. Papers on hydrogenated indole derivatives, e.g., indoline, have been taken into account only as far as they were considered of interest for indole chemistry (intermediates, by-products, etc.). Amino acid derivatives

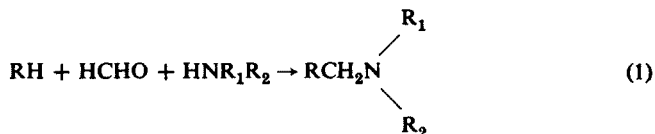
are mentioned only occasionally since they are treated systematically in another chapter.

I wish to thank my co-workers G. Bormann and F. Seemann for reviewing the manuscript, Dr. H. Ott for the revision of the English text, and Dr. H. Brunner and Dr. H. Niggli for their help in the preparation of the appendix of tables.

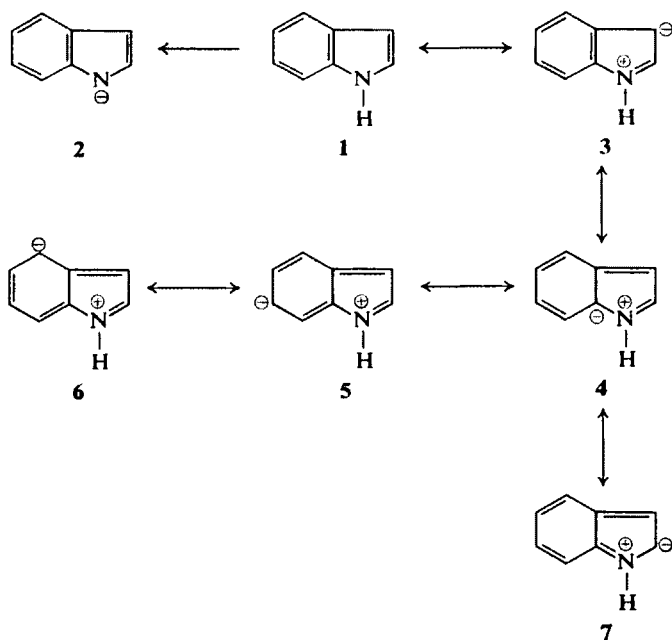
II. Mannich Bases of the Indole Series

A. General

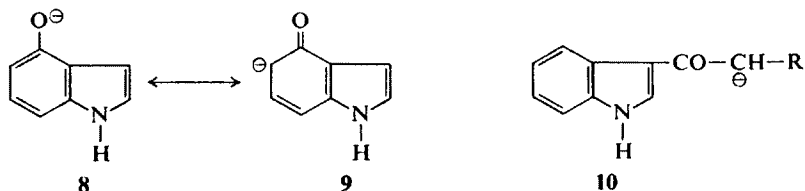
The Mannich reaction, a valuable method to substitute an acidic H of a



nucleophile by an aminomethyl group (Eq. 1) by mechanisms not yet completely clarified and which is discussed in detail by Hellmann and Opitz²²³ (see also Ref. 426a), is widely used for the preparation of basic indoles.



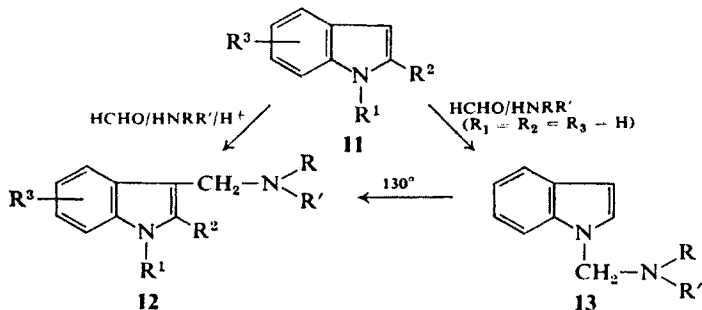
As outlined in Scheme 1, several resonance forms of indole with nucleophilic centers can be formulated either after loss of a proton or by participation of the unpaired electron. If the nucleus contains acidic substituents, especially phenolic groups, additional canonical forms, viz. **8-10**, are



possible. Owing to this structural versatility, indoles undergo the Mannich reaction in diverse manners which allow one to expect several series of reaction products.

B. Preparation of Mannich Bases of the Gramine Type* (see also the Addenda)

Reaction of **11** with formaldehyde and secondary amines in the presence of at least 1 mole of acid per mole of amine affords exclusively **12** carrying the basic side chain in position 3 (Scheme 2). Formaldehyde can be employed

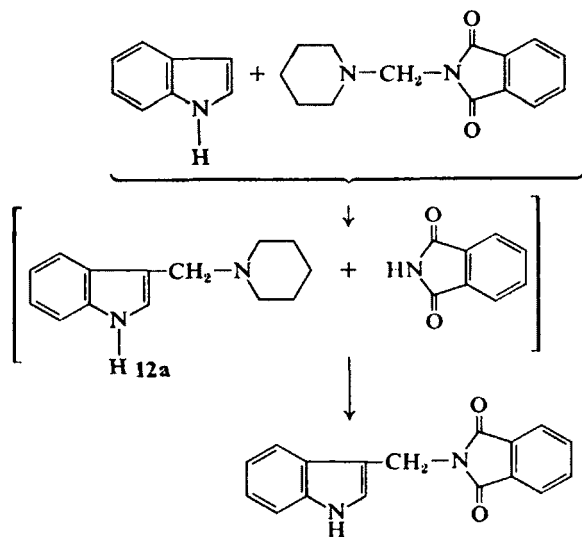


Scheme 2

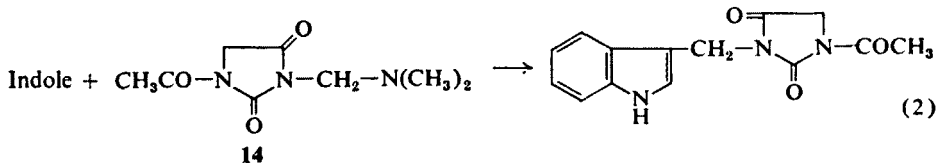
either as paraformaldehyde or as a solution in water or alcohols, with the amine as the free base or in the form of a salt, but generally as the hydrochloride. Useful solvents are water, dioxane, or alcohols, preferably isopropanol (in ethanol the reaction can fail⁵⁶⁷); in many cases acetic acid is preferred. The temperatures recommended are between 0 and 70°C. The optimal conditions vary with the type and position of substituents and have to be evaluated in each case.¹²⁹ Statements in the literature that certain

* Named after the alkaloid gramine (3-dimethylaminomethyl-indole) isolated from Swedish barley by Euler et al.¹³⁶⁻¹³⁹ and identical with the alkaloid donaxine from *Arundo donax*.³⁸⁵

Mannich bases could not be prepared should be treated with reservation. From the large number of papers upon this subject, a few are cited as representative.^{16, 39, 94, 121, 129, 181, 317, 351, 407, 445, 489, 509, 509, 519} This simple reaction, generally applicable to indoles unsubstituted in position 3, is superior to the older method for the preparation of gramine which consisted of the condensation of indolylmagnesium bromide with dimethylaminoacetonitrile (Wieland and Hsing⁶⁰³). The condensation of **11** with formaldehyde/secondary amine can take another course in the absence of acid: according to Swaminathan and Narasimhan,⁵²¹ under these conditions the 1-Mannich base **13** is formed (besides a little 1,3-di-Mannich base), which rearranges into **12** by heating at 130°* or by warming its aqueous solution (Scheme 2). Mannich bases **12**, viz. **12a**, are postulated as intermediates in the reaction of indoles with so-called noncondensing Mannich bases (Ref. 222, p. 292) for instance with piperidinomethylphthalimide (Scheme 3)²²¹ or with the Mannich base **14** of acetyl-hydantoin⁹¹ (see also Atkinson²⁶).

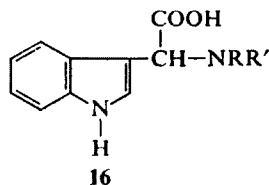
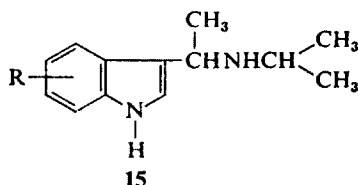


Scheme 3

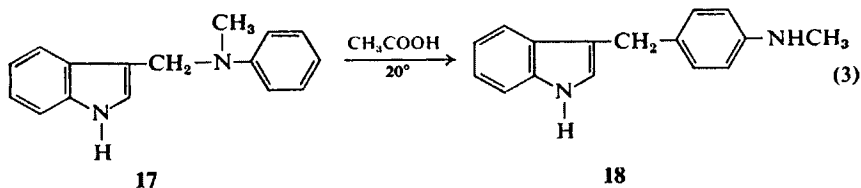


* N-Mannich bases in which position 3 is occupied rearrange to 2-Mannich bases, [J. Wolinsky and J. E. Sundeesen, *Tetrahedron*, **26**, 5427 (1970).]

Compounds of the gramine type are also formed by heating 3-hydroxymethylindoles with secondary amines in the presence of sodium alkoxide.^{443, 444} According to Snyder and Matteson,⁴⁹⁴ the gramine-type reaction can also be effected with acetaldehyde and by substitution of the secondary amine by a branched (sterically hindered) primary amine. However, the yields are low if position 2 of the indole is substituted by alkyl.⁴²⁶ The Mannich bases **15** thus obtained are valuable intermediates in the syntheses of β -methyltryptamines (see Section V.B.3.c). The reagent pair acetaldehyde/primary amine can also be replaced by the corresponding azomethine.^{394, 396} Racemic compounds of formula **15** have been resolved into the antipodes by Albright and Snyder.¹⁸ A further modification of the Mannich reaction uses glyoxylic acid instead of formaldehyde and yields amino acids of type **16**.^{56, 434}



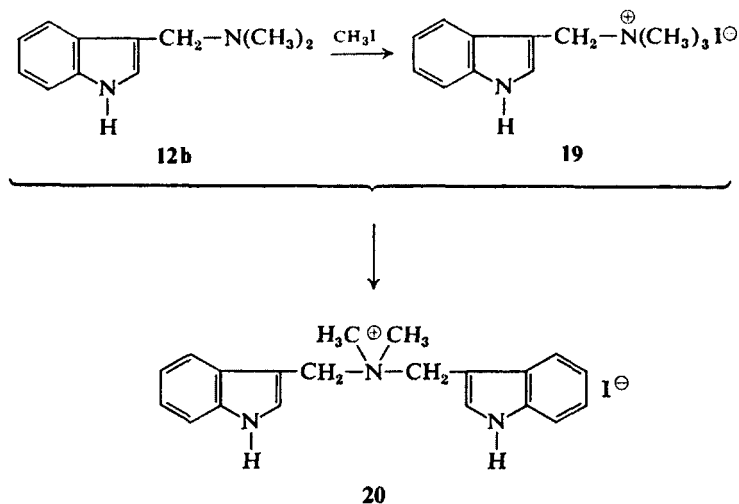
With *N*-methylaniline as the amine component, the Mannich reaction takes an anomalous course: the product obtained is not the Mannich base **17** as supposed by Brehm and Lindwall⁶⁶ but has structure **18**.⁵⁵¹ Compound **17**, however, can be prepared from gramine methosulfate and *N*-methylaniline (amine exchange) in the presence of sodium alkoxide and rearranges into **18** with acetic acid⁵⁵⁰ (Eq. 3) (see also Section V.B.2.d).



C. Quaternization of Gramine

The tertiary Mannich bases **12** can be quaternized by means of alkyl-halides or dialkylsulfates. Due to the high reactivity of these quaternary salts (see Sections V.B.2.d and V.B.3.c), the reaction has to be carried out under special conditions. In 1951 Schöpf⁴⁷³ showed that addition of methiodide to an alcoholic solution of gramine as reported by Snyder et al.⁴⁹⁷ does not lead

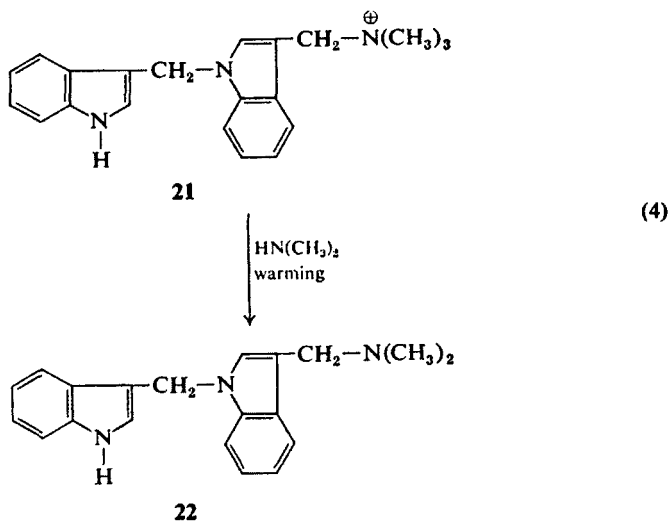
to gramine methiodide (**19**) but to the dimer **20**, which resulted from further reaction of **19** with unchanged **12b** (Scheme 4). Pure **19** is obtained if the



Scheme 4

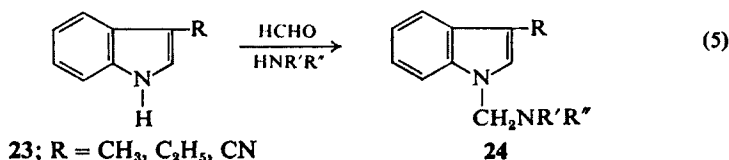
quaternization is carried out in the presence of acetic acid,^{159, 246, 372, 473} or by addition of **12b** to an excess of methiodide.¹⁶⁹

Under the influence of sodium hydroxide, **19** dimerizes to **21**, which yields the tertiary base **22** on warming with dimethylamine⁵⁴⁶ (Eq. 4).



D. *N*-Mannich Bases

Indoles which carry substituents in the 3-position, viz. **23**, give 1-(*N*-)Mannich bases **24** (Eq. 5); the reaction is performed at slightly elevated temperature and/or in acetic acid solution.^{522, 523, 547, 565}

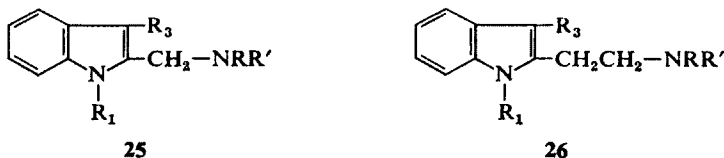


E. Mannich Bases of Indoles with Substituted Positions 1 and 3

These afford the 2-Mannich bases **25** by reaction with formaldehyde and secondary amine in acetic acid at 90°C.⁵⁴⁷

F. 2-Methylindole Mannich Bases

2-Methylindoles carrying substituents in positions 1 and 3 react with formaldehyde and secondary amines in acetic acid at 90° at the methyl group to the Mannich bases **26**.^{554, 485} Treatment of 1,2-dimethylindole with 2 moles of formaldehyde and 1 mole of *primary* amine leads to 3,9-dimethyl-1,2,3,4-tetrahydro- γ -carboline.⁵⁵⁴

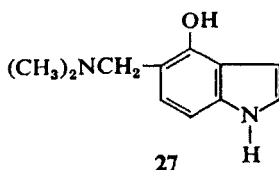


G. Preparation of Mannich Bases of Hydroxyindoles

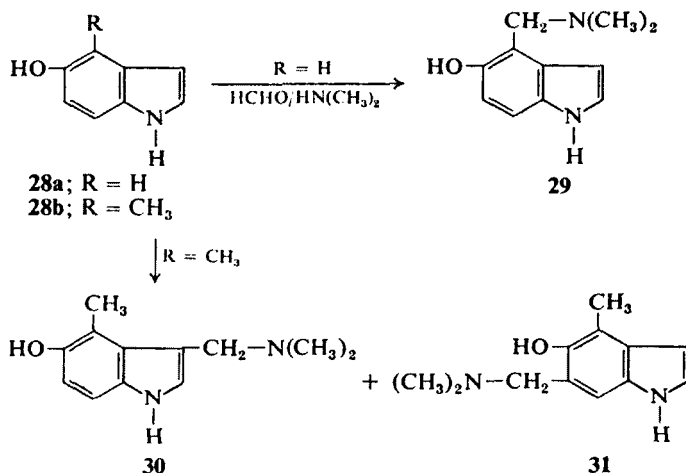
Hydroxyindoles react smoothly with formaldehyde and a secondary amine in the absence of acids, the phenolic group furnishing the required proton. The aminoethyl side chain enters in each case in a position ortho to the phenolic group; 4-Hydroxyindole yields **27**, 5-hydroxyindole **28a** gives **29**.*

* A mechanistic interpretation of the preferred formation of 4-Mannich bases over 6-Mannich bases from 5-hydroxyindole has been given by S. A. Monti, and W. O. Johnson, *Tetrahedron*, **26**, 3685 (1970).

5-Hydroxy-4-methylindole (**28b**), in which one of the positions ortho to the phenolic group is occupied, forms under the same conditions predominantly



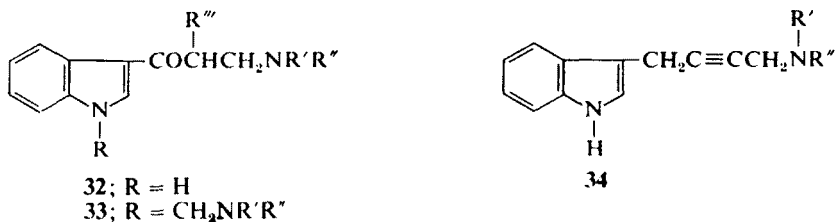
30 besides a small amount of **31** (Scheme 5). 6- and 7-Hydroxyindoles react in an analogous manner (Troxler et al.,⁵⁶³ see also Refs. 40, 197, 284a, 359).



Scheme 5

H. Preparation of Mannich Bases of Indoles with C-acidic Side Chain

Reaction of 3-acylindoles with dimethylamine hydrochloride and para-formaldehyde gives in high yield Mannich bases of type **32**, or if the reagents are used in large excess the di-Mannich bases **33**.⁵²⁷ 3-Propynyindole affords



Mannich bases of type **34**^{370, 505a} and 2-acetyl-1-methylindole yields 2-(3-dimethylamino-1-oxopropyl)-1-methylindole.^{69b}

I. Reactions of Mannich Bases

1. *N*-Skatylations

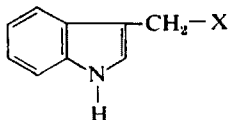
See Section V.B.2.d.

2. *C*-Skatylations

See Sections V.B.3.c and VI.C.

3. Miscellaneous Skatylations

On warming a solution of gramine in water or alcohols with methylmercaptan/NaOH or with zinc methylsulfinate, the *S*-skatylation products **35** and **36**, respectively, are formed³³⁶ (see also Ref. 355a). With benzene-sulfonamide the *N*-skatylated compound **37** has been obtained.³³⁶

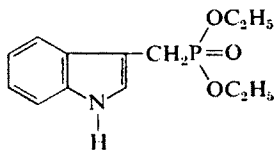


35; X = SCH₃

36; X = SO₂CH₃

37; X = NH-SO₂-C₆H₅

37a has been prepared by warming gramine methiodide with triethylphosphite at 160° (yield 72%) or with sodium diethylphosphite at 20° (20–40%) (Torralba and Myers⁵⁶¹). Analogous reactions with the keto-



37a

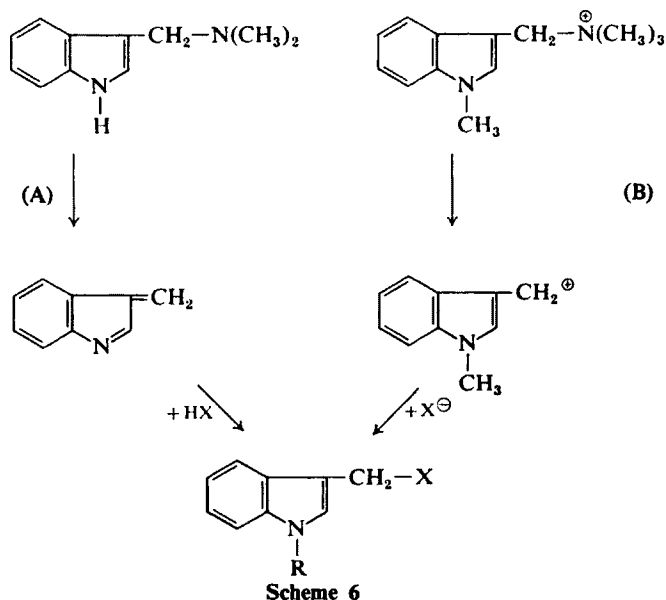
Mannich bases **32** have been described by Szmuszkovicz.⁵²⁶

See v. Strandtmann et al.^{506b} for the reaction of Mannich bases of the types **12** and **32** with phosphonium ylides.

4. Reaction Mechanisms

The mechanisms of the reactions covered by Section II.I have been discussed comprehensively by Hellmann and Opitz (Ref. 222, p. 252ff.). The

two main types are summarized in Scheme 6: reaction of tertiary Mannich bases by an elimination/addition-mechanism (A) and reaction of quaternary



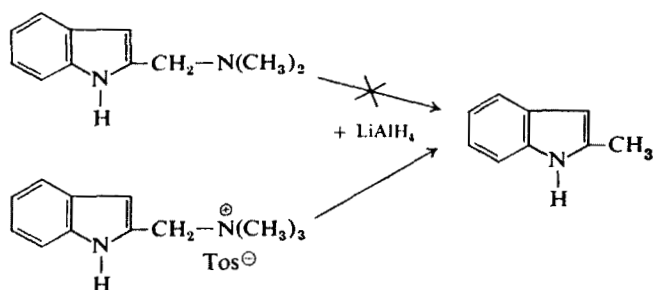
Mannich bases by a S_N -mechanism (B). *N*-Substituted indoles are not capable of amine elimination and, therefore, cannot react according to pathway A.

5. Reductive Desamination

Gramines are transformed into the corresponding skatoles (3-methylindoles) by reduction with zinc dust/NaOH,^{8, 537} platinum/H₂,⁷ or with palladium/H₂.^{214, 347, 566} If benzyloxy groups are present in the molecule, they are catalytically debenzylated at the same time. It is noteworthy that the catalytic reduction of 6-hydroxygramine proceeds beyond the stage of 6-hydroxyskatole and yields 6-hydroxy-3-methyl-2,3-dihydroindole if the reaction is not stopped after consumption of 1 mole of hydrogen.⁵⁶⁷ Salts of gramines are not desaminated when treated with hydrogen and platinum or palladium; e.g., on reduction with palladium/hydrogen, benzyloxygramine hydrochlorides give the corresponding hydroxygramine-hydrochlorides in high yield.^{347, 566}

Mannich bases of hydroxyindoles (Section II.G) behave in an analogous manner. This procedure offers a simple way to introduce methyl groups in distinct positions of the six-membered ring of the indole system.⁵⁶³

Tertiary Mannich bases are not attacked by LiAlH_4 , whereas quaternary salts thereof will be desaminated smoothly¹¹¹ (Scheme 7).

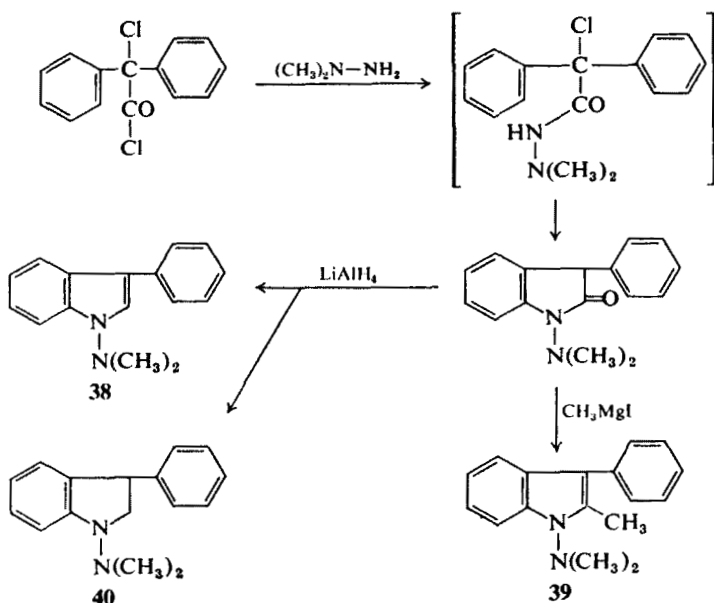


Scheme 7

III. Preparation of Indoles with Basic Function in Position 1

A. 1-Aminoindoles

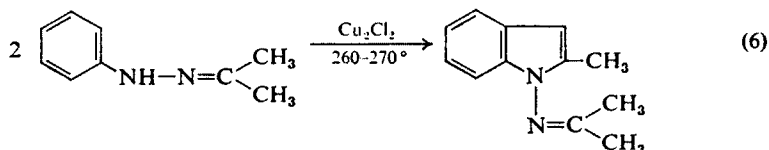
The introduction of an amino group in position 1 of indoles can be effected by reduction of 1-nitrosoindoles (prepared from indoles by means of sodium nitrite/acetic acid,^{148, 235} with zinc/acetic acid,^{55, 202} or with LiAlH_4 ,²⁰²



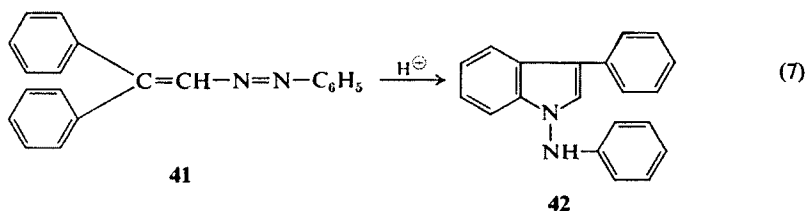
Scheme 8

the latter method giving higher yields. Carefully controlled conditions must be used since the reduction can easily lead to the desaminated indoles.⁵⁶⁷ The 1-aminoindoles **38** and **39** and the 1-aminoindoline **40** have been synthesized by Meyer⁵⁵⁶ as outlined in Scheme 8.

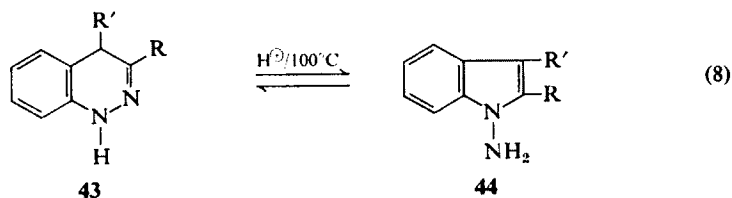
The Arbuzov cyclization of phenylhydrazones of ketones not carrying a CH_2 -group in the α -position leads to 1-aminoindoles²⁴ (Eq. 6). For a further discussion of this reaction, see Ref. 432b.



Warming of **41** with acetic acid and a trace of sulfuric acid yields the 1-anilinoindole **42**, which is cleaved to 3-phenylindole by heating in ethylene glycol⁵⁹⁴ (Eq. 7).



According to Haddelsey, Mayor, and Szinai,²⁰² an equilibrium between 1,4-dihydrocinnolines **43** and 1-aminoindoles **44** which depends on the nature of R and R' exists in acidic medium (Eq. 8).



Refluxing 4-methyl-1,4-dihydrocinnoline with 30% hydrochloric acid affords 1-aminoskatole in 70% yield. A particularly favorable method for the preparation of 1-aminoindoles seems to be heating 4-substituted-1,4-dihydrocinnolines with 80% acetic acid at 100°.⁵⁵

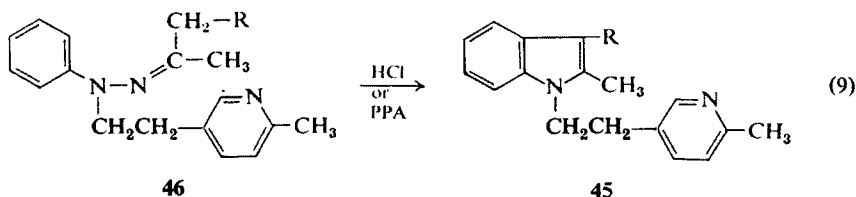
B. Indoles with Basic Side Chain in Position 1

1. Synthesis by Mannich Reaction

See Section II.D.

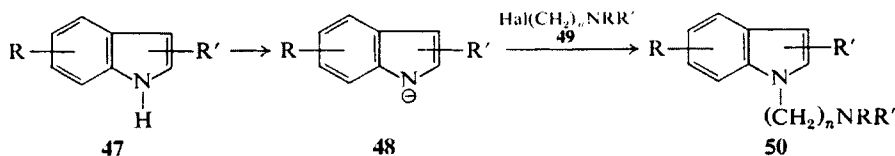
2. Synthesis by Ring Closure (see also the Addenda)

1-Pyridylethylindoles **45** have been prepared by Fischer cyclization of phenylhydrazones **46** (Terent'ev and co-workers^{311, 583}) (Eq. 9).



3. Preparation by Aminoalkylation of Position 1 (see also the Addenda)

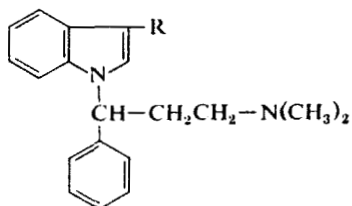
Indoles of the general formula **47** form the anions **48** on treatment with alkali amides, alkali hydrides,^{135, 163, 472, 506, 566, 620} or with lithiumalkyl^{117, 124} in inert solvents like benzene, toluene, dimethylformamide, or liquid ammonia. The alkylation* reaction of these anions with aminoalkylhalides **49** leads to the substitution products **50**. The reaction has also been carried out with 2-halopyridines⁴¹⁶ (yielding 1-pyridylindoles) and aminoalkylmesylates¹¹⁷ or -tosylates^{93, 530} as alkylating agents (Scheme 9).



Scheme 9

* A study of 1-alkylation versus 3-alkylation for the sodium salt of indole depends on the nature of the halide and solvent. B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, **23**, 3771 (1967).

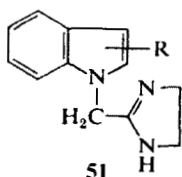
From the alkylation of the lithium salts of 1-benzylindole or 1-benzyl-3-phenylindole with 2-dimethylaminoethylchloride, the basic compounds **50a** has been isolated in low yield.^{161a}



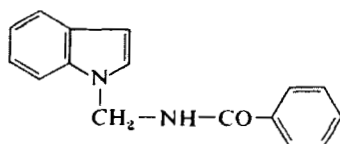
50a; R = H or C₆H₅

1-Aminoalkylindoles **50** arise also in the amination of 1-haloalkylindoles.^{505a} 1-Imidazolylmethylindoles (**51**) have been prepared by melting indoles with 2-chloromethyl-2-imidazolinehydro chloride at 130–160° without addition of a proton acceptor.¹⁶³

Indole reacts with benzamide Mannich bases in the presence of NaOH to 1-benzoylaminoethylindoles **52**.²¹⁹



51

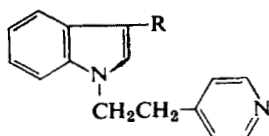


52

Indolylmagnesiumhalides unsubstituted at C-3 are alkylated with aminoalkylhalides **49** in position 3 rather than in position 1^{161, 162} (see Section V.B.3.o).

4. Preparation by Pyridylethylation

Indoles carrying substituents in position 3 form the corresponding 1-pyridylethylindoles **52a** on reaction with 4-vinylpyridine in acidic solution or in the presence of cupric sulfate and sodium ethoxide, the latter reagent giving the better yields.¹⁹⁵ The course of the pyridylethylation of indoles with free position 3 depends on the reaction conditions; basic catalysis leads to

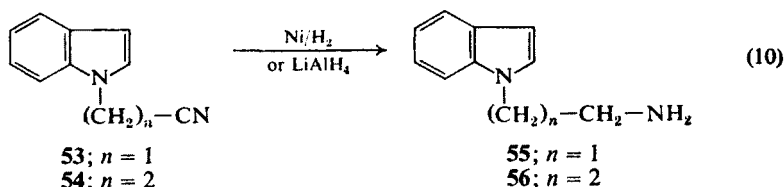


52a

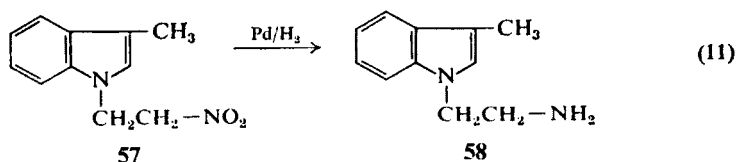
1-substitution, whereas in the presence of acetic acid 3-substitution products are obtained.¹⁹²

5. Preparation by Reductive Procedures

Catalytic reduction of the nitriles **53** (prepared by alkylation of indole with chloroacetonitrile) or **54** (obtained by addition of acrylonitrile on indole, compare Section V.B.5), with nickel/hydrogen gives the corresponding amines **55** and **56**, respectively (Eq. 10).³⁵ In the reduction of **54** with LiAlH_4 ,⁸⁸ we have observed a retro-Michael reaction.⁵⁸⁷

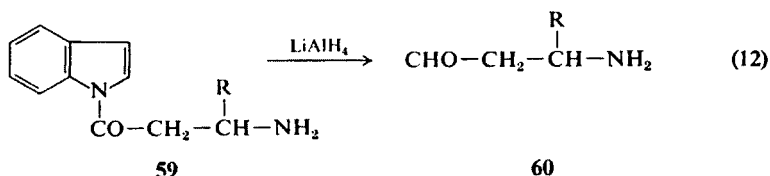


1-(2-Nitroethyl)skatole **57** (prepared from skatyl-magnesiumbromide and nitroethylene) has been reduced to **58** by means of palladium/hydrogen (Acheson and Hands⁶) (Eq. 11).



6. Preparation by Aminoacylation

According to Birkofer and Frankus,⁵⁹ indolylmagnesiumhalides react with esters of β -amino acids to form 1-aminoacylindoles (**59**). Their reduction with LiAlH_4 yields the β -aminoaldehydes **60** and indole (Eq. 12). The authors



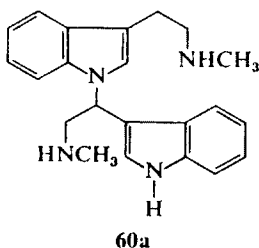
recommend the reaction sequence as a method for the preparation of aldehydes of type **60**.

7. From Oxindoles

Vinogradova et al.⁵⁸⁴ prepared 1-pyridylethylindoles from the corresponding oxindoles by successive reaction with P_2S_5 and nickel.

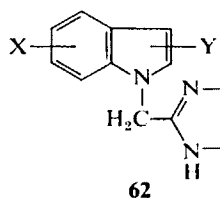
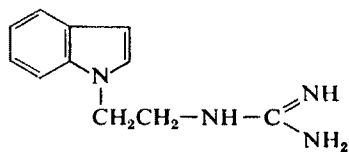
8. Preparation by Oxidative Dimerization of Tryptamines

From the oxidation of *N*-methyltryptamine with potassium ferricyanide in liquid ammonia in the presence of sodium amide, the dimer **60a** has been isolated in low yield by Kametani et al.^{291a}



9. Guanidines, Amidines, and Related Compounds

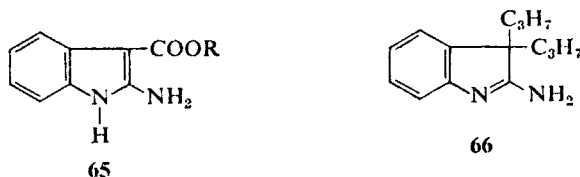
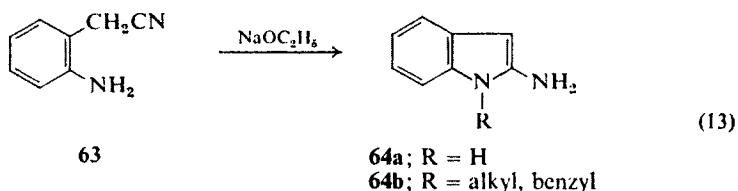
Compound **61** has been prepared from 1-(2-aminoethyl)indole **55** with *S*-methylisothiurea.⁸⁸ The transformation of a number of 1-cyanomethylindoles into 1-imidazolylmethylindoles **62** with ethylenediamine in the presence of CS_2 has been described in a patent.⁵⁰⁶ An alternative synthesis of such compounds by the reaction of indoles with 2-chloromethyl-2-imidazoline has already been mentioned¹⁶³ (see Section III.B.3).



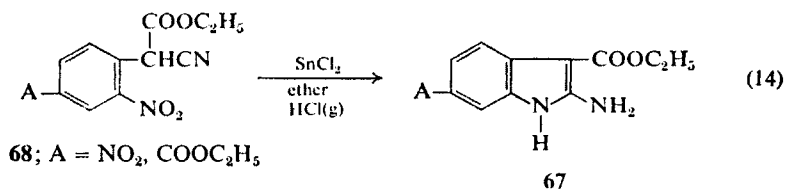
IV. Preparation of Indoles with Basic Function in Position 2

A. 2-Aminoindoles (see also the Addenda)*

Pschorr and Hoppe⁴²² prepared 2-aminoindole (**64a**) by cyclization of *o*-aminophenylacetonitrile (**63**) with sodium ethoxide (Eq. 13). Reduction of **64a** with sodium in ethanol leads to indole.



Compounds **65**¹⁹⁸ and **66**⁶¹ have been prepared in an analogous manner, while Snyder et al.⁴⁹⁵ obtained **67** by Stephen reduction⁵⁰³ of **68** (Eq. 14). Reduction of **68** to compounds of type **67** has also been effected with zinc/acetic acid.^{174a, 174b}

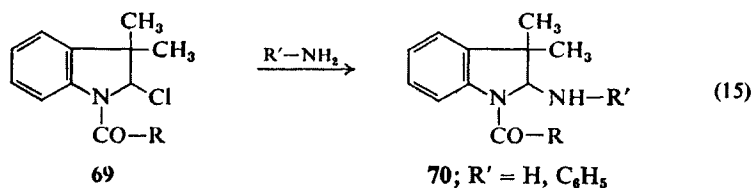


Surprisingly, the reaction of **63** with R-Hal at room temperature proceeds with spontaneous cyclization to the 1-substituted 2-aminoindoles **64b**.^{88a}

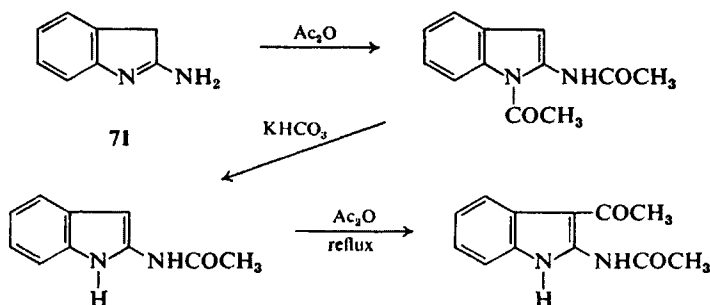
The Curtius degradation of 2-azidocarbonylindoles^{176a, 429} is another method to obtain 2-aminoindoles. Exchange of the reactive chlorine atom in

* *Addition in proof.* Preparation of 2-aminoindoles from thioxindoles and primary or secondary amines [T. Hino, M. Nakagawa, T. Hashizume, N. Yamaji, Y. Miwa, K. Tsuneoka, and S. Akaboshi, *Tetrahedron*, **27**, 775 (1971)].

indolines of type **69** with primary amines affords the 2-aminoindolines **70**^{332, 333} (Eq. 15).



From chemical and physico-chemical arguments, Kebrle²⁹⁸ and Cohen⁶⁶¹ conclude that the base "2-aminoindole" is to be formulated as 2-amino-indolenine (**71**). Its acetylation occurs as outlined in Scheme 10.²⁹⁸

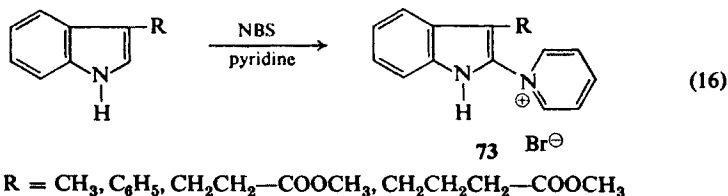


Scheme 10

According to Besford and Bruce,⁵⁵ the reduction of cinnoline and 1,4-dihydrocinnolines to indoles proceeds via the nonisolable 2-aminoindoline.

2-Aminoindoles have been used as starting products in the syntheses of polycyclic indoles.^{174a, 312, 341a, 456}

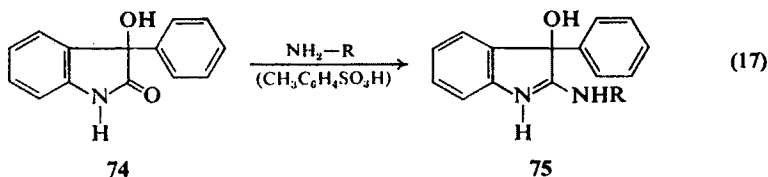
Some (2-indolyl)pyridinium salts **73** have been prepared by Kobayashi and Inokuchi³⁰⁶ by reacting **72** with *N*-bromosuccinimide in pyridine (Eq. 16). Hydrolysis of **73** yields the corresponding oxindoles.*



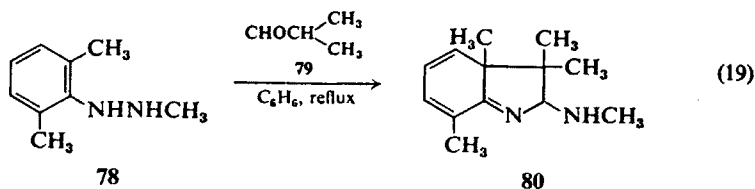
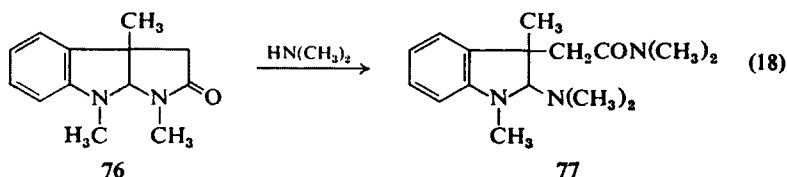
2-Amino-3-hydroxy-3-phenylindolenines **75** are formed in the reaction of 3-phenyldioxindole **74** with primary amines in boiling xylene in the presence

* *Addition in proof.* Preparation of **73** by bromination of skatole with dioxane dibromide/pyridine and the catalytic reduction of **73** have been described by T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967).

of a trace of *p*-toluenesulfonic acid (Eq. 17). The reaction fails with 3-phenyloxindoles.³⁵⁷



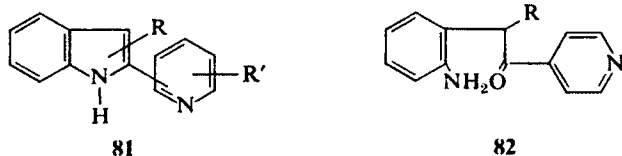
From the ring opening of 76 with dimethylamine, 77 could be isolated⁴⁴¹ (Eq. 18). Condensation of 78 with 79 affords 80 (Eq. 19).³⁰



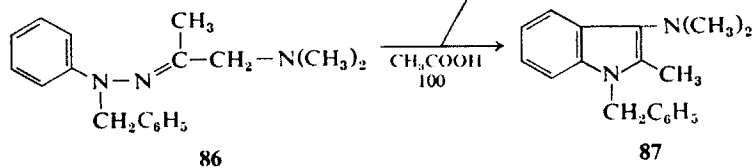
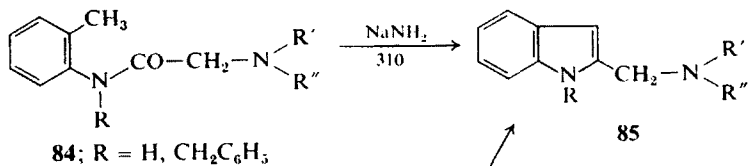
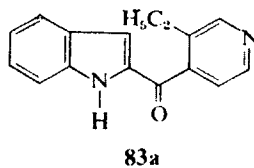
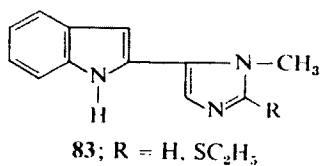
B. 2-Pyridylindoles and Indoles with Basic Side Chain in Position 2

1. By Ring Closure [see also the Addenda]

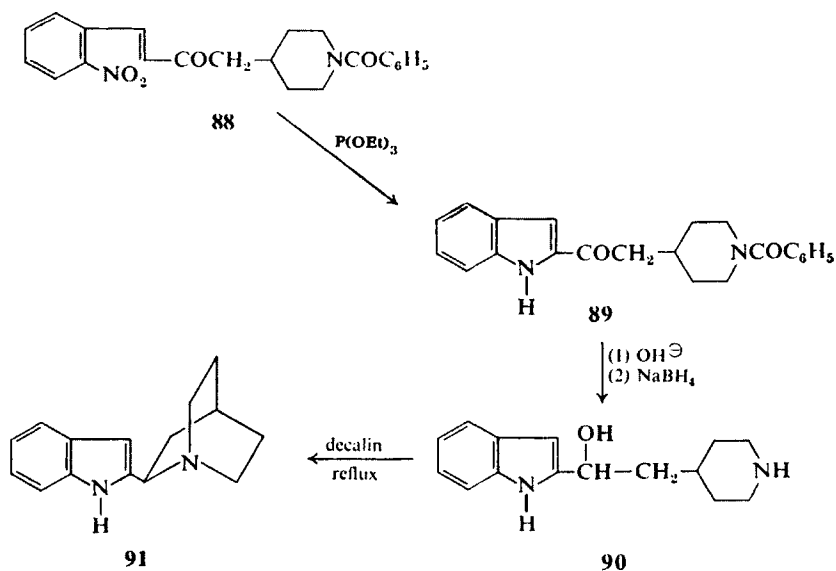
2-Pyridylindoles **81** are easily accessible by Fischer ring closure of phenylhydrazones of suitable acylpyridines^{23, 64, 84, 166, 165, 192, 293, 325, 418, 511} or by cyclization of *o*-aminophenylketones of type **82** with toluenesulfonic acid.^{165, 166}



Other examples of 2-heterocyclic substituted indoles prepared by Fischer cyclization are **83**²⁷⁶ and **83a**.^{262a}



Scheme 11

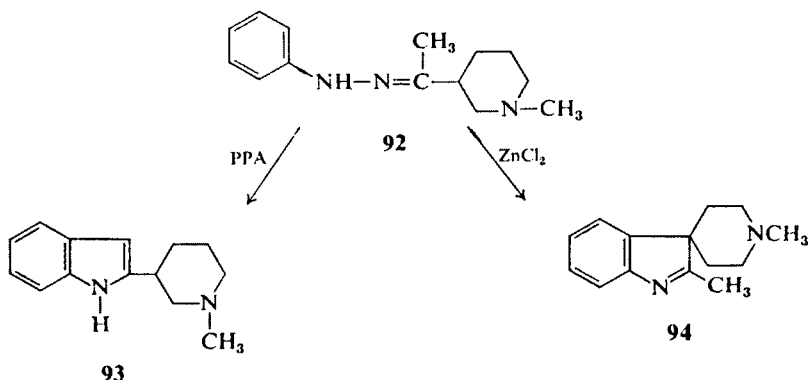


Scheme 12

Cyclization of the basic anilides **84** according to the method of Madelung-Tyson yields **85**.^{310, 613} The Fischer cyclization of the phenylhydrazone **86** does not lead to **85**, but to the 3-dimethylaminoindole **87**⁶¹³ (Scheme 11).

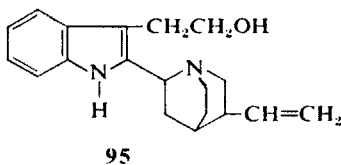
Ring closure of **88** by means of triethylphosphite gave **89**, which was further transformed into the quinuclidine derivative **91**⁵¹³ (Scheme 12).

The course of the Fischer cyclization of **92** depends on the reaction conditions. With polyphosphoric acid the 2-substituted indole **93** is formed; zinc chloride, on the other hand, leads to the spiroindolenine **94**³³⁹ (Scheme 13).



Scheme 13

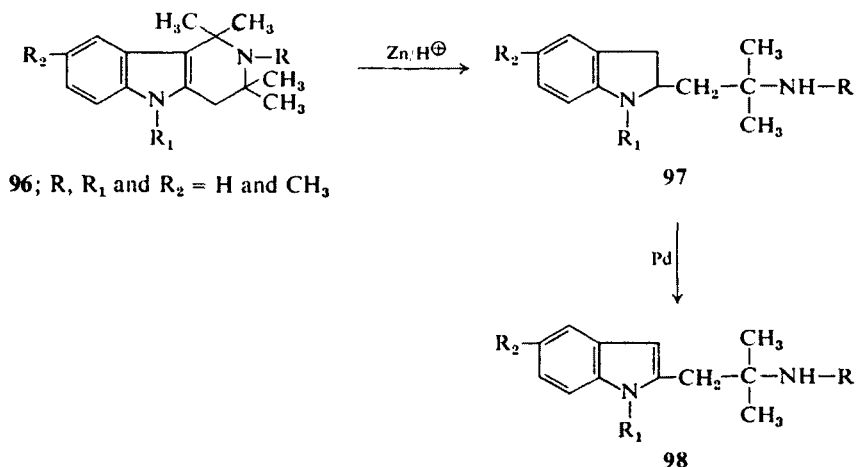
The synthesis of cinchonamine (**95**)⁸⁵ represents another example of a Fischer cyclization to an indole with heterocyclic substituent in position 2.



2. From Polycyclic Indole Compounds by Ring Fission

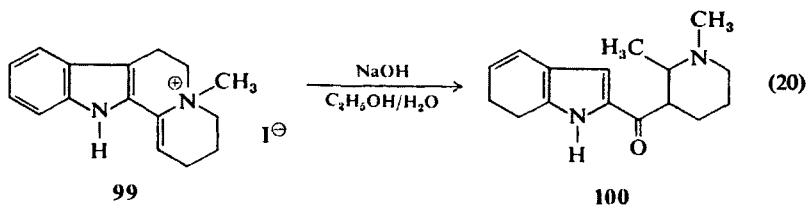
Several authors have isolated 2-pyridylindoles in the dehydrogenation of polycyclic indole alkaloids by means of selenium. Thus alstonine,⁴⁸⁰ serpentine,⁴⁷⁰ akkumigine,⁴³³ and corynantheine^{267, 295} yield alstyrine [3-ethyl-2-(4,5-diethyl-2-pyridyl)indole]. Likewise desethylalstyrine [3-ethyl-2-(5-ethyl-2-pyridyl)indole] has been obtained from the dehydrogenation of corynantheine²⁶⁸ and octahydroflavopereirine.²⁶⁹ According to Komzolova,^{307, 308} γ -carbolines of the general formula **96** are reductively cleaved

with zinc amalgam/dilute acid to the indolines **97**, which are dehydrogenated to the corresponding indoles **98** by palladium (Scheme 14).

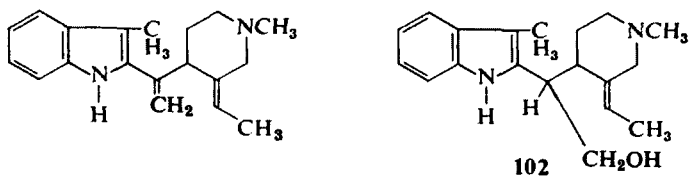


Scheme 14

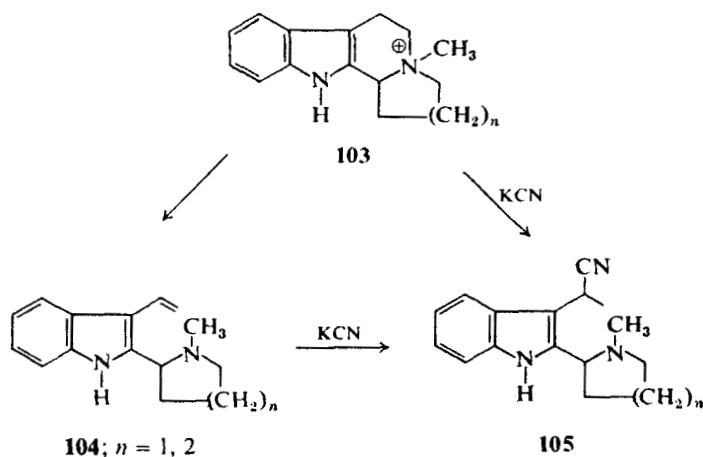
Compound **99**, on boiling with a solution of sodium hydroxide in water/alcohol, yields **100** (Eq. 20).¹¹⁰ A mechanism of this rearrangement is discussed.¹¹⁰



Walser and Djerassi⁵⁹⁰ isolated **101** in the reduction of the alkaloid apparicine as well as in the degradation of vallesamine (via the intermediate **102**).

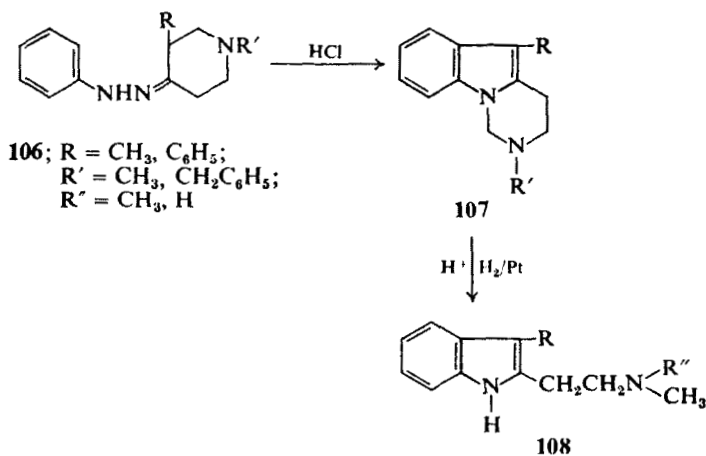


The Hofmann degradation of **103** yields **104**; reaction of the former with KCN gives **105** (Foster and Harley-Mason¹⁵⁹) (Scheme 15).



Scheme 15

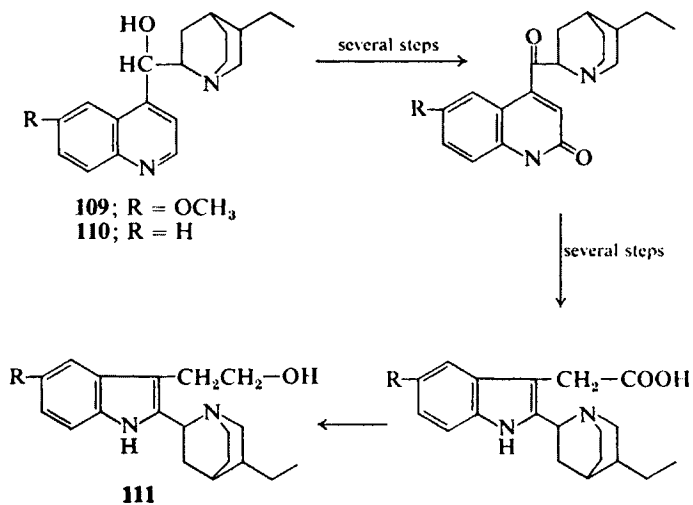
Catalytic hydrogenation of pyrimido[3,4-*a*]indoles of formula **107**, obtained by anomalous Fischer cyclization of hydrazones **106**, results in isotryptamines **108**. The methylene group between the two nitrogen atoms is thereby reduced to a methyl group^{119, 120, 662} (Scheme 16).



Scheme 16

3. By Transformation of Cinchona Alkaloids

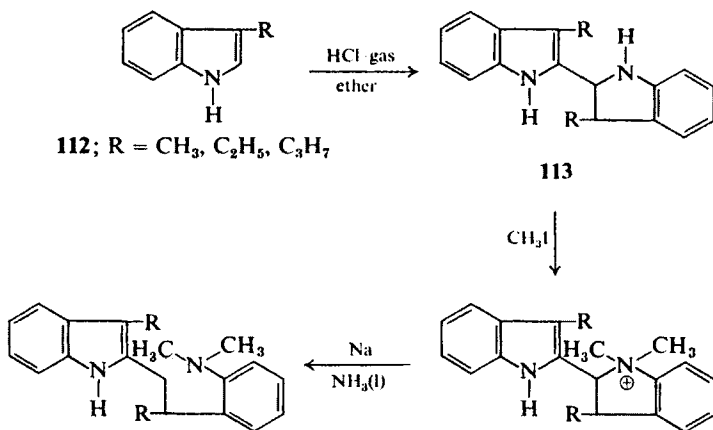
Dihydroquinine (**109**) and dihydrocinchonine (**110**) have been converted into the corresponding dihydrocinchonamines **111** as outlined in Scheme 17 (Ishikawa and Ochiai^{259, 260, 381-383}).



Scheme 17

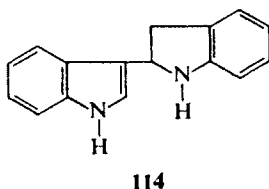
4. By Dimerization of Indoles

Indoles of the general formula **112** dimerize on treatment with acid to products, the structures of which have been shown to be **113** by Emde degradation^{54, 228, 485} (Scheme 18).



Scheme 18

3-Isopropyl- or 3-*t*-butylindoles do not dimerize under these conditions. Indole itself behaves differently, forming the 3,2'-dimer **114**.²³⁴ See G. F. Smith's review for the mechanisms of dimerization.^{484a}

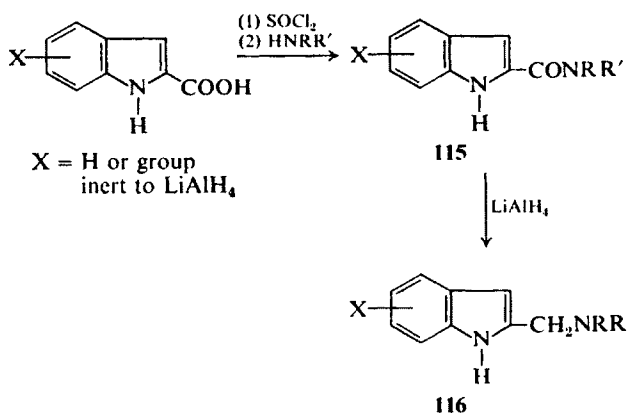


5. By Mannich Reaction

See Sections II.E II.F.

6. From Amides of Indolyl-2-carboxylic Acid [see also the Addenda]

2-Dialkylaminomethylindoles **116** are easily accessible by reduction of the corresponding amides **115**^{310, 468, 488, 524, 566} (Scheme 19). A large number of



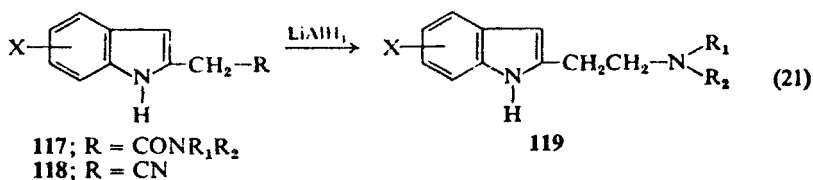
Scheme 19

primary and secondary amides of indolyl-2-carboxylic acid have been reduced by Shaw⁴⁸¹ and Wright and Brabander.⁶¹¹

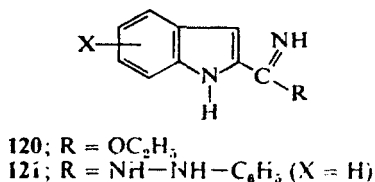
7. By Reduction of Indolyl-2-acetonitrils and Amides of Indolyl-2-acetic Acid

The very easily decarboxylating indolyl-2-acetic acids can be converted into their acid chlorides by careful treating with PCl_5 in ether. Their reaction with amines yields the corresponding amides (**117**) which on reduction with LiAlH_4 give isotryptamines (**119**) (2-aminoethylindoles).^{536, 566} Indolyl-2-acetonitriles (**118**), obtained from quaternary salts of **116** with sodium

cyanide,⁵⁴⁷ also yield isotryptamines **119** on reduction with nickel⁹⁸ or LiAlH_4 ⁴⁶⁸ (Eq. 21).

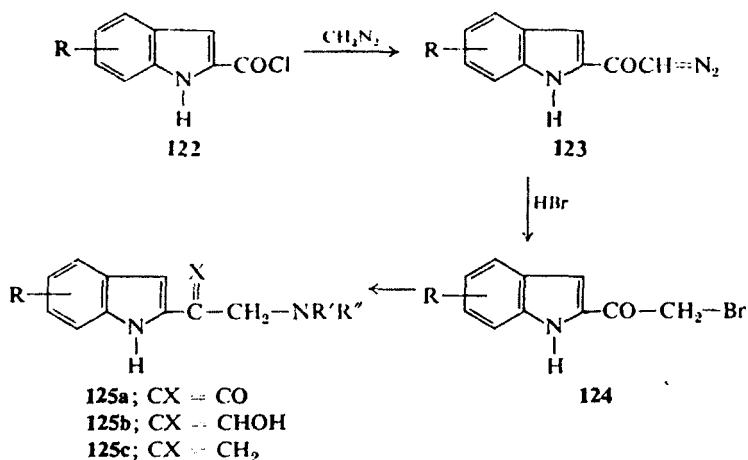


On the other hand, the nitrile **118** was converted to the iminoether **120**; warming of an aqueous solution of its hydrochloride yielded indolyl-2-acetic acid.⁴⁶⁹ Doyle¹¹⁶ has prepared the amidrazone **121** by reaction of the iminoether **120** with phenylhydrazine.



8. From 2-Bromoacetylintroles

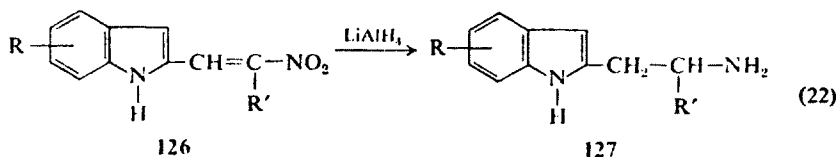
Acid chlorides **122** can be transformed into the bromoketones **124** via the intermediate diazoketones **123**.⁴¹⁵ Amination of **124** and subsequent reduction of the carbonyl group leads to amines of formula **125**²⁵¹ (Scheme 20).



Scheme 20

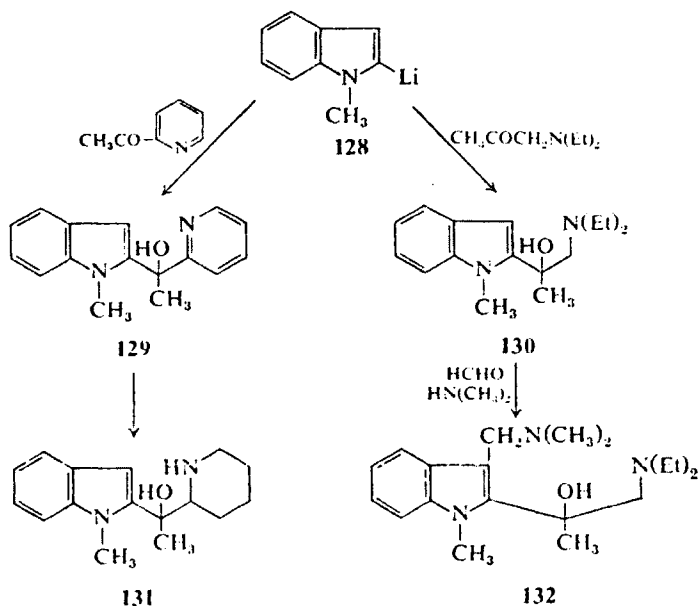
9. By Reduction of 2-Nitrovinylindoles

Another approach to isotryptamines **127** is outlined in eq. 22, the 2-nitrovinylindoles **126** being prepared by condensation of 2-formylindoles with the appropriate nitroalkanes.²¹⁰



10. From Indolyl-2-lithium Compounds [see also the Addenda]*

The indolyl lithium compound of formula **128** (prepared from 1-methylindole and lithium butyl) react with aminoketones, viz. 2-acetylpyridine²⁹⁹ or diethylaminoacetone²⁹⁷ to aminoalcohols **129** and **130**, respectively. Catalytic

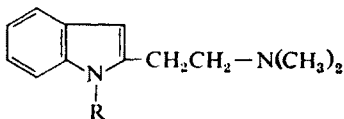


Scheme 21

* Addition in proof. Reaction of **128** with isoquinoline followed by dehydrogenation leads to 1-methyl-2-(2-isoquinolyl)indole in 54% yield [D. A. Shirley and P. A. Roussel, *J. Amer. Chem. Soc.*, **75**, 375 (1953)].

reduction of **129** yields the piperidino compound **131**. On the other hand, **129** and **130** can easily be converted into Mannich bases, viz. **132**, which are useful intermediates in the synthesis of γ -carbolines (Scheme 21).

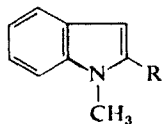
Reaction of 2-dimethylaminoethylchloride with the lithium salt of 1-methyl- or 1-phenylindole gives the corresponding 2-substitution products **133** in very low yield. The lithium salt of 1-benzylindole reacts in a different manner (see Section III.B.3).^{161a}



133; R = CH₃ or C₆H₅

11. From 2-Acylindoles

2-Formyl-1-methylindole has been converted into the hydrazinomethylindoles **134** (by catalytic reduction of the intermediate hydrazones) and the aminoester **135**.²⁹⁷ Analogously, Chastrette⁸⁷ has prepared **136** by reduction of the intermediate azomethine with LiAlH₄.



134; R = CH₂NH—NH—R'

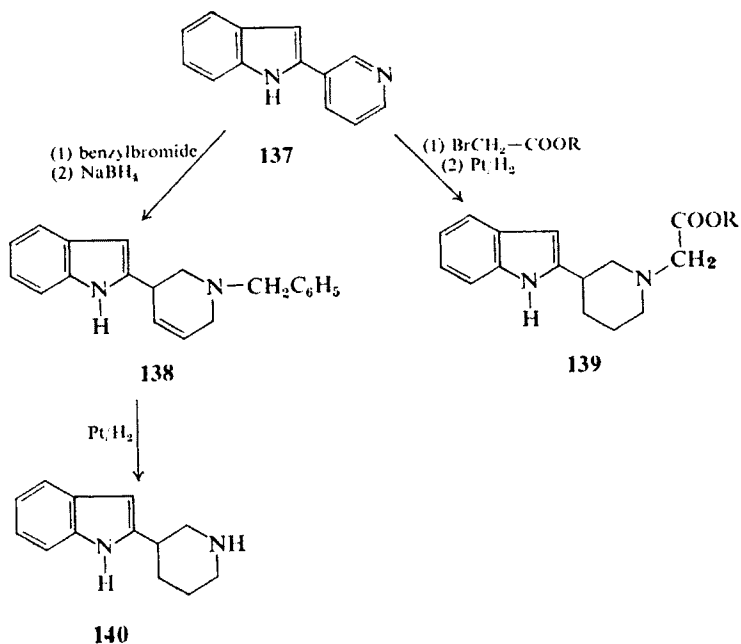
135; R = CH₂NHCH₂—COOR'

136; R = CH—NH—CH(OC₂H₅)₂

CH₃

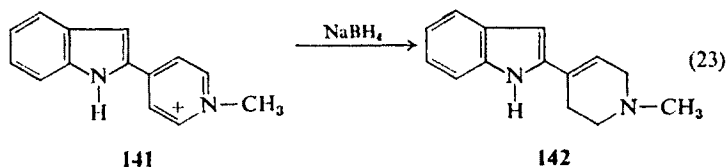
12. By Reduction of 2-Pyridylindoles [see also the Addenda]

Partial or complete reduction of the pyridine ring of 2-pyridylindoles leads to valuable intermediates for the syntheses of alkaloids or alkaloidlike systems. Representative examples along this line have been described by Huffman²⁴⁸ and Beck and Schenker.³⁸ The conversion of **137** into the reduced derivatives **138–140**²⁴⁸ is outlined in Scheme 22.



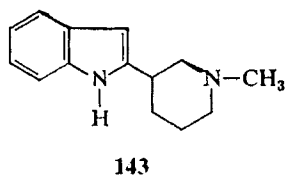
Scheme 22

In an analogous manner, the pyridinium salt **141** has been reduced to **142** by Beck and Schenker³⁸ (Eq. 23).

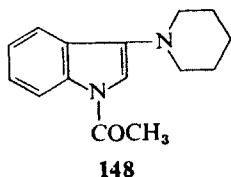


Reduction of 2-pyridylindoles to 2-piperidylindoles has also been effected with sodium in ethanol¹¹⁰ or isoamyl alcohol.⁴³²

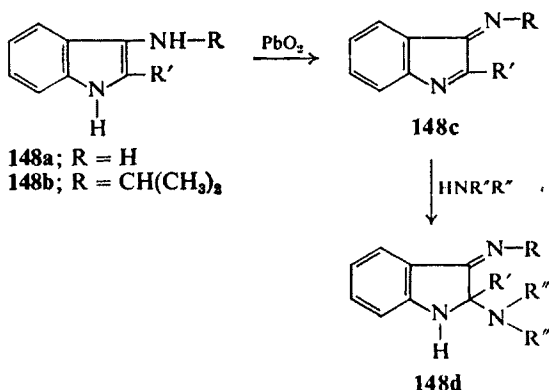
The methobromide of 3-(2-indolyl)-pyridine has been hydrogenated with platinum/hydrogen to 3-(2-indolyl)-1-methyl-piperidine (**143**) by Gray and Archer.¹⁹²



or palladium/hydrogen.⁵⁸ 1-Acetyl-3-piperidinoindole (**148**) has been obtained by Nenitzescu^{424a} from 1-acetylindoxyl and piperidine in acetic acid.*



Schmitt et al. prepared 3-aminoindoles (**148a**) by catalytic reduction of 3-phenylazoindoles. Oxidation of 3-isopropylaminoindoles (**148b**) with PbO_2 led to the indolenins **148c**, the azomethine double bond of which easily adds amines to yield compounds **148d**^{471a} (Scheme 23a).

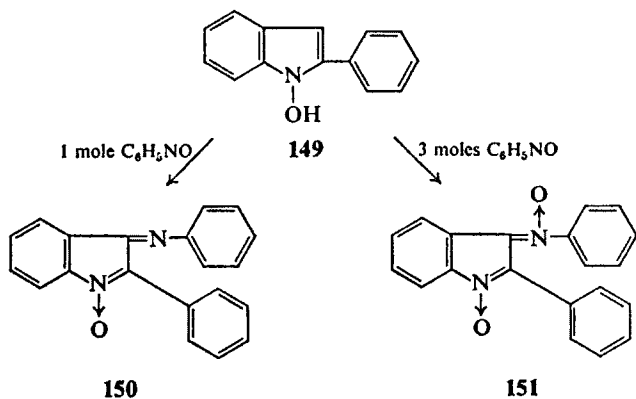


Scheme 23a

The formation of 1-benzyl-3-dimethylamino-2-methylindole (**87**) by Fischer cyclization of the appropriate phenylhydrazone **86** has already been mentioned (Section IV.B.1).

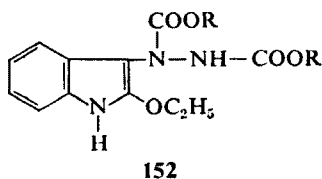
3-Aminoindoline is postulated as an intermediate in the reduction of isatin oxime to indole.¹⁷³ The condensation of 1-hydroxy-2-phenylindole (**149**) with 1 mole of nitrosobenzene yields **150**, while with 3 moles the dinitrone **151** is obtained⁹⁸ (Scheme 24).

* *Addition in proof.* Warming with dimethyl acetylenedicarboxylate transforms **148** into dimethyl 1-acetyl-5-piperidyl-2,3-dihydro-1H-1-benzazepine-3,4-dicarboxylate in high yield. [Mei-Sie Lin and V. Snieckus, *J. Org. Chem.*, **36**, 645 (1971)].



Scheme 24

Addition of an ester of azodicarboxylic acid to 2-ethoxy-indole (equimolar amounts of reactants, refluxing dioxane) leads to **152**.⁴⁰⁸



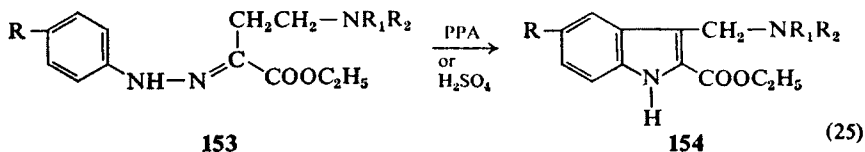
B. Indoles with Basic Side Chain in Position 3

1. *Preparation of Compounds of the Gramine Type by Mannich Reaction*
See Section II.B.

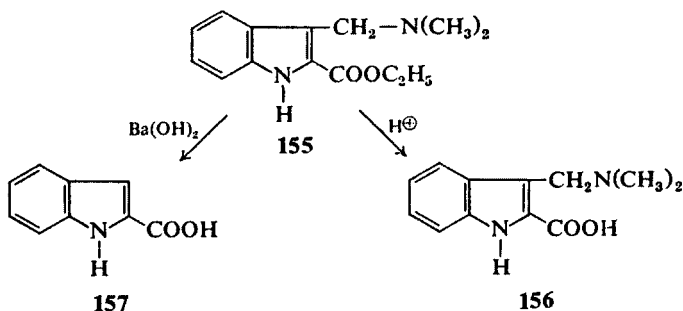
2. *Preparation of Compounds of the Gramine Type by Other Methods*

a. BY RING CLOSURE. A number of 3-(1-piperazinylmethyl)indoles have been prepared¹⁴³ by Fischer cyclization.

Fischer cyclization of the phenylhydrazones **153** leads to the 2-carbethoxy-3-dialkylaminomethylindoles **154**,^{51, 216, 508} the decarboxylation of which failed²¹⁶ or proceeded in very low yield⁵⁰⁸ (Eq. 25).

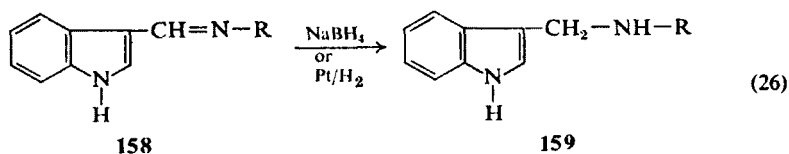


According to Hegedüs,²¹⁶ 2-carbethoxygramine (**155**) is hydrolyzed to **156** by dilute acid whereas the basic side chain is removed by the action of barium hydroxide to give **157** (Scheme 25).

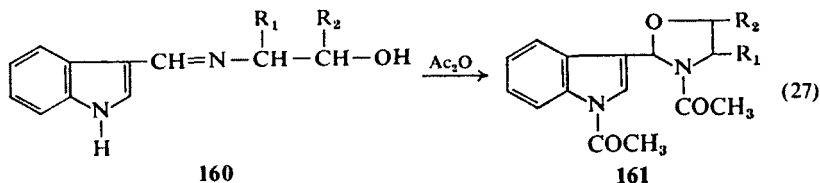


Scheme 25

b. FROM CARBONYL COMPOUNDS. 3-Aminomethylindoles result from the reduction of 3-cyanoindoles with nickel in acetic acid⁵¹² or with LiAlH₄⁵⁶⁷ and of oximes of 3-formylindoles or 3-acetylindoles by means of sodium/ethanol.^{157, 196, 423} Reduction of 3-formylindoles to 3-aminomethylindoles has been effected by nickel in the presence of ammonia.⁷⁹ Sodium borohydride⁵⁸⁹ as well as hydrogenation with Pd³⁶⁹ or Pt⁵⁶⁷ transform the azomethines **158** obtained from 3-formylindole and the appropriate primary amine into the *N*-substituted 3-aminomethylindoles **159** (eq. 26).



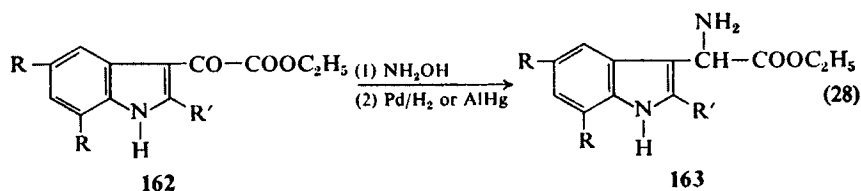
On warming the azomethines **160** with acetic anhydride, the oxazolidinylindoles **161** have been formed⁵⁸⁹ (Eq. 27).



Reduction of hydrazones of 3-formylindole to 3-hydrazinomethylindoles* with Pd/BaSO₄ and hydrogen⁵²⁰ or with LiAlH₄⁵⁵⁶ have been described.

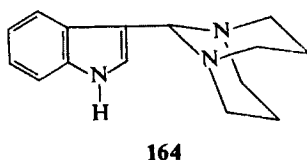
* *Addition in proof.* For the preparation of 3-hydrazinomethylindoles see also M. Bernabé, E. Fernandez-Alvarez, M. Lora-Tamayo, and O. Nieto, *Bull. Soc. Chim. Fr.*, **1971**, 1882.

Casnati and Ricca⁸² prepared the aminoesters of type **163** from indolyl-3-glyoxylic esters **162** (Eq. 28).

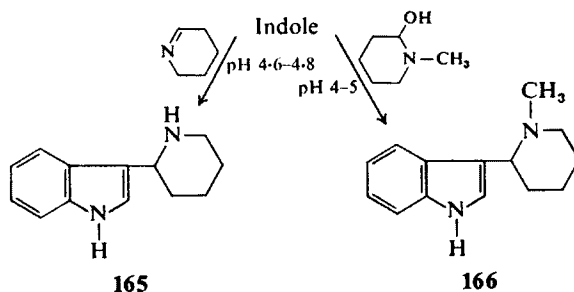


The reduction of amides of indolyl-3-carboxylic acid with LiAlH_4 has been described by Domschke and Fürst.¹¹² The required indolyl-3-carboxylic acid chlorides are accessible either by chlorination of the corresponding acids, or according to Wormser and Elkin⁶¹⁰ by pyrolysis of the appropriate indolyl-3-glyoxylic acid chlorides (see also Peterson et al.³⁹²).

The aminal **164** is formed by warming a solution of 3-formylindole and 1,4-diazacyclooctane at $40-45^\circ$.⁵⁷



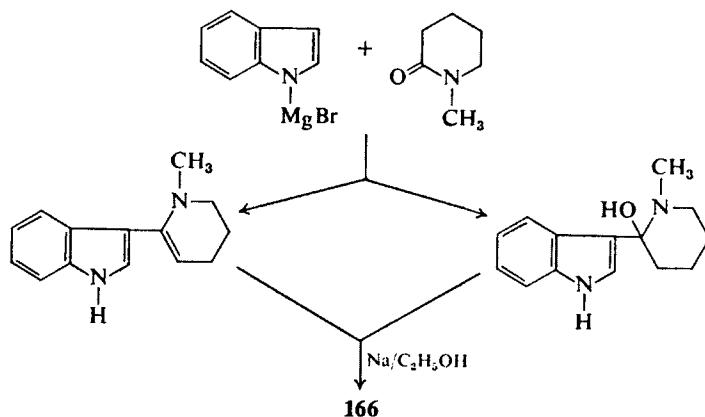
c. 3-(2-PIPERIDYL)- AND 3-(2-PYRROLIDINYL)INDOLES. The preparation of 3-(2-piperidyl)indoles **165** and **166** by reaction of indole with Δ^1 -piperidine or with 2-hydroxy-*N*-methylpiperidine has been described by van Tamelen⁵³⁴ (Scheme 26) (compare also Thesing et al.⁵⁴⁹). The acid-catalyzed condensation



Scheme 26

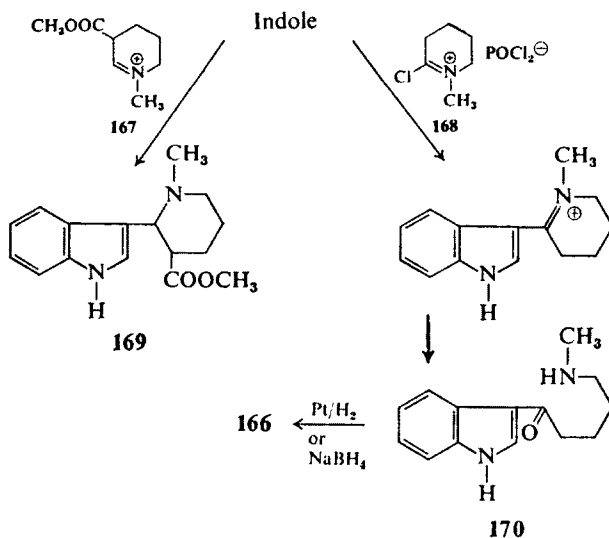
of indoles (with free position 3) with Δ^2 -piperidines leads to the same type of compounds,^{599a, 599b}

Compound **166** has also been prepared by Akkerman and Veldstra¹⁷ from indolylmagnesiumbromide as outlined in Scheme 27.



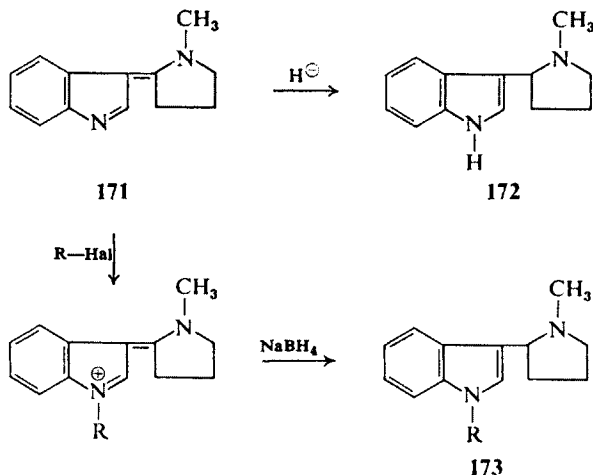
Scheme 27

Reaction of indole with the piperideinium salt **167** in acetic acid or with the "Vilsmeier-adduct" **168** of N -methylpiperidone gives **169** and **170**, respectively. Reduction of the latter compound by platinum/hydrogen^{41b} or NaBH_4 ¹⁰⁹ yields **166** (Scheme 28).



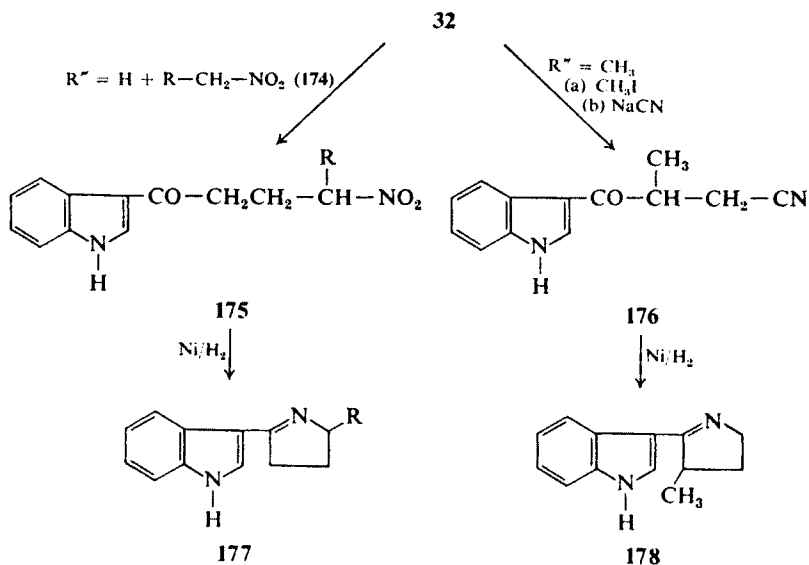
Scheme 28

The "Vilsmeier-adduct" of *N*-methylpyrrolidone behaves similarly to the piperidine analog **168**.⁶²⁰ The reaction product **171** can be reduced to **172** by complex hydrides or converted into **173** by alkylation and subsequent reduction (Scheme 29).



Scheme 29

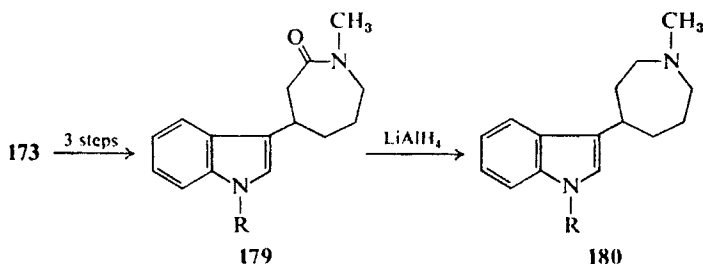
Another synthesis of 3-(2-pyrrolidinyl)indoles starts with Mannich bases **32**. Their reaction either with nitroalkanes **174** (reaction with **174** wherein $\text{R} = \text{H}$ failed)⁶²⁰ or of their quaternary salts with sodium cyanide leads to



Scheme 30

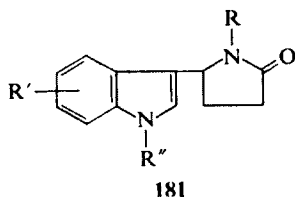
intermediates **175** and **176**, respectively, which are reduced to pyrrolinyl-indoles **177** and **178**, respectively, by means of Raney nickel. Further reduction of the latter compounds with platinum/hydrogen or, after quaternization of the pyrrolino nitrogen, with NaBH_4 yields the corresponding pyrrolidinyl-indoles^{218, 577} (Scheme 30).

The pyrrolidine ring of **173** is enlarged to an azepino ring by alkali-catalyzed condensation with ethyl malonate. Reduction of **179** with LiAlH_4 yields the 3-(4-azepinyl)indole **180**²²⁶ (Scheme 31).



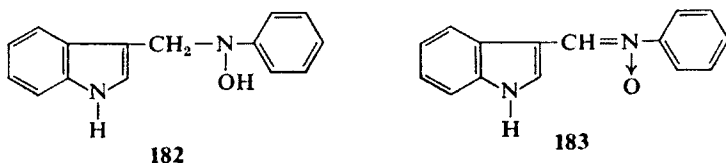
Scheme 31

The preparation of compounds of formula **181** by reaction of the appropriate indolyl-Grignard salts with succinimides followed by reduction is described in a patent.⁵⁹²



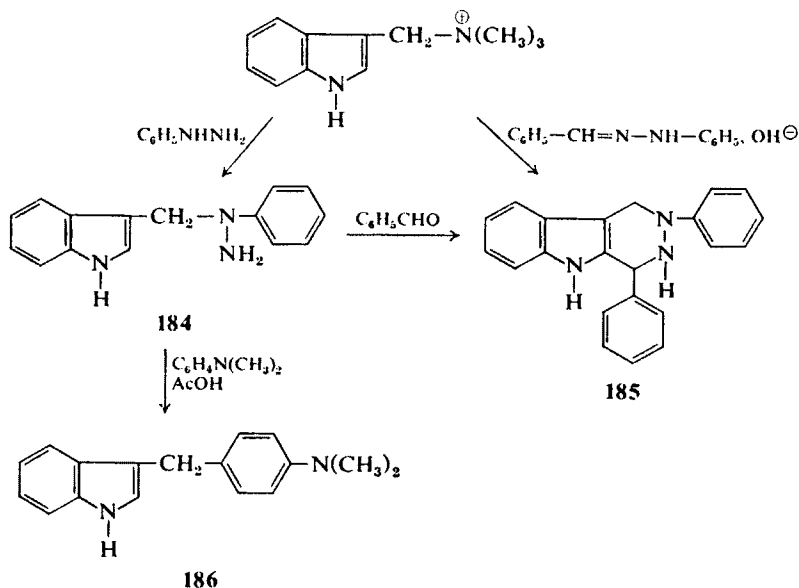
d. FROM GRAMINES BY AMINE EXCHANGE (see also the Addenda). On warming certain gramines not carrying a substituent in position 1 in an inert solvent such as toluene or benzene with a secondary amine in the presence of a catalytic amount of NaH , amine exchange occurs by an elimination-addition mechanism, i.e., the skatyl radical is transferred to the added amine. The same reaction products are formed if quaternary salts of gramines, either substituted in position 1 or not, are warmed with a secondary amine, preferentially in ethanol in the presence of 1 mole of sodium ethoxide (S_N -mechanism) (see Hellmann and Opitz, Ref. 222, pp. 277-278). Gramines substituted in position 1 are not capable of amine exchange by an elimination-addition mechanism. Thus 1-methylgramine does not react with piperidine. Warming its methiodide with piperidine leads to 3-piperidinomethylindole in 89% yield. The same product is obtained on warming piperidine with 1-methylgramine hydrochloride or with 1-methylgramine in the presence of

BF_3 .⁴⁹¹ Amine exchange occurs also on heating gramine with high boiling primary amines; addition of solvents or a basic catalyst is not necessary.⁵⁶⁷ The reaction of gramine methiodide with phenylhydroxylamine in the presence of alkali affords **182**, which is oxidized to the nitrone **183** by PbO_2 or nitrobenzene. Hydrolysis of **183** gives 3-formylindole.^{545, 552}



As reported in Section II.B, treating gramine methosulfate with *N*-methylaniline and sodium hydroxide at 20° gives **17**, a base not accessible from indole by a Mannich reaction.⁵⁵⁰

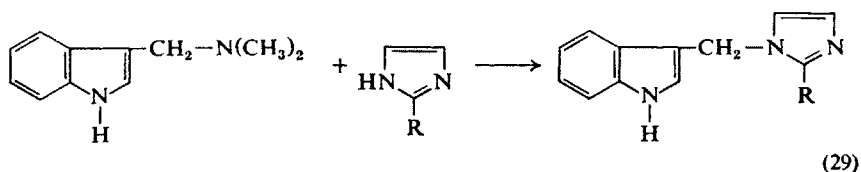
Gramine methosulfate and phenylhydrazine lead to the *N*-phenyl-*N*-skatylhydrazine **184**, while the former reacts with *N*-phenyl-*N*-benzylidenehydrazine to **185**. This compound is also obtained by reaction of **184** with benzaldehyde. Treatment of **184** with dimethylaniline and acetic acid gives **186** (Scheme 32).⁵⁵⁶



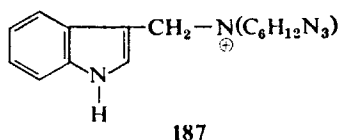
Scheme 32

The analogous reaction of gramine methosulfate with methylhydrazine is described in a patent.⁴⁸⁶ Other examples of amine exchange are the skatylation

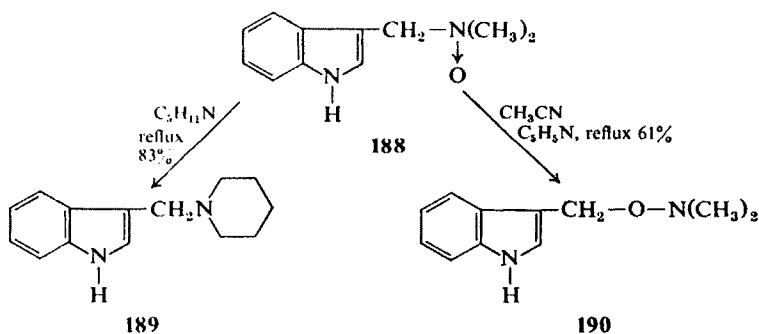
of imidazoles¹⁰⁴ (Eq. 29) and the preparation of *N,N'*-diskatylpiperazine by heating gramine with piperazine.³⁰⁹



Warming a dilute acetic acid solution of gramine and hexamethylenetetramine leads to 3-formylindole via the quaternary salt **187**,⁴⁹⁸ which has not been isolated.



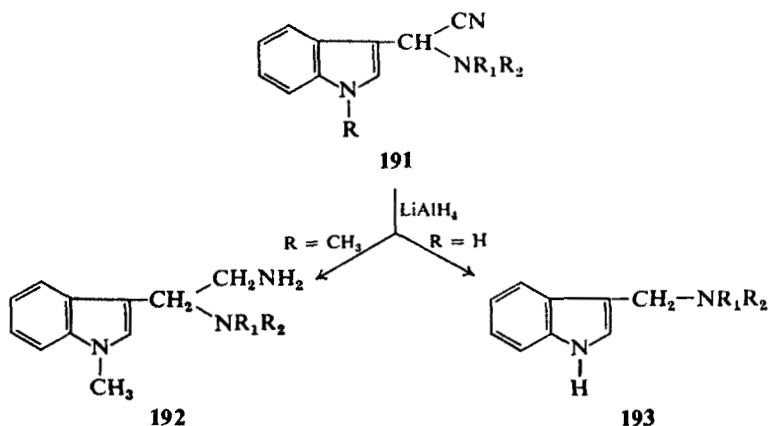
Amine exchange occurs also with gramine-*N*-oxide (**188**) (prepared from gramine and aqueous hydrogen peroxide), e.g., reaction with piperidine leads to 3-piperidinomethylindole (**189**) in high yield. Rearrangement to **190** occurs²²⁵ (Scheme 33) on heating **188** at 125° or by boiling it in acetonitrile



Scheme 33

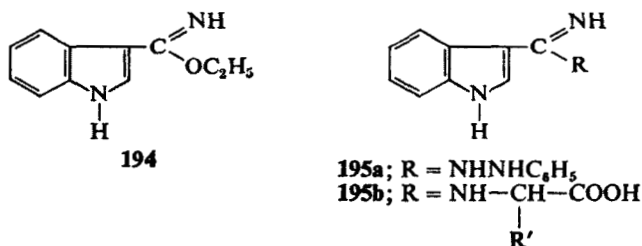
solution containing a trace of pyridine, the latter method giving better yields.

e. AMINONITRILES. 3-Formylindoles form aminonitriles on reaction with sodium cyanide and secondary amines (Strecker synthesis), viz. **191**. Compounds of type **191** react with secondary amines by amine exchange.²⁶⁶ The course of the reduction of **191** with LiAlH_4 depends on the substituent R; the nitrile group is reduced to the aminomethyl group if R is alkyl (**192**), elimination to **193** proceeds if R is H (Scheme 34).^{425, 266}



Scheme 34

f. AMIDINES AND RELATED COMPOUNDS. 3-Cyanoindole forms the iminoether **194** on treatment with ethanol and hydrochloric acid. Reaction of **194** with phenylhydrazine and α -aminocarboxylic acids yields the amidrazone **195a**¹¹⁶ and the amidines **195b**.^{145a} The latter compounds have been cyclized to the corresponding 2-(3-indolyl)imidazolones.^{145a}



3-Guanidinomethylindole has been prepared by guanylation of 3-amino-methylindole with *S*-alkylisothiourea.^{506a}

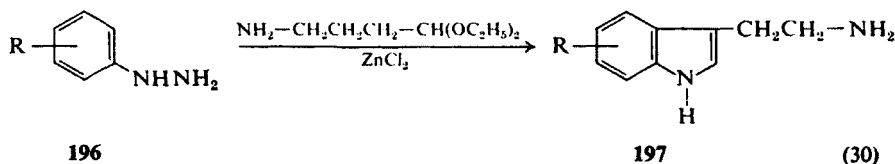
g. DIMERIC INDOLE (see also the Addenda).* The structure of the dimeric indole, shown to be compound **114**, which is formed on the action of gaseous hydrochloric acid on a solution of indole in ether, has been mentioned^{234, 484, 484a} (see Section IV.B.4).

For Section V.B.2.h, see the Addenda.

* *Addition in proof.* According to J. Bergman [*J. Heterocycl. Chem.*, **8**, 329 (1971)], formyl-**114** (formylated at the indoline nitrogen) is formed in moderate yield in the reduction of indole with formic acid/acetic anhydride.

3. Methods for the Preparation of Tryptamines

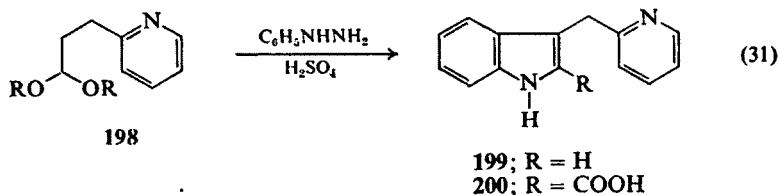
a. BY RING CLOSURE. Various tryptamines **197** have been synthesized by heating substituted phenylhydrazines **196** with γ -aminobutyraldehyde diethyl-acetal and zinc chloride (Eq. 30).^{52, 124, 141, 242a, 424, 498a, 499} The yields are



often higher if the cyclization is carried out in acetic acid at 80° (no zinc chloride added).^{105, 106, 300}

For examples of Fischer syntheses of 3-(2-piperidinoethyl)- and 3-[2-(piperazin-1-yl)ethyl]indoles, see Refs. 505a, and 143 and 505b, respectively.

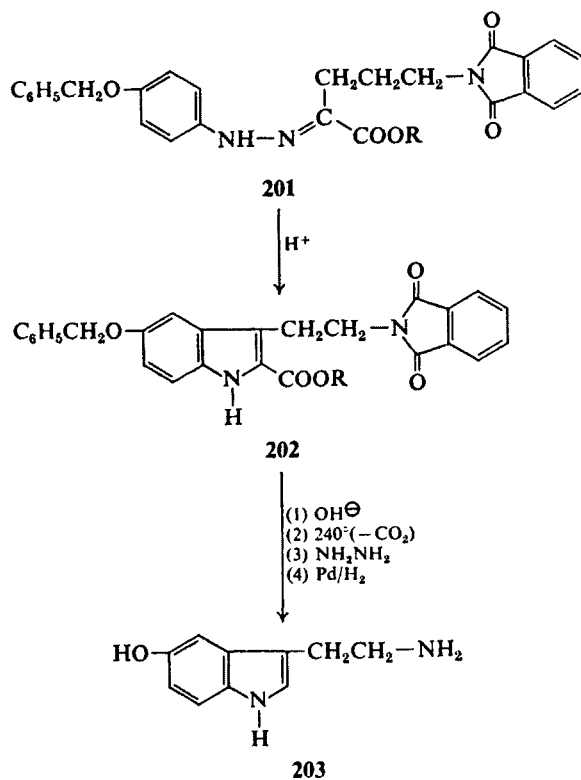
Reaction of the acetal **198** with phenylhydrazine and sulfuric acid yields the pyridylmethylindole **199** (Eq. 31).⁵⁹³ Analogous cyclization to **200** followed by decarboxylation to **199** has been described by Röder.⁴³⁹



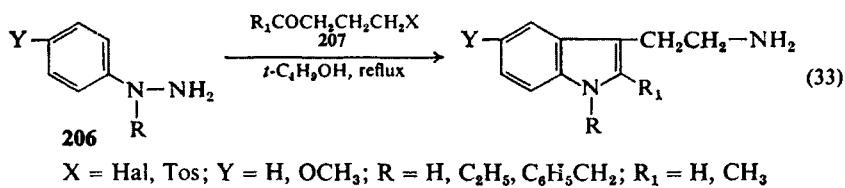
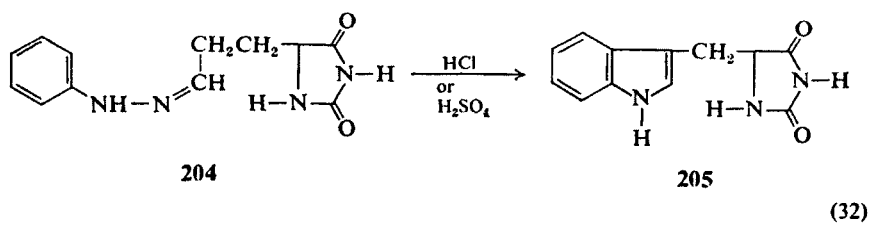
In a similar manner Bretherick et al.⁶⁷ have cyclized the phenylhydrazone **201** to **202**, from which serotonin (**203**) has been obtained in four steps (Scheme 35). For an analogous synthesis of 2-methyl-serotonin, see Ref. 353.

Cyclization of **204** with hydrochloric or sulfuric acid yields **205**, an intermediate in the synthesis of tryptophane¹⁴ (Eq. 32).

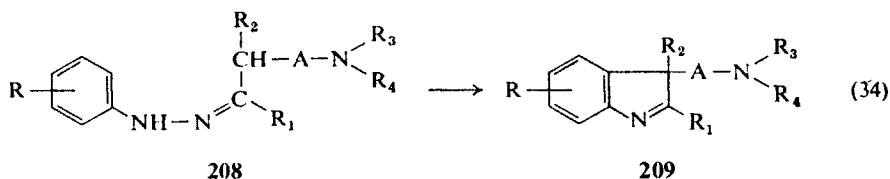
Tryptamines are also obtained by boiling phenylhydrazines of formula **206** with γ -haloketones **207** in *t*-butanol/methanol^{177a, 179, 179a} (Eq. 33). Condensation of **206** with **207** in the presence of hydrochloric acid yields, however, 3-(2-haloethyl)indoles.^{350, 353} The Fischer ring closure of phenylhydrazones **208** of branched ketones affords indolenines of structure **209**⁵⁵⁷⁻⁵⁵⁹ (Eq. 34).



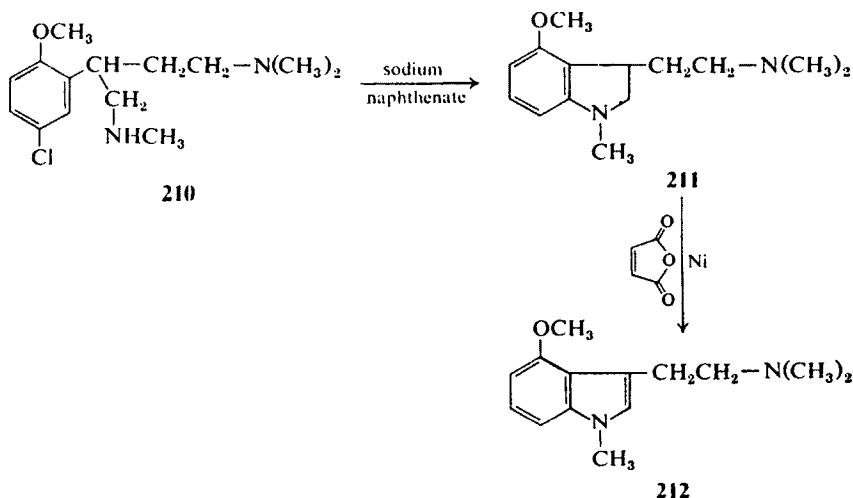
Scheme 35



Tryptamines are also accessible by other cyclization methods. Julia and Gaston-Breton²⁸⁰ describe the preparation of **212** by aryne cyclization of **210**

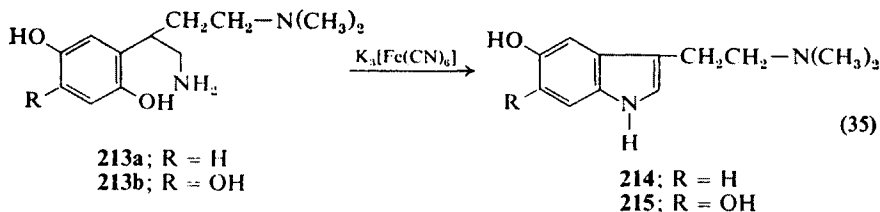


and subsequent dehydrogenation of the intermediate indoline **211** (Scheme 36).

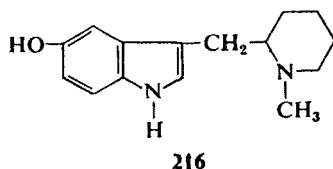


Scheme 36

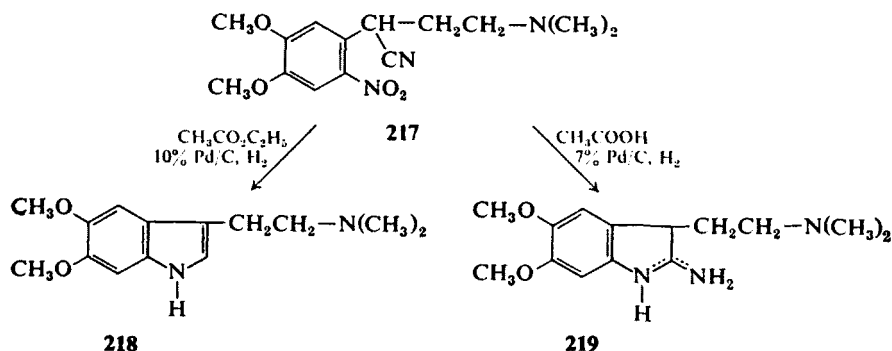
The oxidative ring closure of **213a** and **b** leads directly to bufotenine (**214**) and 6-hydroxybufotenine (**215**), respectively (Harley-Mason and Jackson^{208, 209}) (Eq. 35).



By the same procedure, **216** has been prepared by Moore and Capaldi.³⁶⁰

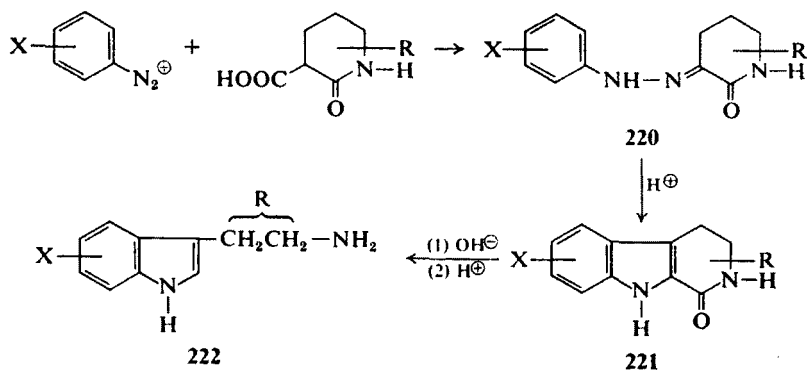


The reductive cyclization of **217** leads to **218** or **219** depending on the reaction conditions⁵⁸⁸ (Scheme 37).



Scheme 37

b. FROM POLYCYCLIC INDOLES BY RING FISSION. The process developed by Abramovitch et al.^{4, 5} for the preparation of tryptamines is outlined in Scheme 38. A diazonium salt is condensed according to Japp and Klingemann^{271, 272} with a piperidone-carboxylic acid to a hydrazone **220** and the latter is cyclized to a β -carbolinone **221**. Alkaline hydrolysis of **221** leads to the tryptamine-2-carboxylic acid, which is decarboxylated to **222** with acid.

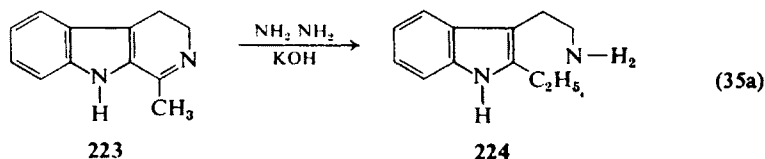


Scheme 38

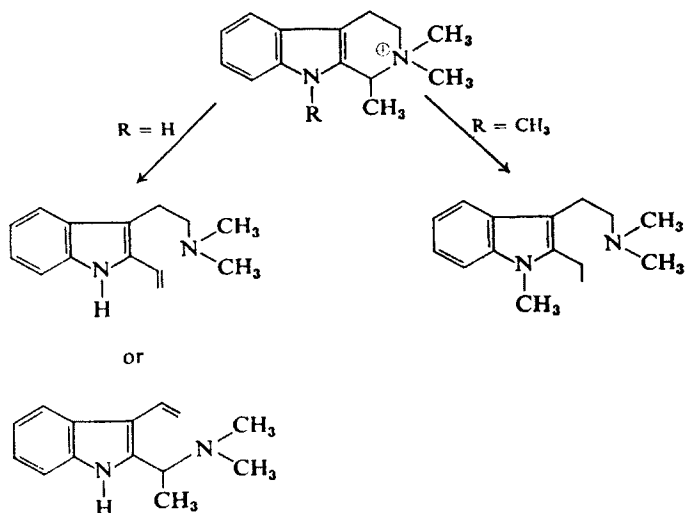
X stands for H, alkyl, alkoxy, alkylthio, halogen, acetyl, or dialkylsulfamoyl; R signifies H or one or several alkyl groups. Furthermore, **221** can be alkylated selectively at the indole or the piperidon nitrogen.²

If X stands for a *p*-hydroxy group, the acid-catalyzed indolization of **220** leads directly to 5-hydroxytryptamine-2-carboxylic acid.^{428a} This versatile method has been widely used in the synthesis of tryptamines. The following examples serve as illustrations: preparation of α -methyltryptamine⁵¹⁷; β -methyltryptamine³; β -methyl- and β,β -dimethyltryptamines¹⁹⁰; α -methyl-, β -methyl-, and α,β -dimethyltryptamines²⁴⁰; and ring-substituted tryptamines.^{12, 158, 190, 240, 241, 442, 507, 507a, 518, 518, 518a}

Fleming and Harley-Mason¹⁵² reported on the ring fission of the β -carboline **223** (prepared from acetyltryptamine according to Bischler-Napiralski) by the action of hydrazine and KOH, yielding **224**. The method allows for the introduction of an ethyl group in position 2 of tryptamines (Eq. 35a).

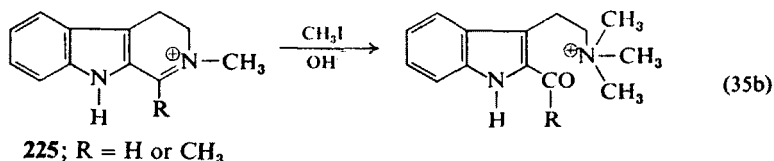


Emde degradation of quaternized 1,2,3,4-tetrahydro- β -carboline has been described by Leete,³²⁸ and Hofmann degradation by Yurashevskii⁶²¹ (Scheme 39).

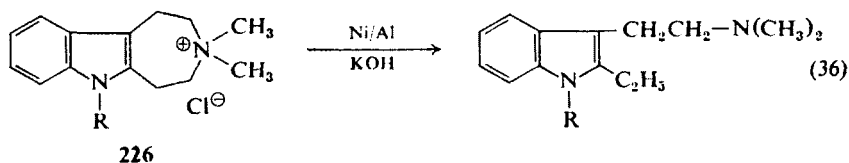


Scheme 39

Quaternary salts of 3,4-dihydro- β -carbolines (**225**) undergo ring fission on methylation in alkaline medium^{199, 200} (Eq. 35b).

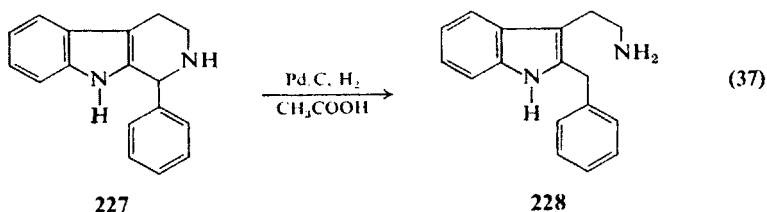


Emde degradation has also been effected with the azepinoindoles **226**⁴⁶⁵ (Eq. 36).

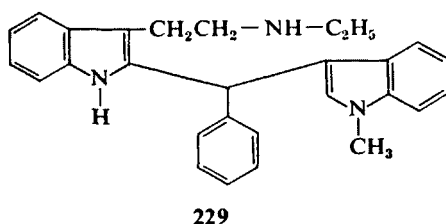


Dehydrobufotenine (see Section V.B.4) yielded bufotenine on Emde degradation^{348a} as well as by catalytic hydrogenation (Pt/H₂, dilute HCl).⁶⁰²

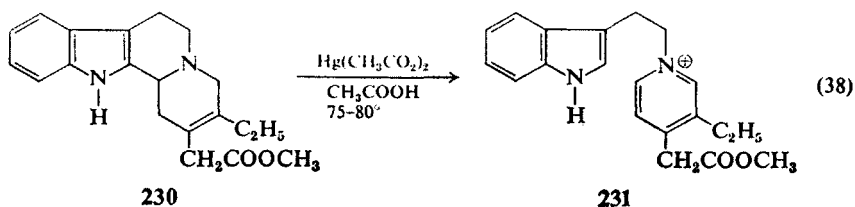
1-Phenyl-1,2,3,4-tetrahydro- β -carbolines (viz. **227**) are reduced to 2-benzyltryptamine (**228**) by palladium/hydrogen in glacial acetic acid^{63a} (Eq. 37).



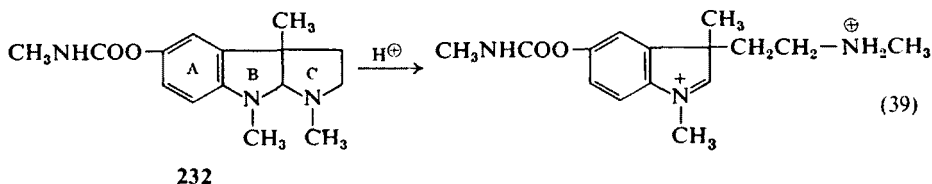
Ring fission of 2-ethyl-1-phenyl-1,2,3,4-tetrahydro- β -carboline occurs on boiling with 1-methylindole in acetic acid containing some phosphoric acid, giving **229** in quantitative yield.¹⁵⁵



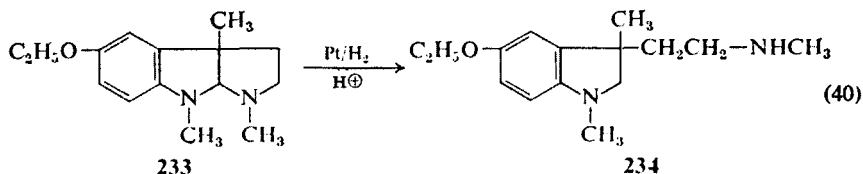
Oxidative ring fission of **230** to **231** by means of Hg(II) acetate has been described by Weisbach et al.⁵⁹⁷ (Eq. 38).



Ring C of eserine (**232**) opens readily on treatment with acid (Eq. 39).^{265*}



Reduction of eserethole (**233**) to the 2,3-dihydrotryptamine **234** either by the action of zinc and hydrochloric acid^{410a} or by platinum and hydrogen in acetic acid^{502a} is an example of a similar ring opening (Eq. 40). No reduction can be achieved in neutral or alkaline solution. The alkaloid folicanthine is reduced to *N,N*-dimethyl-2,3-dihydrotryptamine²³³ by zinc and hydro-



chloric acid in much the same way. Hofmann degradation of eserethole methiodide to eserethole methine has been described by Polonovski.^{410b}

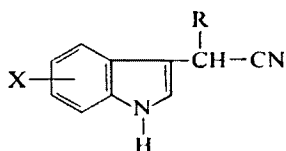
c. FROM MANNICH BASES. Quaternary salts of gramines react with alkali cyanide in water/alcohol to form indolyl-3-acetonitriles **235**^{169, 246, 414, 471, 489, 555}. The yields are high in general, but in some cases controlled conditions have to be observed. Thus Brown and Garrison⁷⁰ isolated only 15% of indolyl-3-acetamide on heating 6-nitro gramine methiodide with KCN in ethanol/water; reaction with NaCN in a buffered amyl alcohol/water solution (pH 4.5–5.5), however, led to a 64% yield of 6-nitroindolyl-3-acetonitrile.

* Addition in proof. For the ring-chain tautomerism of compounds of the eserine type see also H. Fritz and P. Losacker, *Ann. Chem.*, **709**, 135 (1967); I. I. Grandberg, T. A. Ivanova, and N. G. Jaryšev, *Chim. Geterocikl. Soed.*, **1970**, 1276.

The reaction has also been effected in dimethylformamide,²⁰ while Kamal et al.²⁹¹ have reported on a complex course of the reaction in aqueous medium.

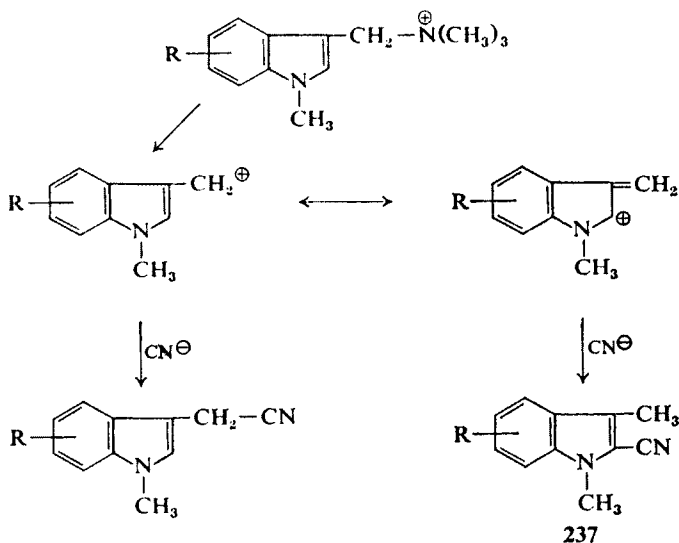
Mannich bases of type **15** have been converted by the above method to **236**, valuable intermediates in the syntheses of β -methyltryptamines.⁵⁶⁶

A modification of the procedure has been described by Henbest et al.²²⁴ (see also Ref. 529): an aqueous solution of potassium cyanide is added to the solution of a gramine in methanol, then methyl iodide is added slowly while keeping the reaction temperature below 20°, and finally the reaction mixture is stirred at 20–25°.



235; R = H
236; R = CH₃

The procedure frequently leads to 2-cyanoindoles (**237**) as by-products, this side reaction being attributed to the fact that the intermediate carbonium ion can be formulated in two canonical forms⁴⁹⁰ (Scheme 40).



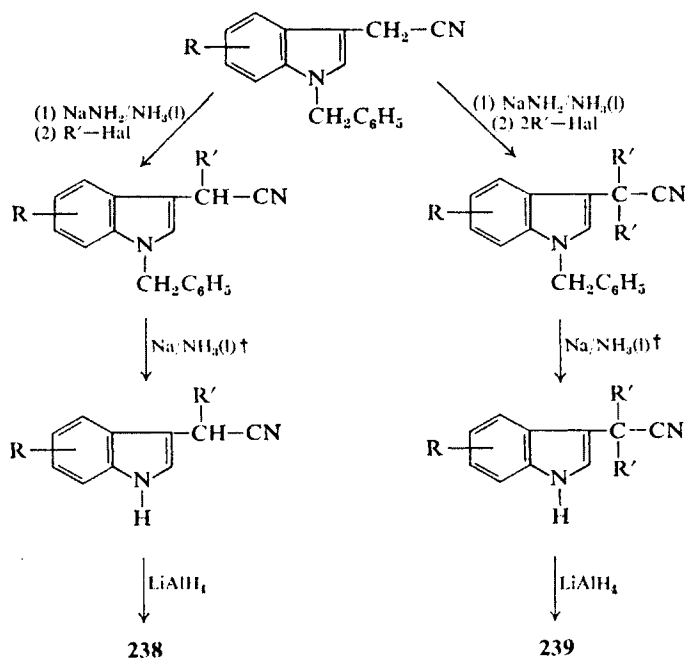
Scheme 40

Indolyl-3-acetonitrile (**235**; X = H) has also been prepared by reaction of indole with potassium cyanide and formaldehyde in aqueous solution in the

presence of phosphate buffer ($\text{pH} > 7$). If the pH is kept below 7 only di(indolyl-3)-methane is formed.^{92, 118} Furthermore, **235** has been obtained in fair yield from indole and diethylaminoacetonitrile by a transamination reaction^{127, 220} or by elimination of water from indolyl-3-acetaldehyde oxime.¹³

A favorable method for obtaining nitriles of types **235** and **236** consists in the reaction of indolylmagnesium halides with α -haloalkylnitriles.^{15, 245, 318, 342, 501, 601} gramines unsubstituted in position 1 and therefore capable of amine elimination (see Section II.1.4) react as free bases with sodium cyanide yielding predominantly indolyl-3-acetamides^{1, 205, 206} or indolyl-3-acetic acid⁴⁹⁶ and not the expected nitriles.

The reduction of the nitriles **235** and **236** to the corresponding tryptamines has been effected catalytically with nickel,^{230, 246, 555} with LiAlH_4 ^{352, 501, 509, 529} or with sodium and ethanol.^{342, 489, 601} * Tryptamines with a branched side chain [i.e., β -alkyltryptamines (**238**) and β,β -dialkyltryptamines (**239**)] are obtained by a process outlined in Scheme 41.^{352, 323}

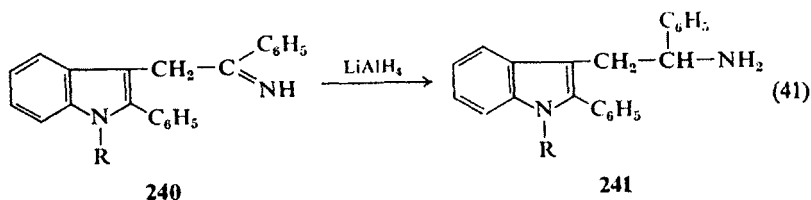


Scheme 41

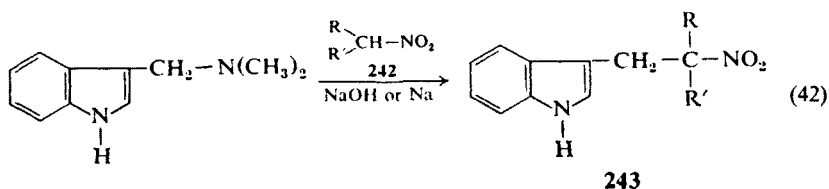
* *Addition in proof.* Catalytic reduction of indolyl-3-acetonitriles in the presence of dimethylamine yields the corresponding dimethyltryptamines [M. Julia and Y. R. Pascal, *Chimie Therapeutique*, **5**, 274 (1970)].

† According to Julia, Manoury, and Igolen.²⁸⁶

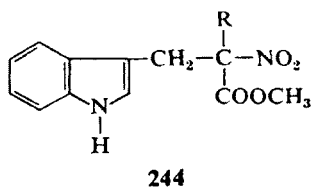
α -Phenyltryptamines (**241**) can be prepared from indolyl-3-acetonitriles, which carry a substituent in position 1, by reaction with phenylmagnesium bromide to the imines **240** followed by reduction²⁰ (Eq. 41).



Another versatile tryptamine synthesis starting with gramines proceeds via 3-nitroethylindoles (**243**) by the method first reported by Snyder and Katz^{215, 217, 227, 340, 492, 581} (Eq. 42). Compounds of type **243** are obtained in



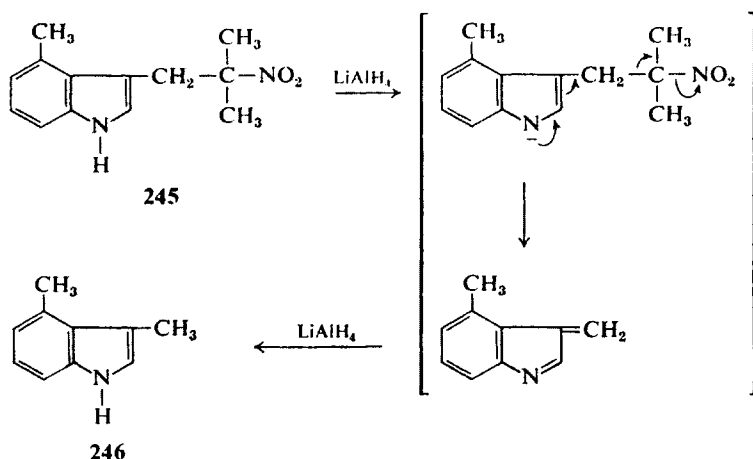
high yield when R and R' are alkyl. Reaction with nitromethane or nitroethane (**242**, R = H, R' = H or CH₃, resp.) leads mainly to diskatylated products.⁴⁹² Diskatylation is suppressed if metallic sodium rather than sodium hydroxide is used as a proton acceptor⁵⁶⁶ or if gramine is replaced by gramine-N-oxide as the reaction partner.^{225*} An analogous reaction of α -nitroesters with gramines affords the nitroester **244** which on hydrolysis gives **243** (R' = H).^{217, 340} Compounds **243** have also been prepared by Fischer cyclization.⁵⁹²



Reduction of the above nitro compounds to the corresponding tryptamines has been effected catalytically with nickel,^{25, 215, 227, 340, 492, 566, 581} palladium,^{217, 253, 580, 592} or platinum.²¹⁵ According to Heinzelman et al.^{217, 227} LiAlH₄ can also be used (see also Ref. 215). In our hands the reduction of

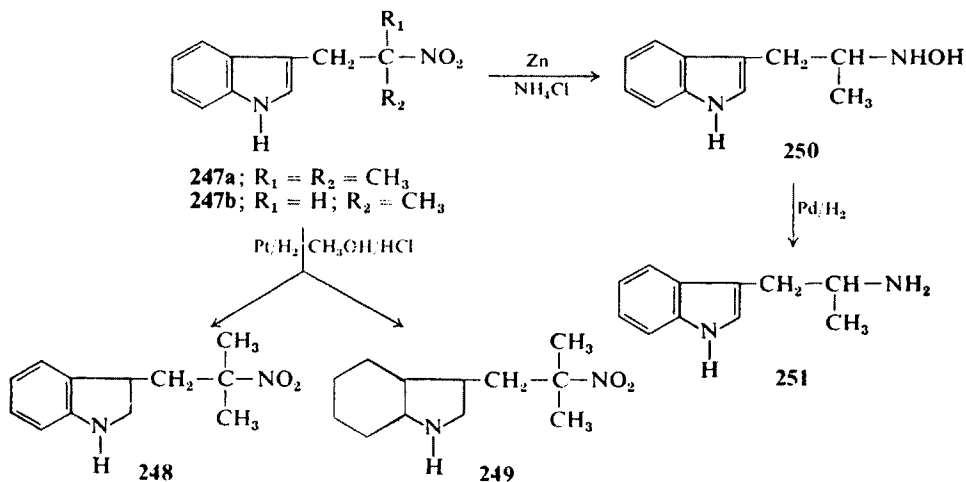
* *Addition in proof.* According to Plieninger et al., such C-skatylations proceed more readily in the presence of esters of acetylenedicarboxylic acid as dimethylamine acceptors. [H. Plieninger, Ch. Wagner, and H. Immel, *Ann. Chem.*, **743**, 95 (1971)].

245 with LiAlH_4 led predominantly to 4-methylskatole (**246**), supposedly by a fragmentation mechanism outlined in Scheme 42⁵⁶⁷ (see also the Addenda).



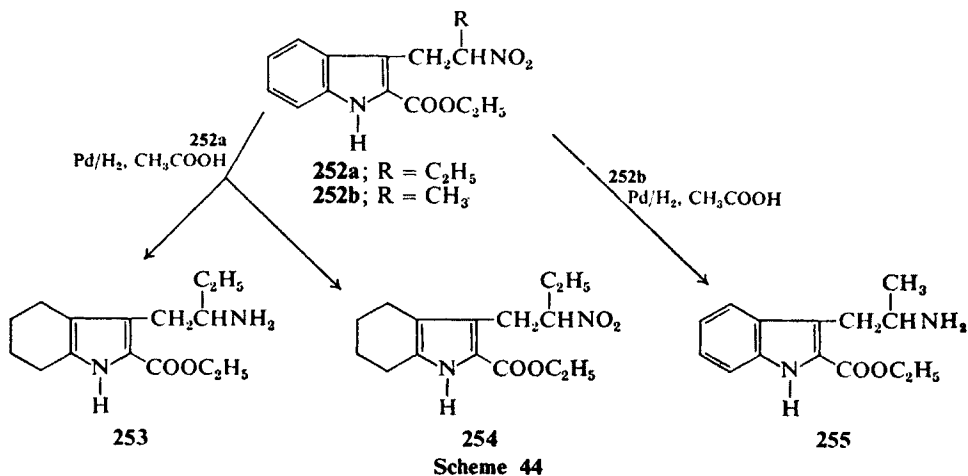
Scheme 42

Anomalous reductions of compounds of formula **243** have been reported by Cohen and Heath-Brown⁹⁰ and Young and Snyder.⁶¹⁹ According to the former authors, hydrogenation of **247a** with platinum in methanolic hydrochloric acid leads to a mixture of the dihydro- and octahydroindoles **248** and **249**. By means of zinc and ammonium chloride **247b** is reduced to the hydroxylamine derivative (**250**) (see also Ref. 436), the further reduction of which yields the tryptamine **251** (Scheme 43).

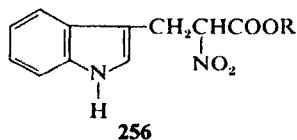


Scheme 43

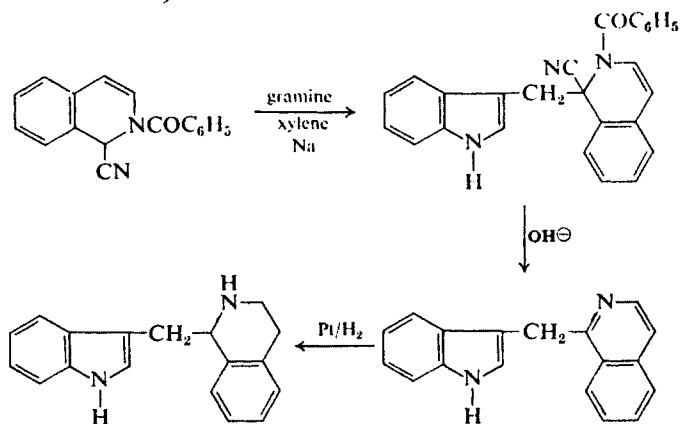
Young and Snyder reported difficulties in the hydrogenation of the nitro group of **252a**; reduction with palladium in acetic acid at 20°C and approximately 45 psi yielded a mixture of **253** and **254**. In contrast to this, the



reduction of the less hindered nitro group of **252b** occurred easily, yielding the normal reduction product **255**⁶¹⁹ (Scheme 44).

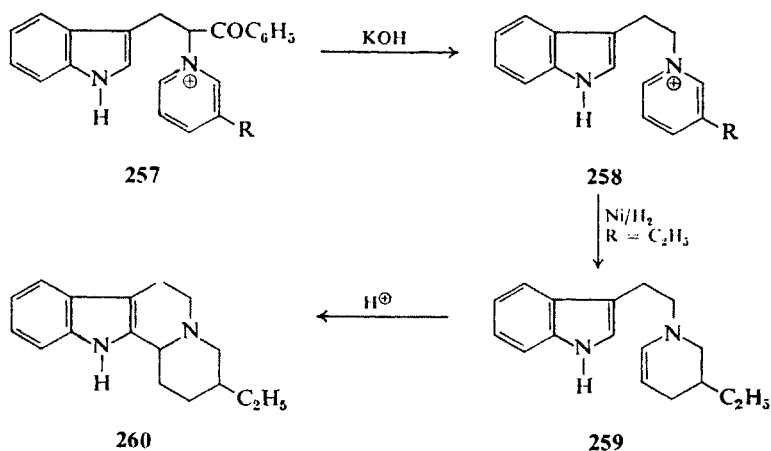


The reduction of the nitroester **256** with LiAlH₄ leads directly to tryptamine (Hellmann and Starck²²³).



Gramines can be condensed with Reissert compounds (for reviews on the chemistry of Reissert compounds, see McEwen and Cobb³⁴⁹ and Popp⁴¹¹) to isoquinolylmethylindoles⁶³ as outlined in Scheme 45.

The tetrahydropyridylethylindole **259** has been obtained by condensation of graminemethiodide with phenacylpyridinium salts to **257**, followed by alkaline cleavage to **258** (for other methods of preparation see Section V.B.3.i and V.B.3.j) and reduction of the latter by means of nickel. The resulting **259** cyclizes to **260** under the influence of acid^{548, 553} (Scheme 46).

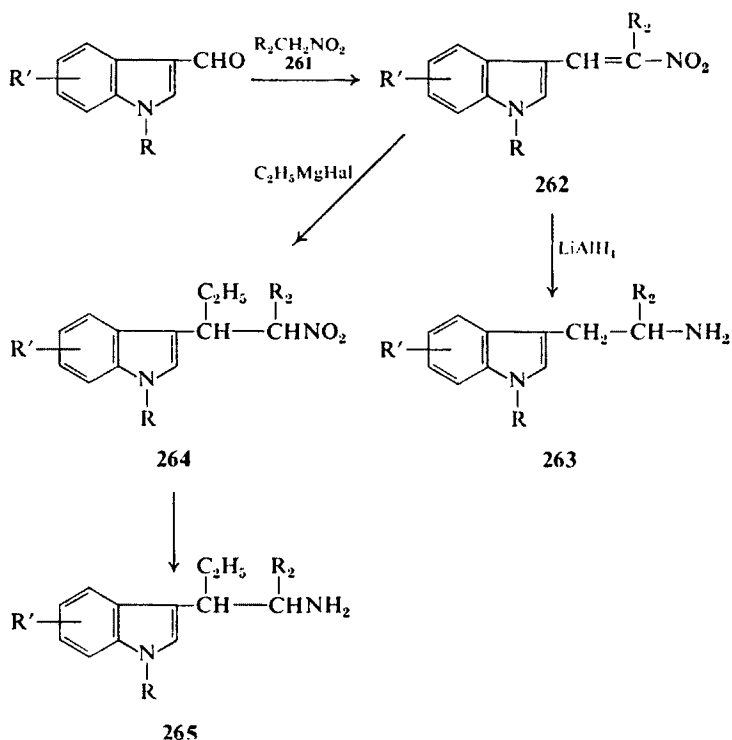


Scheme 46

For partial and complete reduction of the pyridinium ring of compounds of type **258** by means of palladium, LiAlH_4 , or NaBH_4 , see also Ref. 125 and 599. (see also Addenda).

d. FROM 3-(NITROVINYL)INDOLES. This method is one of the most useful for the preparation of tryptamines either with branched or unbranched side chain, viz. α -alkyl, β -alkyl-, and α,β -dialkyltryptamines. It is particularly valuable because the starting materials are easily accessible and the intermediates crystallize readily. The procedure was first applied by Seka⁴⁷⁹ and Onda³⁸⁴ and further developed by Young⁶¹⁸ and Ash and Wragg.²⁵ Heating 3-formylindoles with nitroalkanes **261** ($\text{R}_2 = \text{H}$, alkyl, benzyl, aryl) in the presence of piperidine or ammonium acetate at $100\text{--}110^\circ$ leads in nearly quantitative yield to the crystalline intermediates **262** which afford the tryptamines **263** on reduction with LiAlH_4 .^{25, 114, 181, 215, 217, 252, 529, 567, 600, 618} (Scheme 47) (see also the Addenda).

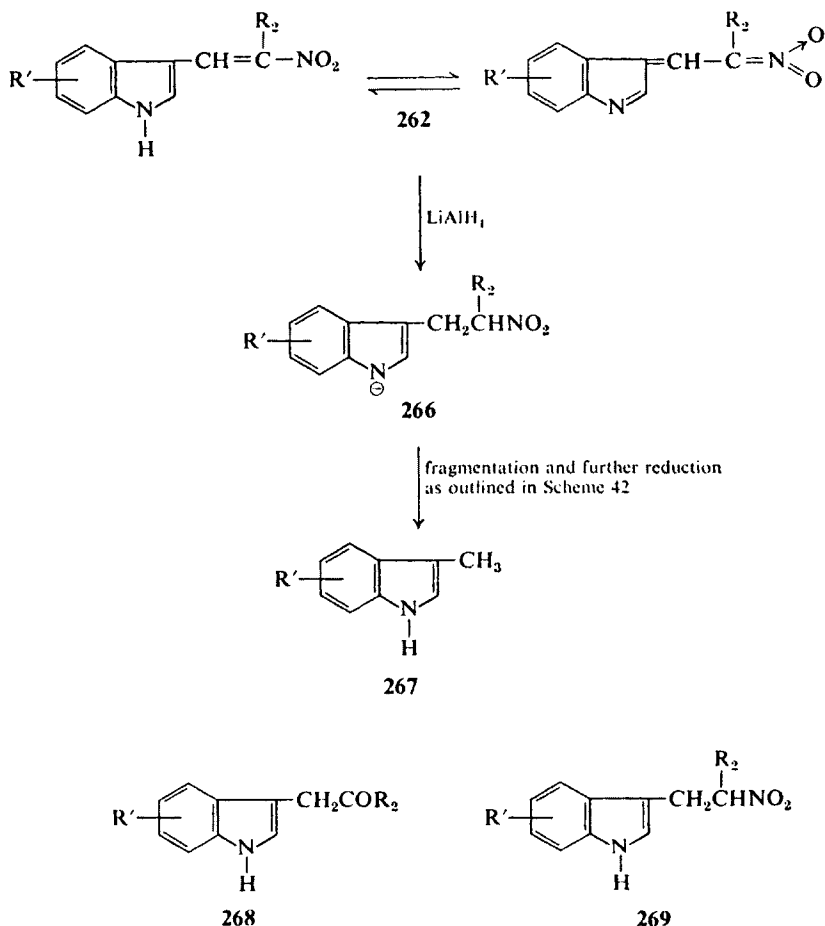
Unfortunately, the reduction of **262** to **263** quite often results in low yields (e.g., 27% of 5-methoxytryptamine from 5-methoxy-3-nitrovinylindole⁵²⁹)



Scheme 47

and by-products have been isolated. In the reduction of 5-benzyloxy-3-nitrovinylindole, Ash and Wragg isolated 5-benzyloxy-3-hydroxymethylindole as a by-product.²⁵ The latter substance may have been formed from some 5-benzyloxy-3-formylindole contaminant in the nitrovinylindole. More important is the observation that, especially under mild conditions, a large amount (up to 50%) of the corresponding skatole **267** is formed in the reduction of **262**, probably via an intermediate **266**, which yields **267** by the mechanism outlined in Scheme 42⁵⁶⁷ (Scheme 48).

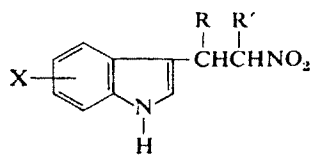
Reduction of **262** to **263** can also be achieved with hydrogen/Pd at 20°C and 1400 psi.²⁵⁴ Treatment of **262** with iron in dilute acetic acid affords the ketones **268**, which are transformed into **263** by reductive amination (nickel, ammonia, hydrogen).³⁸⁶ Meyers and Sircar³⁵⁸ have reported the partial reduction of **262** to **269** with $NaBH_4$ at pH 3–6. The 1,4-addition of alkylmagnesium halides to **262** followed by reduction leads to β -alkyl-substituted tryptamines **265** (if $R_2 = H$) and α,β -dialkyltryptamines (if $R_2 = \text{alkyl}$)^{320, 586} (Scheme 47). On reduction of **264** ($R = H$, $R' = 4-CH_3$, $R_2 = CH_3$) with $LiAlH_4$, a large amount of 3-ethyl-4-methylindole has been isolated as a by-product.⁵⁶⁷



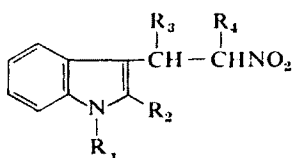
Scheme 48

e. BY NITROETHYLATION. The Michael addition of 3-unsubstituted indoles to nitroolefins and nitrostyrenes takes place at room temperature to yield compounds **270** and **271**.^{20, 374-377, 447} The best yields are obtained when R_3 is phenyl.³⁷⁷

The condensation of indolylmagnesium halides with nitroethylenes has been examined by Acheson and Hands.⁶ They found that 5,6-dimethoxyindolylmagnesium halide is substituted exclusively in position 3, whereas in the case of 5-benzyloxyindole the 1,3-disubstitution product is obtained. Indoles with blocked position 3 are substituted in position 1. Catalytic reduction of **270** and **271** with palladium,⁶ platinum,³⁷⁴⁻³⁷⁶ or nickel³⁷⁷ leads to tryptamines in good yield.

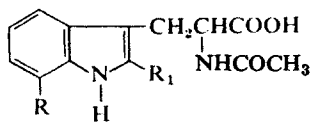
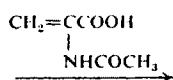
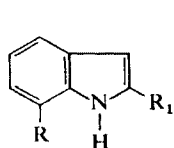


270



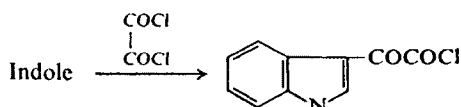
271

R	R'	R ₁	R ₂	R ₃	R ₄
H	H	H(CH ₃)	CH ₃	H	H
CH ₃	H	H(CH ₃)	CH ₃	C ₆ H ₅	H
C ₆ H ₅	H	H(CH ₃)	CH ₃	C ₆ H ₅	CH ₃ (C ₆ H ₅)
C ₆ H ₅	CH ₃	CH ₃	H	C ₆ H ₅	H
		H	C ₆ H ₅	C ₆ H ₅	H(CH ₃)

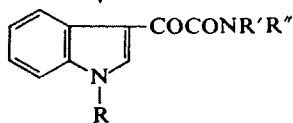


(43)

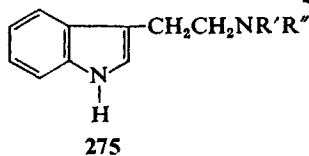
272



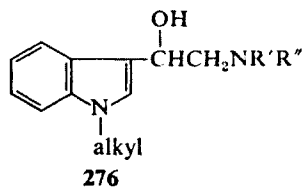
273



274



275

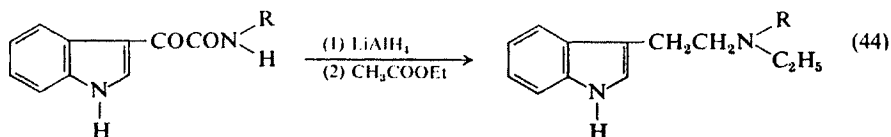


276

Scheme 49

Snyder and MacDonald have prepared the acetyltryptophans **272** by a modification of the above method⁴⁹³ (Eq. 43).

f. PREPARATION BY THE OXALYLCHLORIDE PROCEDURE. The procedure outlined in scheme 49 has been developed by Speeter and Anthony^{500, 573, 578} as a preferred method for the preparation of tryptamines not branched at the α -carbon atom. The course of the reduction of **274** with LiAlH_4 ⁷⁴ depends on the nature of the substituent R: if R is H, tryptamines **275** are obtained in general, whereas 1-substituted 3-indolylglyoxylamides **274** (R = alkyl) are transformed into hydroxytryptamines **276**.^{254b, 572} The rule is not without exception, however, since the course of the reduction depends on the reaction conditions as well. From the LiAlH_4 reduction of 3-indolylglyoxylamide in refluxing tetrahydrofurane, Brutcher and Vanderwerff⁷⁴ isolated 41 % of **275** and 11 % of **276** (R' = R'' = H) while in boiling dioxane, **275** was formed exclusively. Buzas, Hoffmann, and Regnier⁷⁸ reduced **274** (R = alkyl) with LiAlH_4 in dioxane to the tryptamines **275**. The ease of reduction of 3-indolylglyoxylamides depends of the nature and position of substituents in the six-membered ring.^{566*} In the usual decomposition of the lithium aluminate complex with ethyl acetate, *N*-ethylation at the basic nitrogen has been observed⁵⁰² (Eq. 44).

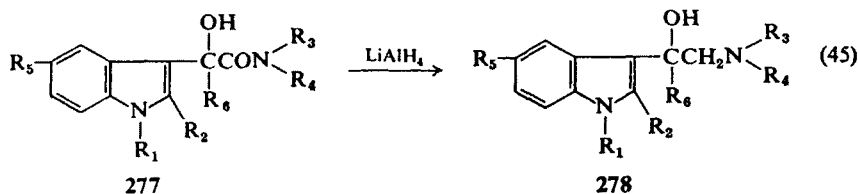


Reduction of **274** with NaBH_4 ⁷⁴ or KBH_4 ²⁰ leads to the corresponding α -hydroxyamides which can be further reduced with LiAlH_4 to the tryptamines **275**.⁷⁴ Reduction of **274** to **275** has also been effected with diborane.⁶⁰ Giua¹⁷⁴ was the first to report on the reaction of indole with oxalylchloride but erroneously assigned the reaction product as indolyl-2-glyoxylic acid chloride. The optimum conditions of this reaction depend on the nature and position of substituents in the six-membered ring.³⁵⁰ From the numerous applications of Speeter and Anthony's method, we cite the following References: 12, 19, 45, 46, 81, 86, 231, 440, 458, 566.

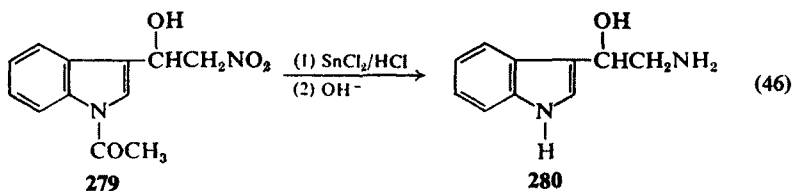
Hydroxytryptamines of type **278** are obtained from 3-indolylglyoxylamides **274** by reaction with Grignard compounds and subsequent reduction of the obtained hydroxyamides **277** with LiAlH_4 ²⁰ (Eq. 45).

g. OTHER METHODS FOR THE PREPARATION OF HYDROXYTRYPTAMINES. The procedure of Speeter and Anthony described above represents the best method for the synthesis of β -hydroxytryptamines. Less important methods

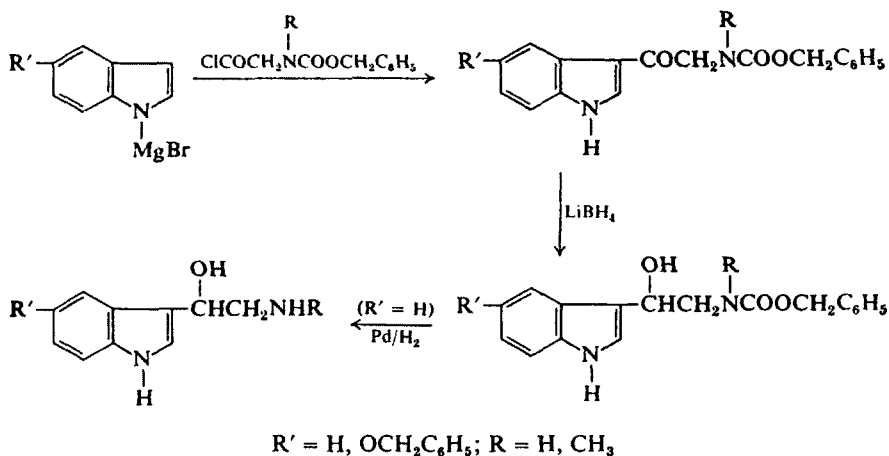
* Attempts to reduce *N,N*-di(2-propynyl)indolyl-3-glyoxylamide with LiAlH_4 to *N,N*-di(2-propynyl)tryptamine failed.³⁶⁹



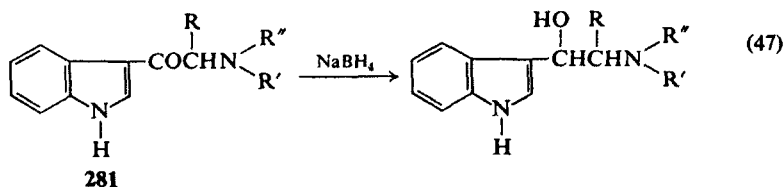
are those of Majima and Kotake³⁴³ who have prepared **279** by addition of nitromethane at 1-acetyl-3-formylindole. Reduction with stannous chloride/hydrochloric acid and subsequent deacetylation led to the hydroxytryptamine **280**, isolated as a picrate (Eq. 46). Attempts to reduce **279** with AlHg, Fe/H⁺, or Pt/H₂ failed.



Because the results of the Japanese authors could not be reproduced by Ames et al.,²¹ they developed a new procedure, outlined in Scheme 50.

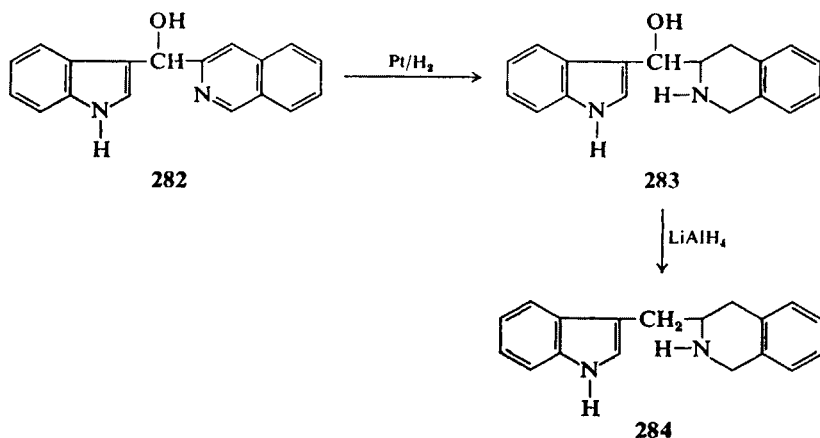


Scheme 50



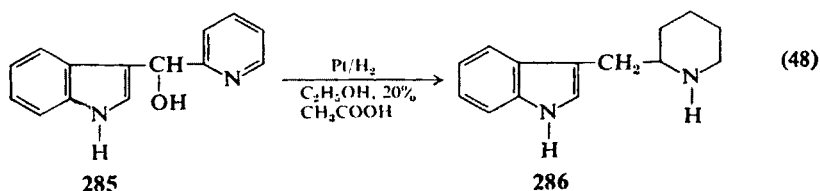
Another route to hydroxytryptamines of type **276** consists in the reduction of 3-aminoacylindoles with NaBH_4 ^{579, 335a} or Raney nickel^{335a} (Eq. 47). If in **281** R is a methyl group, the former method leads to the erythro-form of the resulting amino alcohol. With nickel, a mixture of threo- and erythro-forms has been obtained^{335a} (see also the Addenda).

Bader and Oroshnik²⁹ reduced **282** to **283** with platinum/hydrogen. Further reduction with LiAlH_4 yielded the oxygen-free compound **284** (Scheme 51).



Scheme 51

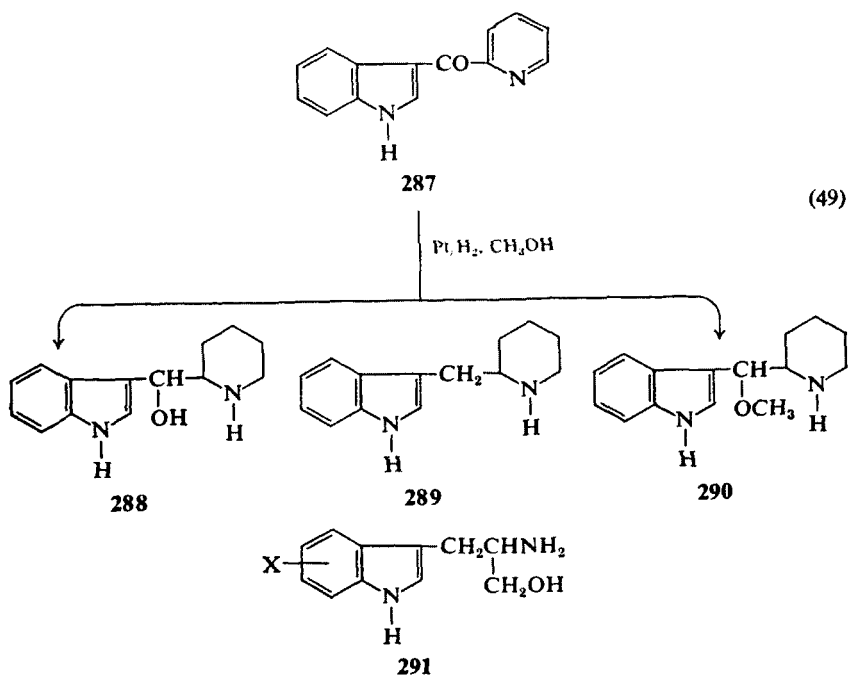
Hydrogenation of **285** with platinum/hydrogen afforded directly the oxygen-free piperidylmethylindole **286**²⁸ (Eq. 48).



Compounds of type **285** have been obtained either by reaction of 3-formylindoles with 2-pyridyllithium (yield 80%)²⁸ or from indolylmagnesium-bromide with 2-formylpyridine (50%).²⁹

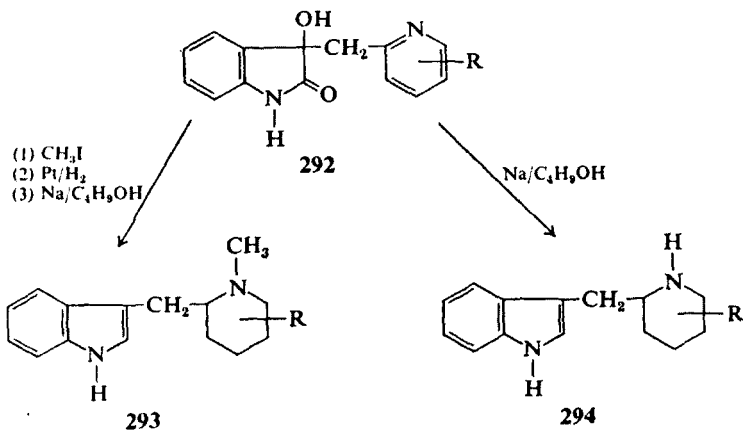
Reduction of **287** with platinum/hydrogen in methanol leads to a mixture of **288–290**⁴³¹ (Eq. 49).

A different type of hydroxytryptamines, tryptophanols, represented by formula **291**, is obtained on reduction of esters of tryptophans with LiAlH_4 .^{296, 481}



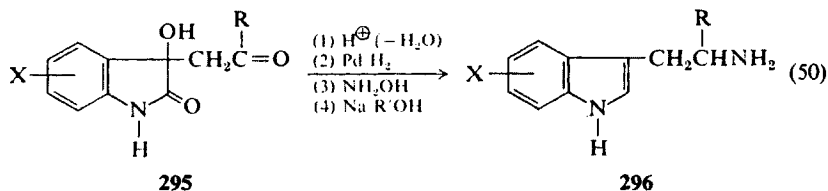
(49)

h. FROM ISATINS, OXINDOLES, AND INDOXYLS. In 1954 Akkerman and Veldstra¹⁷ prepared the tryptamine-like compounds **293** by addition of (substituted) α -picolines to isatins, quaternization of the intermediates **292**, followed by hydrogenation. Reduction of **292** with sodium/butanol yielded **294** in poor yield (Scheme 51a). For other syntheses of compounds of type **294**, see Eqs. (48) and (49).



Scheme 51a

The syntheses of tryptamines from isatins or oxindoles have been thoroughly investigated by Pietra and Tacconi. They condensed isatins with methylketones in the presence of diethylamine to dioxindoles of type **295** which are transformed into tryptamines of formula **296** by successive dehydration, catalytic hydrogenation, reaction with hydroxylamine, and reduction with sodium in a high-boiling alcohol (Eq. 50). By this method,



α -alkyl- and α -phenyltryptamines (**296**; R = alkyl, phenyl) have been prepared from isatin and 5-methoxyisatin⁴⁰⁰ and from 1-methylisatin.⁴⁰¹ In an analogous manner the following tryptamines have been obtained: α -phenyl- β -methyltryptamines **297** from isatins and propiophenone,⁴⁰² α -methyl- β -benzyltryptamine **298** from isatin and benzoylacetone,⁴⁰³ and α,β -diphenyltryptamine **299** from isatin and desoxybenzoin.⁴⁰³ The aldol condensation of isatin with ethyl methyl ketone takes place at the methyl group and finally leads to α -ethyltryptamine **301** and not to α,β -dimethyltryptamine **300**⁴⁰³ (Scheme 52).

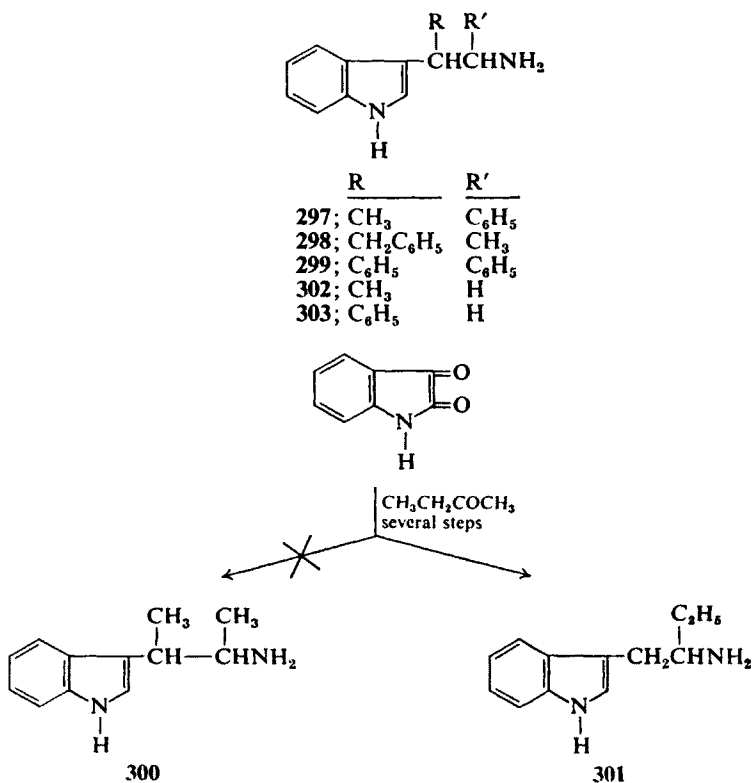
Tryptamine and 5-methoxytryptamine have been synthesized in a similar manner from isatins and cyanoacetic acid ester,^{398, 399} and compound **304** from isatin and cyclohexanone.⁴⁰⁴

The aldol condensation with isatins succeeded also with the oximes of the corresponding ketones.⁵³² A further modification of the procedure consists in the condensation of oxindoles with isonitrosoketones and stepwise reduction of the condensation products **305** with Pd/H₂ and Na/propanol.⁵³²

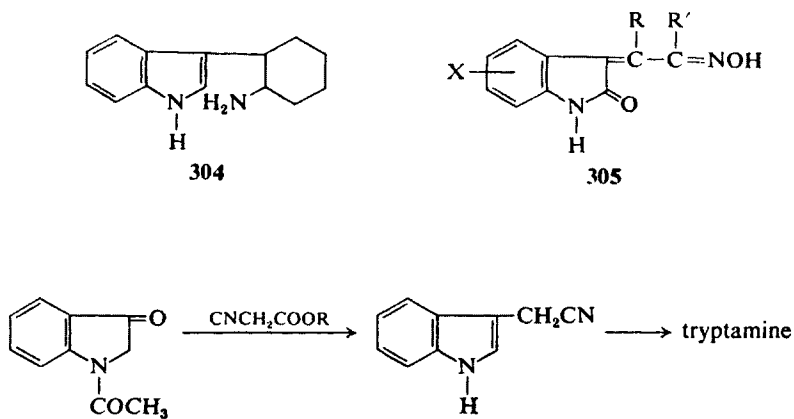
β -Methyltryptamine (**302**) and β -phenyltryptamine (**303**) have similarly been prepared from oxindole and acetylcyanide and benzoylcyanide, respectively.^{405, 531}

Franklin and White^{154, 387} obtained α -alkylated-tryptamines of type **296** from the addition of methylketones to isatins to compounds **295** followed by reduction (low yield) of their oximes with LiAlH₄ or NaBH₄/AlCl₃. 1- α -Dimethyltryptamine has been prepared from 1-methylisatin in an analogous manner.²⁶¹

The preparation of 3-alkyl-2,3-dihydro-1-phenyl-tryptamines by reduction of the corresponding oxindoles is described in a patent.³⁹⁵ As reported by Nenitzescu and Răileanu,³⁶⁸ tryptamine can also be obtained from 1-acetyl-indoxyl as outlined in scheme 53.

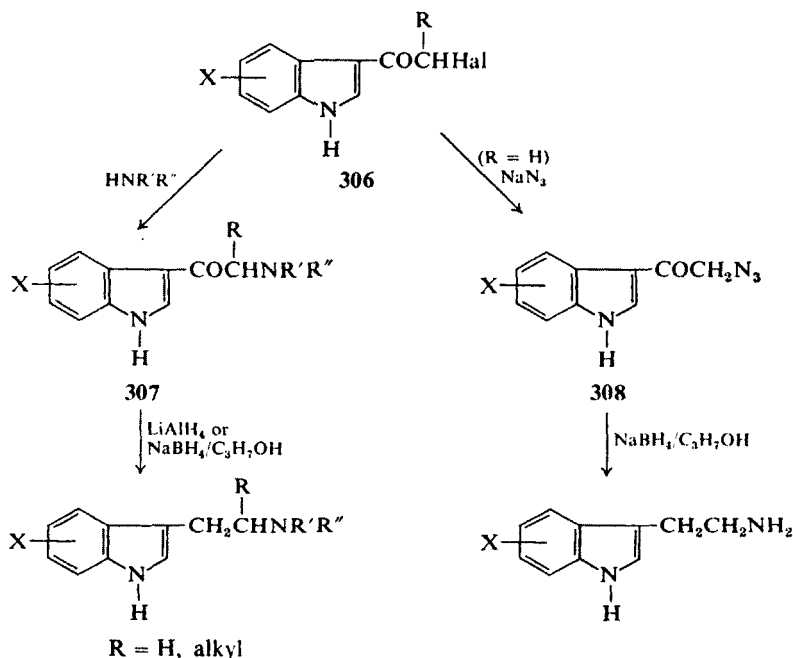


Scheme 52



Scheme 53

i. From 3-HALOACYLINDOLES. 3-Haloacylindoles **306** (prepared either from indolylmagnesium halides and haloacylchlorides^{44b}, by bromination of 3-acyl-indoles,¹⁸¹ or by reaction of indole with *N,N*-dimethylchloroacetamide/ POCl_3 ⁴⁴) have been aminated with secondary amines^{44, 181, 181, 566} to **307** which were reduced to tryptamines with LiAlH_4 ^{181, 556} or with NaBH_4 in propanol.¹⁸⁹ The course of the latter reduction is surprising in view of the reduction of **281** (see Eq. 47). Tryptamines with a primary amino group result from the reaction of **306** with sodium azide and subsequent reduction of the azidoketone **308** with NaBH_4 in propanol¹⁸⁹ (Scheme 54).

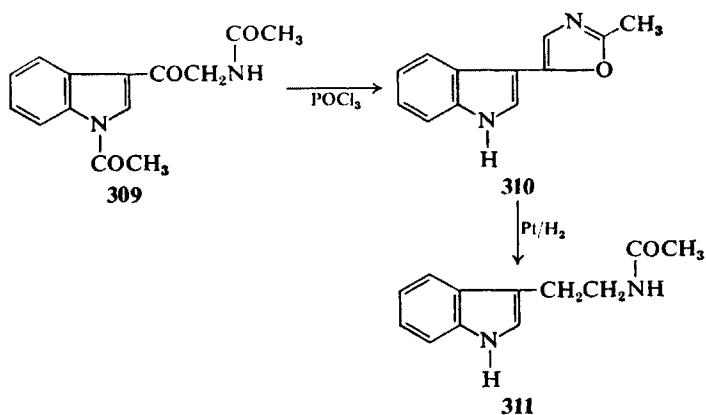


Scheme 54

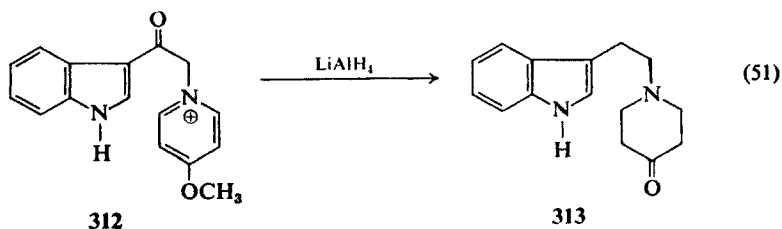
For the reduction of 3-aminoacylindoles to tryptamines, compare also refs. 62 and 614. Cyclization of the acetaminoacetylindole **309** with POCl_3 leads to the alkaloid pimprinine (**310**).²⁷⁷ Catalytic reduction of the latter yields the acetyltryptamine **311**⁵⁶⁷ (Scheme 55).

3-Bromoacetylindole reacts with 4-methoxypyridine to give the quaternary salt **312**, the reduction of which yields the piperidone derivative **313** and a tetracyclic indolo[2,3-*a*]quinolizidine⁴¹³ (Eq. 51).

Quaternary salts of type **312** also result from the reaction of 3-acetylindoles with pyridines or isoquinolines in the presence of iodine³³⁸ according

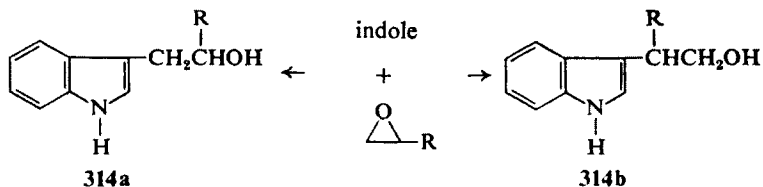


Scheme 55



to the method of King^{301a} (see also Kröhnke^{315, 316}). Partial reduction of the quaternary salts leads to products that cyclize to polycyclic indoles either spontaneously or in a second reaction step^{337, 412, 414} (see also Scheme 57).

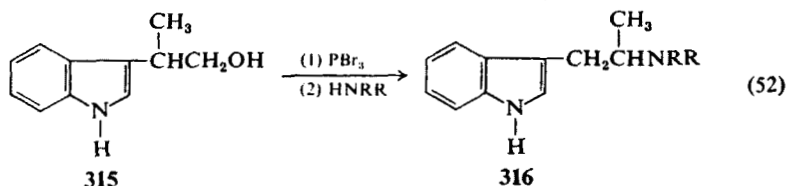
j. FROM 3-HALOETHYLINDOLES.* The title compounds are obtained from 3-hydroxyethylindoles by halogenation with PBr_3 ^{244, 283, 369} or with SOCl_2 ¹²⁴ under carefully controlled conditions. The required alcohols **314** are prepared either by reduction of indolyl-3-acetic acid esters or of indolyl-3-glyoxylic acid esters,³⁷³ or by addition of (substituted)ethyleneoxides to 3-unsubstituted indoles^{284, 215} (Scheme 56).



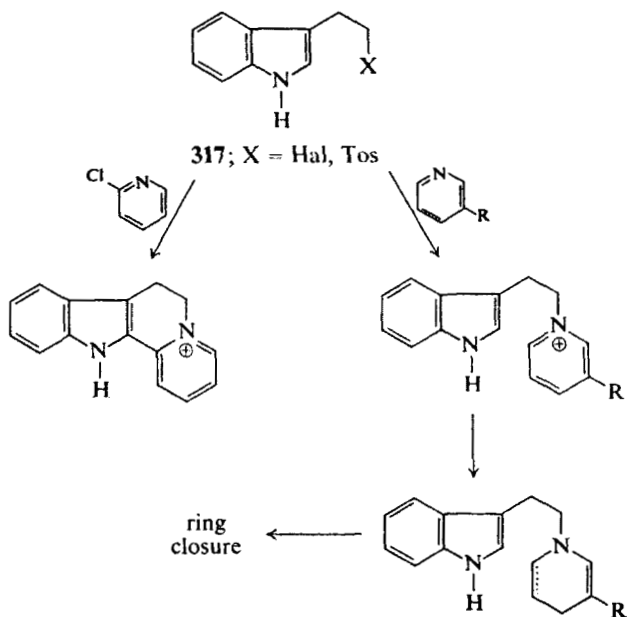
Scheme 56

* *Addition in proof.* 3-(2-Hydrazinoethyl)indoles from 3-(2-haloethyl)indoles and hydrazine (M. Bernabé, E. Fernandez-Alvarez, M. Lora-Tamayo and O. Nieto, *Bull. Soc. Chim. Fr.*, 1971, 1882).

The amination of the halides can be effected with ammonia^{224, 284} or with primary and secondary amines.^{244, 283, 284, 350, 369, 505a, 614} However, 3-(2-chloroethyl)indoles could not be aminated with secondary amines.²⁸³ In the course of the transformation of the branched tryptophols **315** into tryptamines, rearrangement to **316** has been observed²⁸⁴ (Eq. 52).



Reaction of the halides **317** with (substituted)pyridines leads to quaternary salts which cyclize either directly³²⁻³⁴ or after partial reduction of the pyridine ring^{247, 414, 514, 599, 605} to indolo[2,3-*a*]quinolizines (Scheme 57). For partial

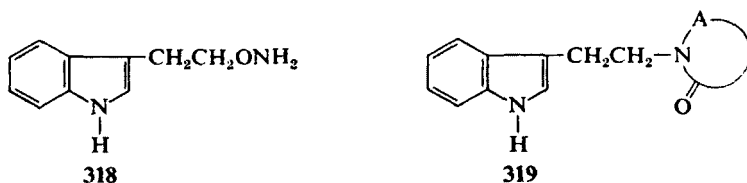


Scheme 57

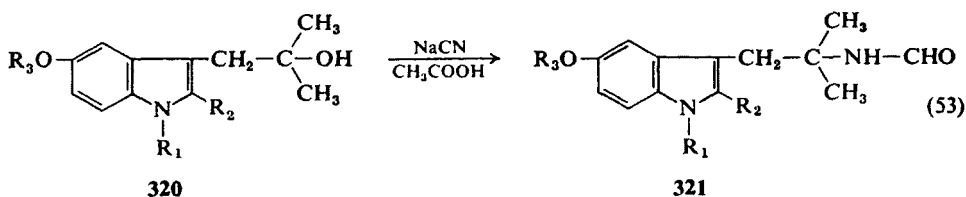
reductions of pyridinium compounds of this type, see Ref. 125 and Section V.B.3.c in the Addenda.

Another interesting example of the diversity of **317** is the reaction with *N*-hydroxyphthalimide which, after elimination of the phthalyl radical, leads to **318**,⁴⁸⁷ whereas with α -aminoacid halides, lactams of formula **319**⁴³⁰ may be obtained.

The corresponding tosylates have also been used in place of the halides in such amination reactions.^{32, 616}



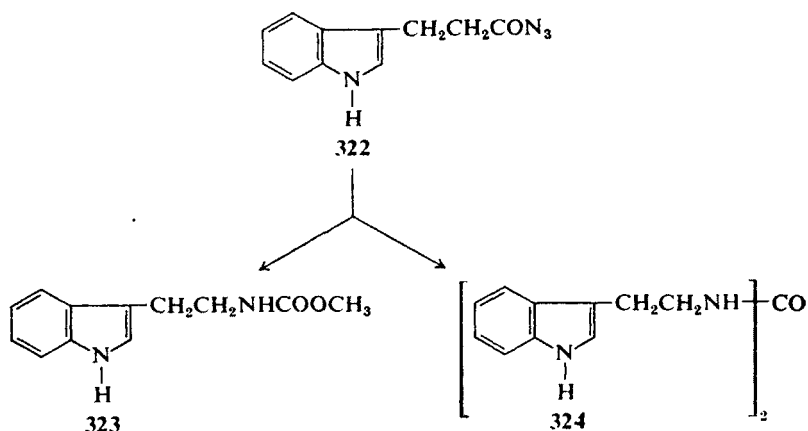
k. FROM TRYPTOPHOLS BY RITTER REACTION OR BY DIRECT AMINATION. Tryptophols **320** (prepared from indolyl-3-acetic acid ester and methyl magnesium halide) yield *N*-formyltryptamines **321** on reaction with HCN.³⁵⁴ The procedure represents a simple way to obtain α,α -dimethyltryptamines (Eq. 53). For direct amination of tryptophols, see the Addenda.



l. BY REDUCTION OF AMIDES OF INDOLYL-3-ACETIC ACIDS. The LiAlH_4 -reduction of indolyl-3-acetic acid amides is a widely used method for the preparation of tryptamines^{1, 283, 285, 481, 509, 570} and has also been applied to obtain β,β -dimethyltryptamine.^{134, 275} The reduction of primary or secondary amides proceeds often with low yield even under forcing conditions which tend to cleave benzyloxy groups present in the molecule.⁵⁶⁶ The starting amides have been obtained either from the acid chlorides (accessible according to the method of Shaw and Woolley⁴⁸²) or by reaction of indolylmagnesium halides with α -haloalkanoylamides.⁵⁷⁰

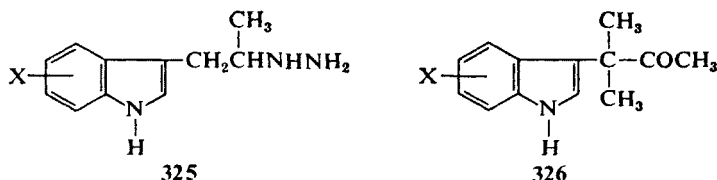
m. BY CURTIUS DEGRADATION OF INDOLYL-3-PROPIONYL AZIDE. Curtius degradation of the azide **322** in methanol leads to a mixture of the urethane **323** and the urea **324**^{344, 345, 256} (Scheme 58). In the presence of hydrochloric acid the intermediate isocyanate cyclizes readily to 1,2,3,4-tetrahydro- β -carbolin-1-one.^{346, 452, 454} Additional applications of this method are given in Refs. 289 and 485a.

n. BY REDUCTIVE AMINATION OF CARBONYL COMPOUNDS. The reductive amination of indolyl-3-acetone with ammonia leads to α -methyltryptamine.³⁸⁸ The reduction of the hydrazones of substituted indolyl-3-acetones with platinum in methanol containing acetic acid yields the hydrazine derivatives

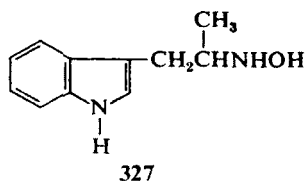


Scheme 58

325.⁴⁷⁷ Preparation and reductive amination of the branched ketone **326** have been described by Julia et al.²⁸³

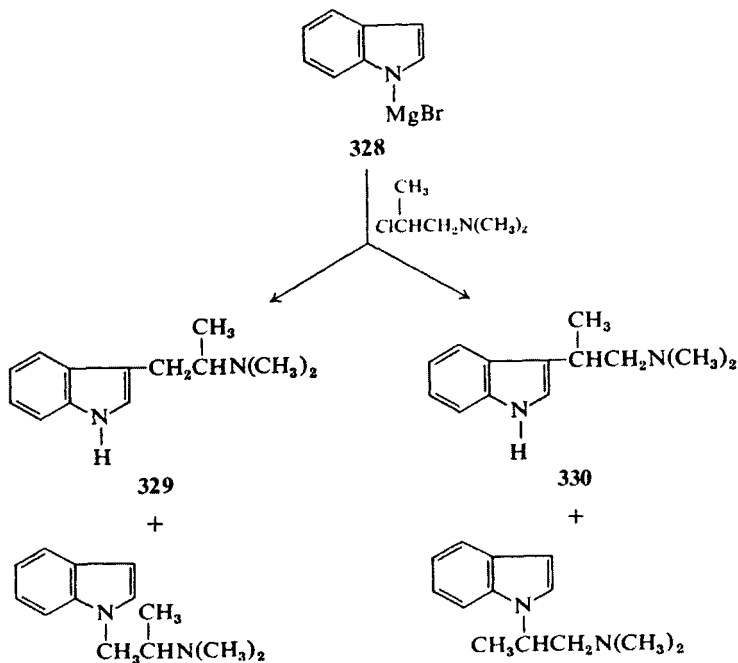


The hydroxylamine derivative **327** has been prepared from indolyl-3-acetone oxime with platinum/hydrogen in acidic solution.⁴⁷



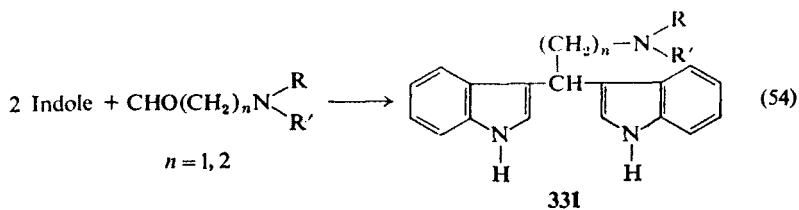
o. BY AMINOALKYLATION OF INDOLES WITH FREE POSITION 3. One mole of indolylmagnesiumiodide reacts with 2 moles of 2-dimethylaminoethylchloride to give *N,N*-dimethyltryptamine in 15–30% yield.¹⁶² Under the same conditions 2-chloro-1-dimethylaminopropane (**328**) leads to a mixture of the isomeric tryptamines **329** and **330** as well as the corresponding 1-substituted derivatives¹⁶¹ (Scheme 59). Alkylation of indolylsodium salts leads exclusively to 1-substituted products¹⁶¹ (see also Section III.B.3).

Another tryptamine synthesis consists in the addition of ethyleneimine to indolylmagnesium halides.^{77, 319} Indole as such reacts with the tetrafluoroborate of ethyleneimine and yields a mixture of tryptamine and 1-(2-aminoethyl)indole, the ratio of which depends on the reaction temperature. 2-Methylindole leads exclusively to 2-methyltryptamine.³⁹³

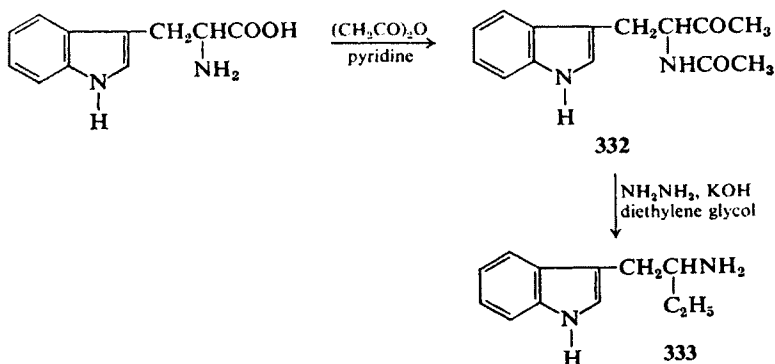


Scheme 59

Condensation of amino aldehydes with indoles affords diindolylalkylamines of formula **331** (Eq. 54).²⁸⁸

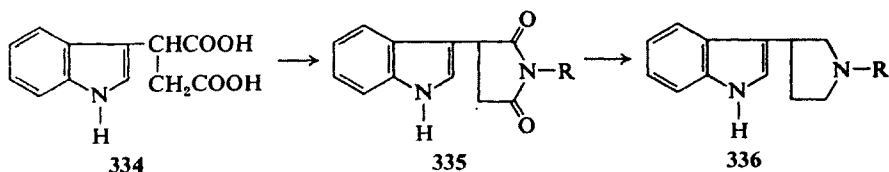


p. α -ALKYLATED TRYPTAMINES FROM TRYPTOPHANS. Tryptophan reacts with acetic anhydride and pyridine to give **332**.^{101, 176} (Dakin-West reaction). The Huang-Minlon reduction of the latter compound yields α -ethyltryptamine (**333**)²¹⁷ (Scheme 60).



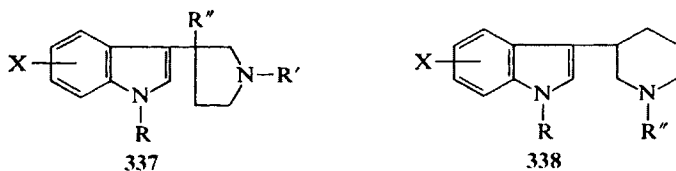
Scheme 60

q. INDOLES WITH CYCLIC TRYPTAMINE SIDE CHAIN. 3-(3-Pyrrolidinyl)-indoles (**336**) have been prepared by cyclization of the dicarboxylic acid **334** with amines and subsequent reduction of the 3-(3-indolyl)succinimide **335**³⁹⁰ (Scheme 61).



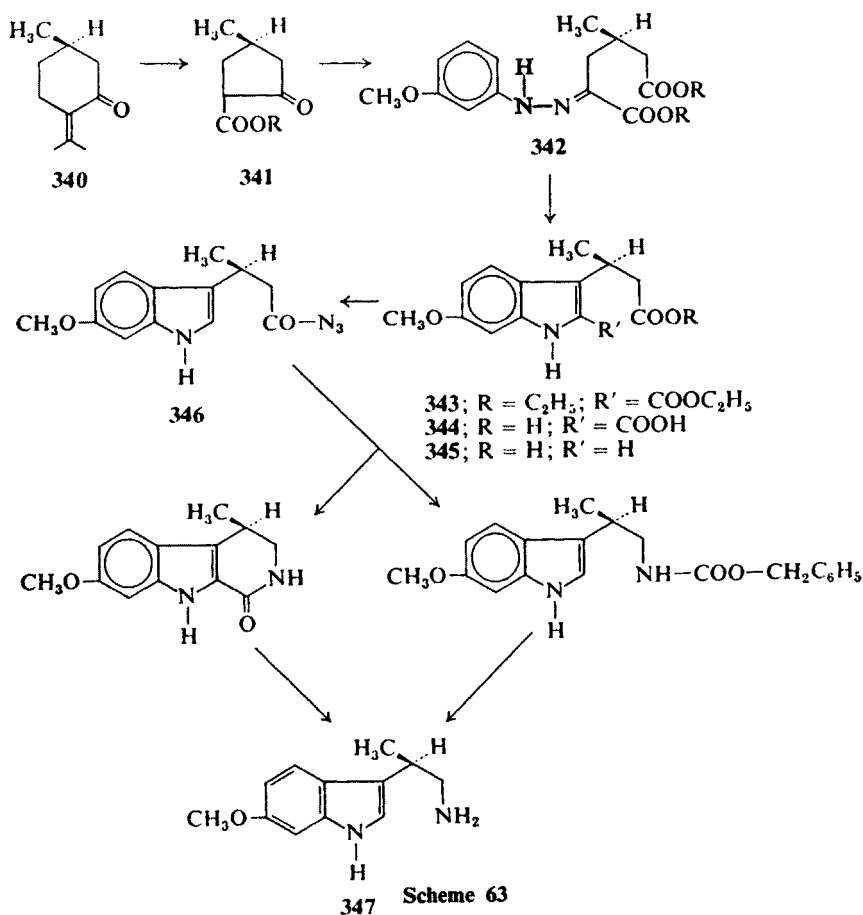
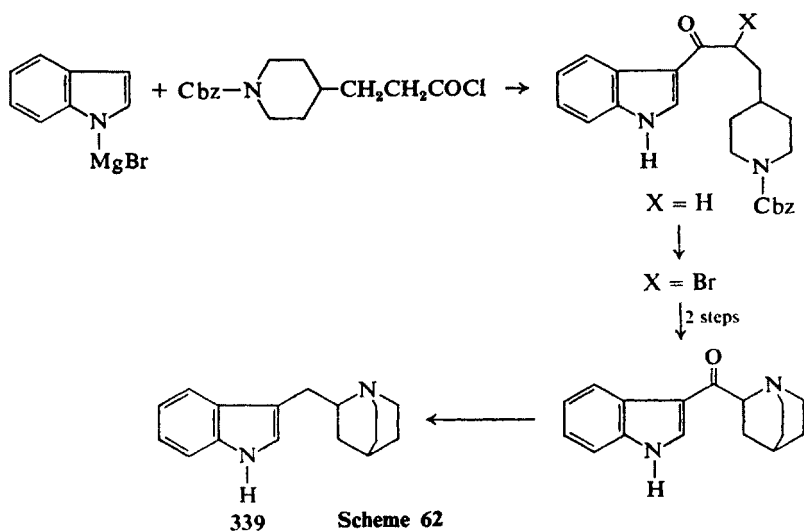
Scheme 61

Compounds of the types **337** and **338** have been synthesized in an analogous manner.^{278, 279}



The synthesis of **339** as outlined in Scheme 62 has been described by DeGraw and Kennedy.¹⁸⁷

r. SYNTHESIS OF OPTICALLY ACTIVE 6-METHOXY- β -METHYLTRYPTAMINE FROM (D)-(+)-PULEGONE. An elegant procedure for the preparation of (D)-(+)-6-methoxy- β -methyltryptamine **347** has been developed by Frey et al.^{156, 449, 452, 454} and is outlined in Scheme 63. (D)-(+)-Pulegone (**340**) was oxidized and the dicarboxylic acid obtained was cyclized to **341**. Coupling of the latter with the diazonium salt of *m*-anisidine (Japp-Klingemann

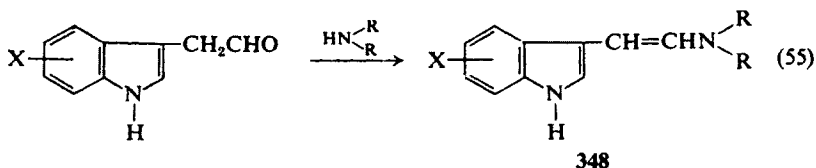


reaction) followed by esterification gave the diester **342**, which led to the indole **343** by Fischer cyclization. The 2-carbomethoxy group of **343** was removed by hydrolysis and decarboxylation of **344** to **345** and the tryptamine derivative **347** was finally obtained by Curtius degradation of the azide **346**.

For Section V.B.3.s, see the Addenda.

4. Dehydrotryptamines

Dehydrotryptamines, viz. **348**, are available by condensation of 3-indolyl-acetaldehydes with secondary amines¹⁰² (Eq. 55). From the comparison of

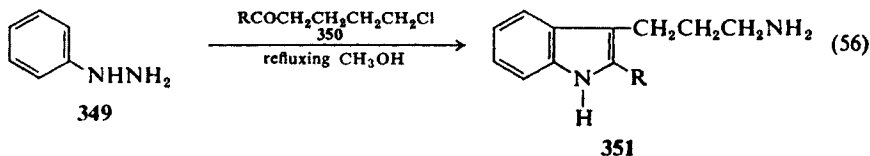


spectral data of compounds **348** with those of "dehydrobufotenine," Daly and Witkop conclude that the latter is not a derivative of type **348** as supposed by Wieland⁶⁰² but has a tricyclic structure¹⁰² (compare also Refs. 348a and 432a).

Reduction of **348** (X = H, R = CH₃) with LiAlH₄ or NaBH₄ affords dimethyltryptamine whereas catalytic reduction fails.¹⁰²

5. Homotryptamines (3-[3-Aminopropyl]indoles)* (see also the Addenda)

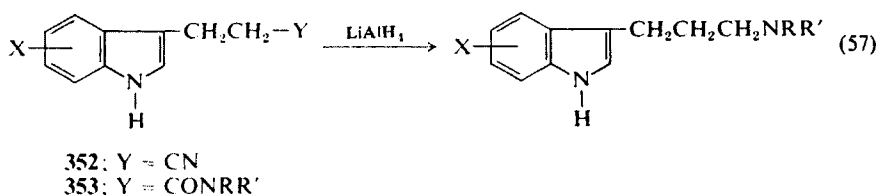
Grandberg¹⁸⁰ obtained homotryptamines **351** on refluxing equimolar amounts of **349** and **350** in methanol (Eq. 56).



* *Addition in proof.* A new synthesis of homotryptamines unsubstituted in position 2: (I. I. Grandberg and S. B. Nikitina, *Khim. Geterocikl. Soed.*, **1971**, 54). 3-(3-Hydrazinopropyl)indoles from 3-(3-halopropyl)indoles and hydrazine (M. Bernabé, E. Fernandez-Alvarez, M. Lora-Tamayo, and O. Nieto, *Bull. Soc. Chim. Fr.*, **1971**, 1882).

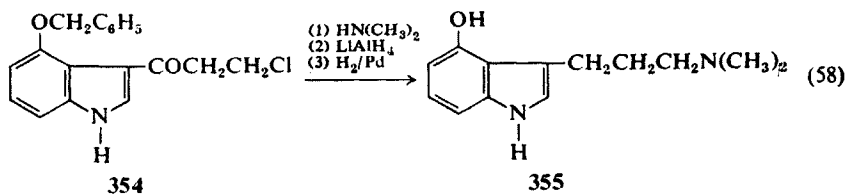
A number of 3-[3-(1-piperazinyl)propyl]indoles have been prepared by Fischer cyclization.¹⁴³

Homotryptamines have been prepared by amination of 3-(3-halopropyl)-indoles^{505a, 614} and homotryptamine itself (**351**; R = H) by Curtius degradation of indolyl-3-butyric acid.^{265a} Other routes leading to homotryptamines are the reduction of 3-(2-cyanoethyl)indoles (**352**) with nickel/hydrogen^{322, 367} or with sodium/ethanol,³⁴² and the reduction of amides of indolyl-3-propionic acid (**353**) with LiAlH_4 ^{505a, 570} (Eq. 57).



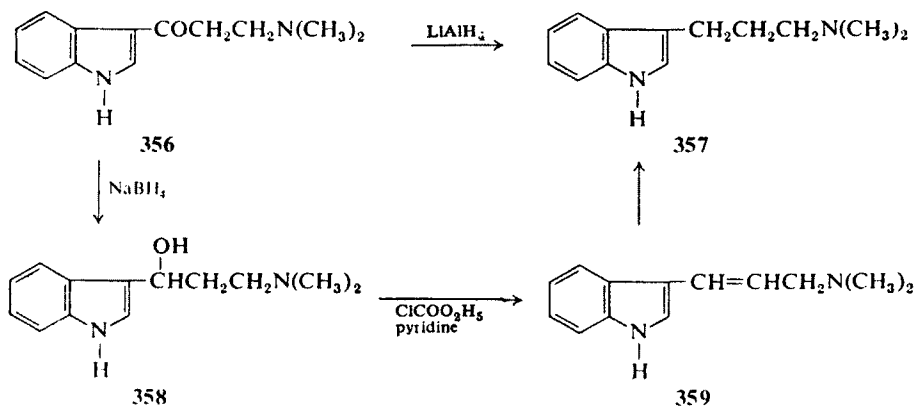
The starting nitriles **352** have been prepared by addition of acrylonitrile to indoles in the presence of cupric acetate and boric acid,⁵³⁸ from 3-(2-hydroxyethyl)-indoles (tryptopholes) by conventional methods,¹²⁴ or from indolylmagnesiumiodide and 3-chloropropionitrile.⁵³⁵ The required amides **353** result from the reaction of indolylmagnesiumhalides with the appropriate amides of 3-chloropropionic acid.⁵⁷⁰

3-(3-Dimethylaminopropyl)-4-hydroxyindole **355** has been synthesized by reaction of 4-benzyloxyindolylmagnesiumhalide with 3-chloropropionyl-chloride to the 3-chloropropionylindole **354** followed by treatment with dimethylamine, LiAlH_4 , and palladium/hydrogen⁵⁶⁶ (Eq. 58).

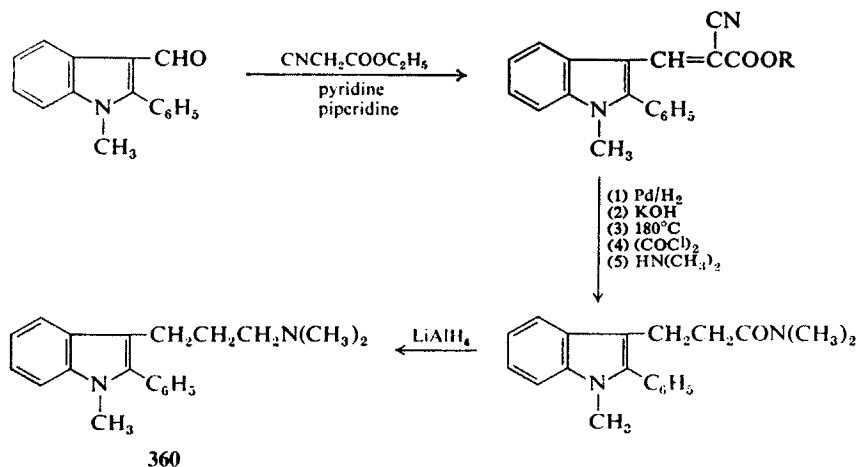


As reported by Szmuszkovicz⁵²⁷ the reduction of 3-(3-dimethylamino-propionyl)indole (**356**) with LiAlH_4 yields directly the homotryptamine **357**, whereas the reduction with NaBH_4 leads to the hydroxy compound **358** which can be converted into **357** by dehydration to **359** followed by reduction (Scheme 64). The preparation of compounds of type **356** by the Mannich reaction has already been mentioned (see Section II.H).

Another synthetic approach to a homotryptamine (**360**), used by Ames et al.,²⁰ is depicted in Scheme 65.

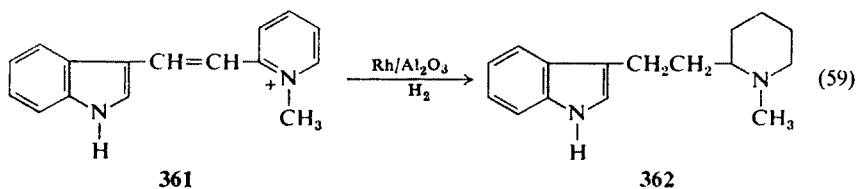


Scheme 64



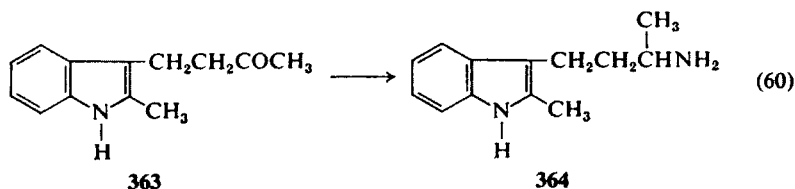
Scheme 65

The homotryptamine-type Compound **362** has been obtained by condensation of 3-formylindole with picolinium salts in the presence of piperidine and subsequent catalytic reduction of the intermediate **361** (Eq. 59).^{17, 83, 204, 437}

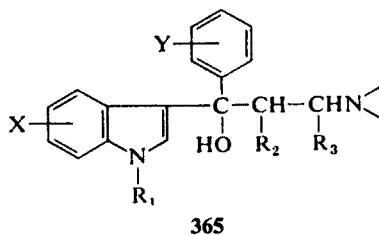


Reduction of the oxime of **363** (obtained by addition of methyl vinyl ketone to 2-methylindole) leads to the α -methylhomotryptamine **364**.⁵²⁵

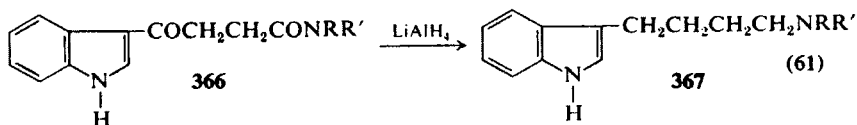
(Eq. 60). The reductive amination of compounds of type **363**, which affords also α -methylhomotryptamines, is described in a patent.⁴⁷⁸ Aryl-substituted



hydroxyhomotryptamines of formula **365** have been prepared by reaction of compounds of type **356** with (substituted)phenylmagnesiumhalides.⁵⁷⁵



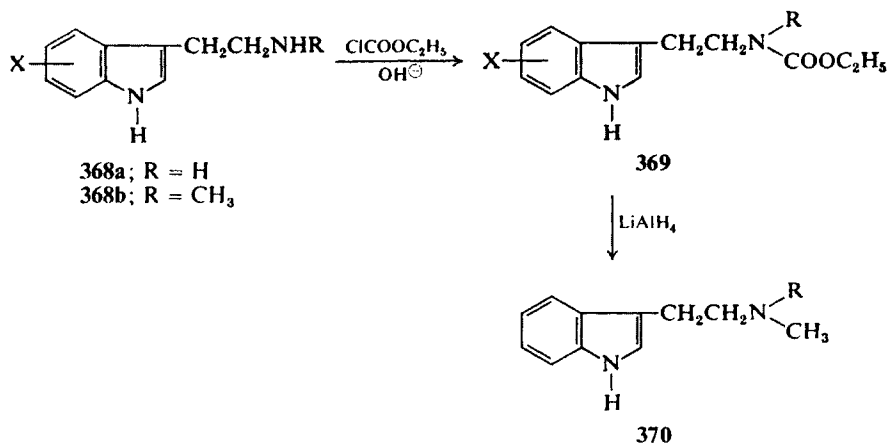
Reduction of **366** with LiAlH_4 yields 3-(4-aminobutyl)indoles (**367**) (bishomotryptamines) (Eq. 61).^{312a}



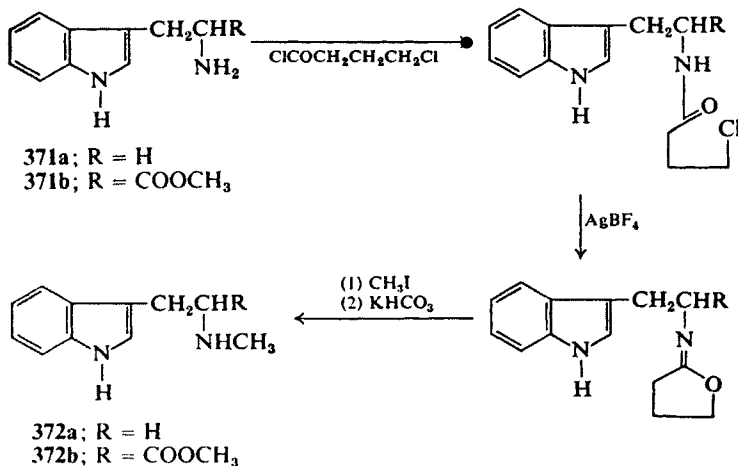
6. Methods for the Selective Alkylation of Tryptamines

Monomethyltryptamines **370a** are obtained in high yield by the method of Knabe³⁰⁵ and Dannley, Lukin, and Shapiro¹⁰³ by reaction of the tryptamine **368a** with ethyl chloroformate followed by LiAlH_4 reduction of the obtained urethanes **369**. The same reactions starting with **368b** lead to the dimethyltryptamines **370b** (see also Horner et al.²⁴²) (Scheme 66). This methylation method seems to be superior to the older one that consists of tosylation, methylation, and finally detosylation either by means of aniline-hydrochloride²⁴³ or sodium in liquid ammonia.⁶⁰⁴ Reduction of *N*-formyltryptamines⁴³⁵ and of *N,N'*-diformyltryptamines¹²³ with LiAlH_4 also affords monomethyltryptamines.

A new monoalkylation method, which allows the preparation of monomethyltryptamines and monomethyltryptophans in high yield (**371b** $\rightarrow$ **372b**: 84%), has been developed by Eschenmoser et al.³⁹¹ (Scheme 67).



Scheme 66



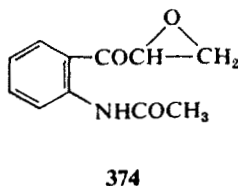
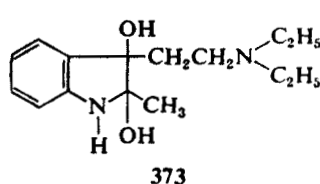
Scheme 67

7. Tryptamine-*N*-oxides, 2,3-Dihydrotryptamines, Guanidines, and Related Compounds* (see also the Addenda)

Tertiary tryptamines, viz. dimethyltryptamine and bufotenine (5-hydroxy-dimethyltryptamine), form the corresponding *N*-oxides^{149, 574} in ethanol with

* *Addition in proof.* The formation of isothiuronium salts from tryptamines or 3-(2-bromoethyl)indoles [V. S. Murasheva V. N. Buyanov and N. N. Suvorov, *Chem. Heterocycl. Comp.*, USSR, **4**, 211 (1968)] and indolyl-3-thioformamidinium salts from indoles and *S,N,N*-trialkylchlorothioformamidinium salts (R. L. N. Harris, *Tetrahedron Lett.*, **1970**, 5217).

hydrogen peroxide. According to Yee-Sheng Kao,²⁹⁴ 2-methyl-*N,N*-diethyltryptamine resists oxidation with a 3% hydrogen peroxide solution while 10 and 15% solutions lead to **373** and **374**, respectively.

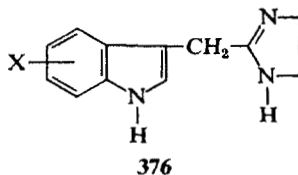
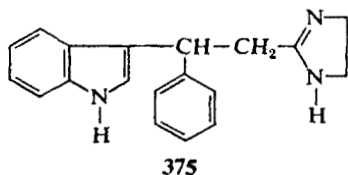


On heating in DMSO at ca. 80°, *N,N*-dimethyltryptamine-*N*-oxide is converted in 56% yield to 3-vinylindole³⁸⁰; treatment of the former compound with ferrous nitrate and oxalic acid results in demethylation and yields monomethyltryptamine.¹⁵⁰

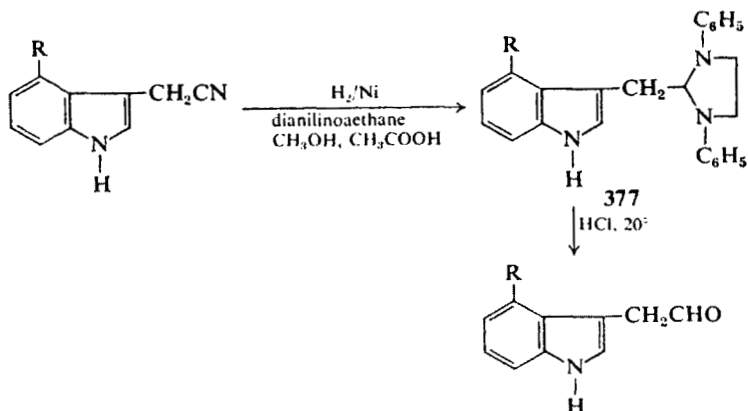
Reduction of serotonin (5-hydroxytryptamine) to 2,3-dihydro-5-hydroxytryptamine has been effected with hydrogen/palladium.¹⁴⁶

For the Birch reduction of 5-methoxytryptamines see Section V.B.g.

Tryptamines are transformed to guanidines by means of cyanamide.³⁹⁷ A number of amidines have been prepared from indolyl-3-acetonitriles via the



corresponding iminoethers.^{145, 475, 609} The imidazolyl compound **375** has been prepared by the same method.²³⁶ Imidazolylmethylindoles **376** have

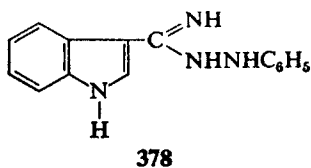


Scheme 68

been obtained by reaction of indolyl-3-acetonitriles with ethylenediamine toluene sulfonate.¹¹⁵

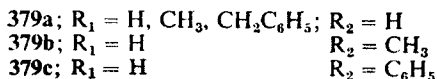
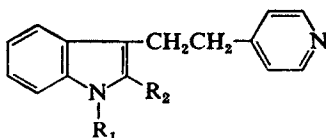
3-Imidazolidinylmethylindeoles **377** are intermediates in the preparation of indolyl-3-acetaldehydes according to the method of Plieninger^{409, 410} (Scheme 68).

The amidrazone **378** has been synthesized by Doyle¹¹⁶ from the iminoether of 3-cyanoindole.



8. Miscellaneous Methods for the Preparation of Indoles with Basic Side Chain in Position 3 [see also the Addenda]

Indoles with a free position 3 react with 4-vinylpyridine in acetic acid to give 3-pyridylethylindoles **379a** and **379b**.^{192, 195, 258} The 2-phenyl derivative **379c** has been obtained by dehydrogenation of the corresponding indoline compound.⁷³ 2-Vinylpyridine has been reported to react analogously.⁴³

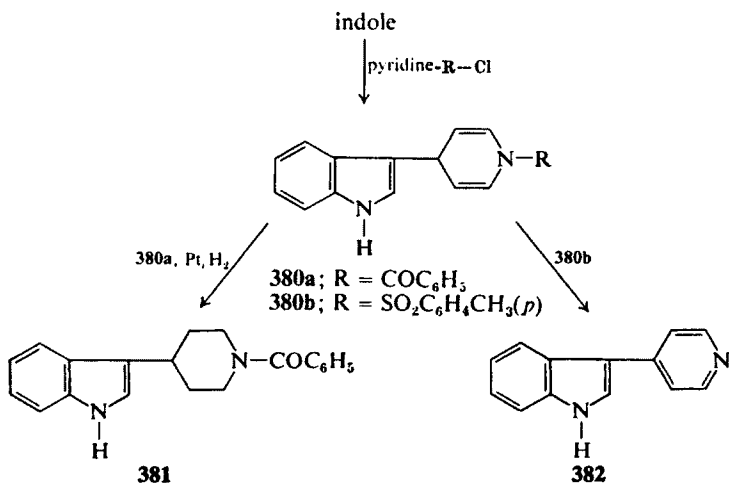


Compounds **379** and their quaternary salts have been reduced to the corresponding piperidine derivatives with platinum/hydrogen,^{43, 194} while NaBH_4 reduction of the quaternary salts leads to the 1,2,3,6-tetrahydropyridine compounds.¹⁹⁴

Indole and pyridine react in the presence of acid chlorides to give the 3-(1-acyl-1,4-dihydropyridyl)indoles **380a** and **380b**. Substituted pyridines as well as quinolines react in a similar manner. * The *N*-benzoyl derivative can be reduced to **381** with platinum and hydrogen, and the *N*-tosyl derivative

* *Addition in proof.* For further work on this reaction see also: J. Bergman, *J. Heterocycl. Chem.*, **7**, 1071 (1970) and H. Deubel, D. Wolkenstein, H. Jokisch, T. Messerschmitt, S. Brodka, and H. v. Dobeneck, *Chem. Ber.*, **104**, 705 (1971).

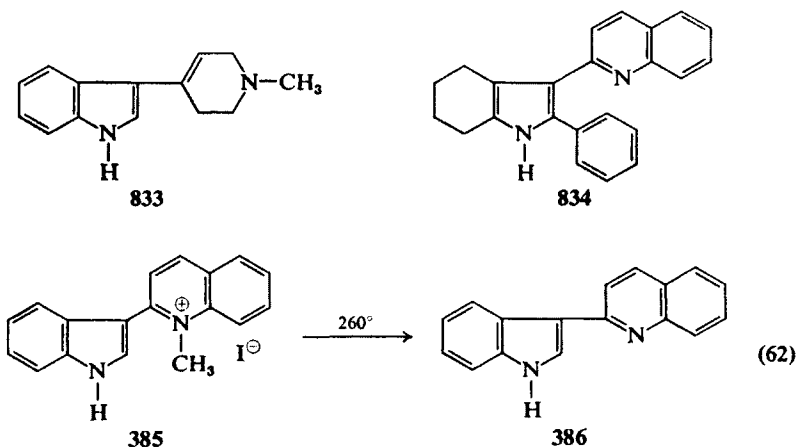
380b readily eliminates *p*-tolylsulfonic acid to form **382**¹⁰⁷ (Scheme 69). The transformation of compounds of type **380a** into pyridylindoles of



Scheme 69

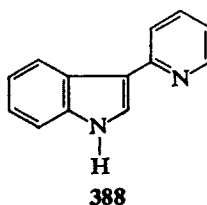
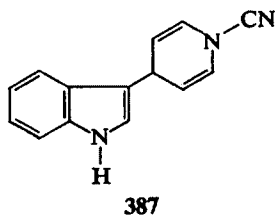
type **382** has also been accomplished by means of oxygen as described in a patent.^{429a}

The reduction of the methiodide of **382** with NaBH₄ to **383** has been reported by Beck and Schenker.³⁸ 2-Phenyl-4,5,6,7-tetrahydroindole condenses with quinoline-*N*-oxide in the presence of benzoylchloride to give **384**.⁹⁵

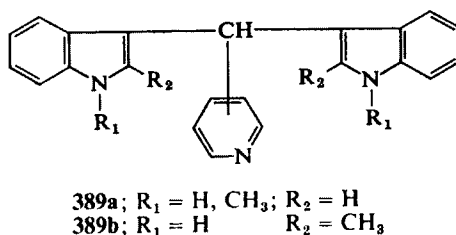


The reaction of indole with quinoliniummethiodide in the presence of sodium ethoxide is thought to lead to the oxidation product **385**, the pyrolysis of which yielded **386**¹⁰⁷ (Eq. 62).

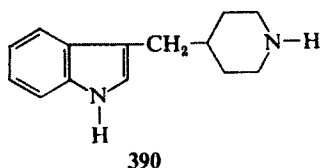
3-(1-Cyano-1,4-dihydro-4-pyridyl)indole (**387**) has been obtained from the reaction of indole with cyanogen bromide and pyridine.⁴¹⁶ Hydrolysis of this compound with either potassium hydroxide (yield 90 %) or dilute hydrochloric acid (yield 41 %) regenerates indole.⁴¹⁷ 3-(2-Pyridyl)indole (**388**) is formed in the reaction of indolylmagnesiumhalides with 2-chloropyridine.⁴¹⁶

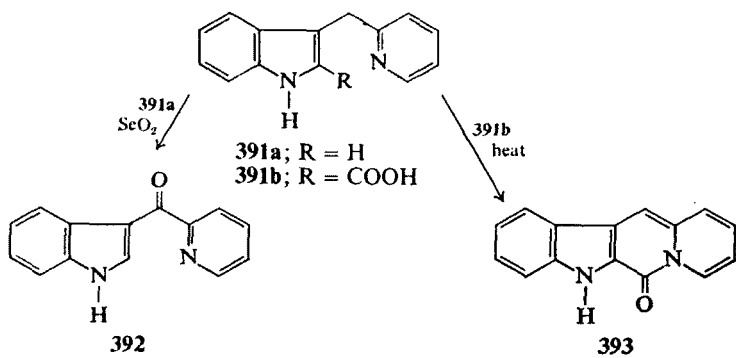


The condensation of indoles with formylpyridines in acidic solution affords diindolypyridylmethanes **389**.^{192, 508a}

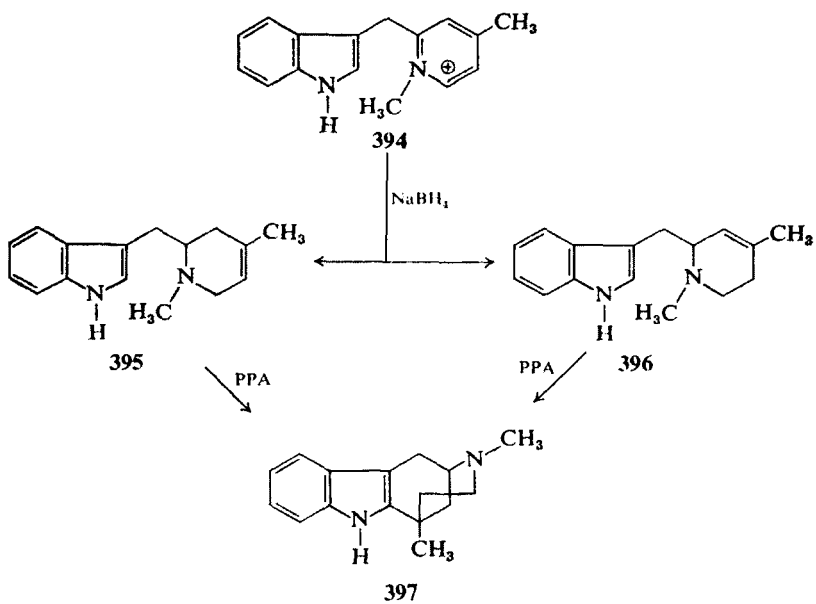


Catalytic reduction of a mixture of indole and 4-formylpyridine with platinum yields **390** in 30 % yield and products of type **389**.¹⁹¹ Compounds





Scheme 70



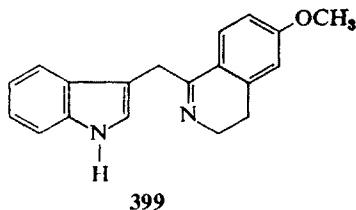
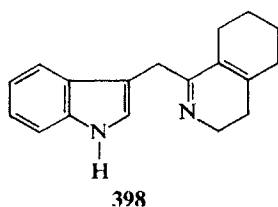
Scheme 71

of type **390** have also been prepared by reduction of 3-pyridylmethyloindoles with sodium in butanol¹⁸⁸ and **390** itself by condensation of isatin with 4-picoline followed by reduction⁵³³ (compare also Section V.B.3.h).

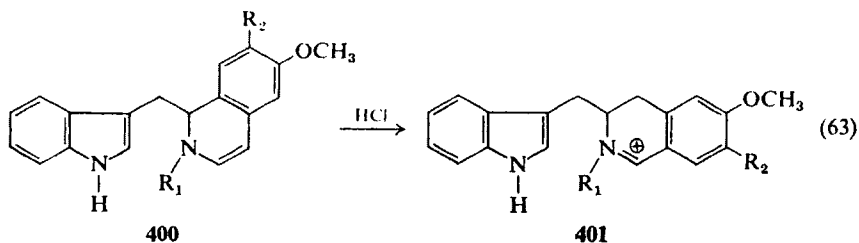
The pyridylmethyloindole **391a**, which is accessible by the Fischer cyclization^{89, 593} (see Section V.B.3.a), has also been obtained by reaction of indolylmagnesiumhalide with 2-chloromethylpyridine or by heating the sodium salt of indole with 2-hydroxymethylpyridine.⁴³⁹ Oxidation of **391a** with selenium dioxide leads to the ketone **392**⁸⁹ while the 3-pyridylmethyl-2-indolylcarboxylic acid **391b** cyclizes on heating to the indolo[3,2-*b*]quinolizine **393**⁸⁹ (Scheme 70).

Reduction of the quaternary salt **394** with NaBH₄ leads to a mixture of **395** and **396**, the former being the main product. Both compounds cyclize to the indolo[2,3-*f*]morphane **397** on heating with polyphosphoric acid³⁶³ (Scheme 71).

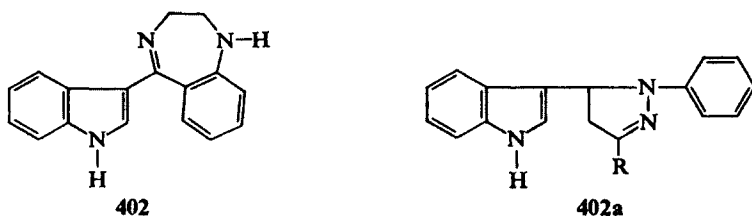
The 3-isoquinolinylmethylindole derivatives **398** and **399** have been prepared from the appropriate indolyl-3-acetic acid amide by Bischler-Napiralski ring closure.^{364, 365}



As reported by Zinnes et al.,⁶²² compounds of type **400** rearrange with acid to compounds of type **401** (Eq. 63).



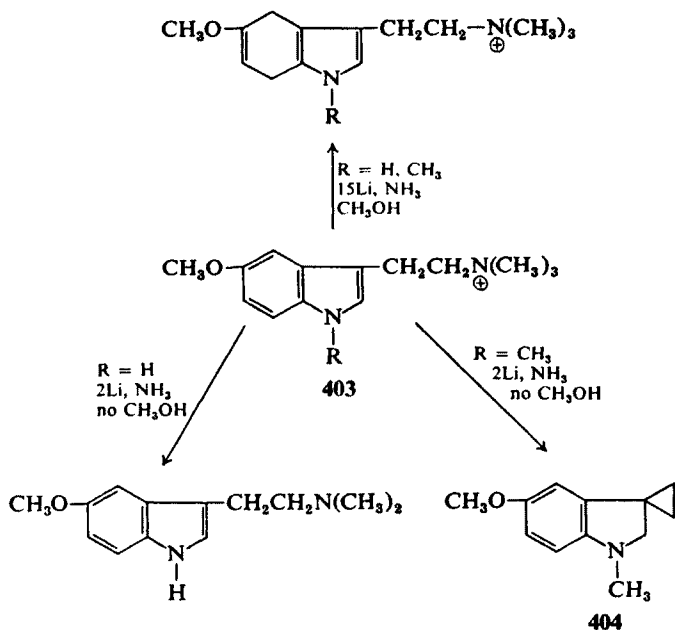
The 5-(3-indolyl)-benzodiazepine **402** has been obtained by reaction of 3-(*o*-halobenzoyl)indoles with ethylenediamine.^{438, 162a} The condensation of



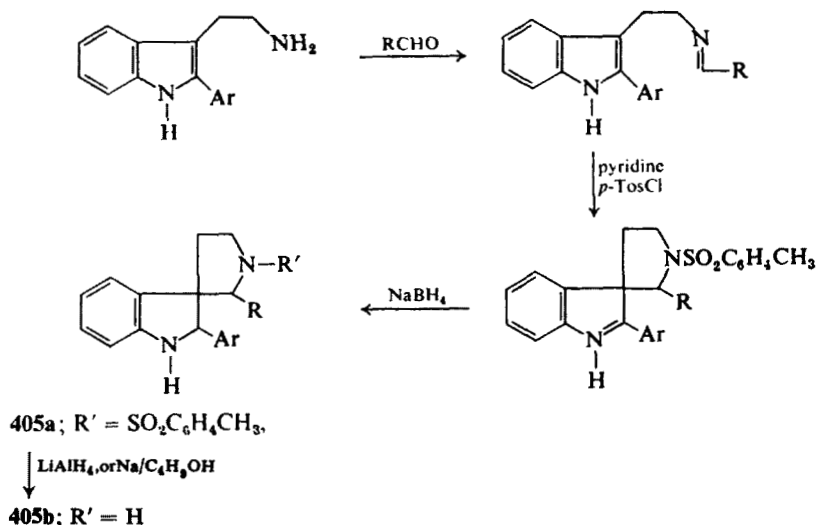
3-arylvinyloindoles with phenylhydrazine led to 3-(2-pyrazolin-4-yl)indoles of formula **402a**.^{567a}

9. *Spirocyclic Indolines and Indolenines; 4,7-Dihydroindoles*
(see also the Addenda)

The course of the reduction of the 5-methoxytryptamine methiodides **403** with lithium in liquid ammonia depends on the reaction conditions and on the substituent in position 1.⁴²⁷ These relations are displayed in Scheme 72.



Scheme 72

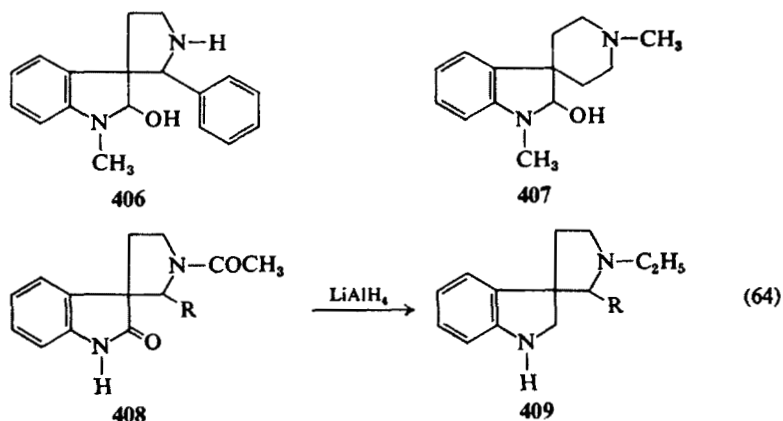


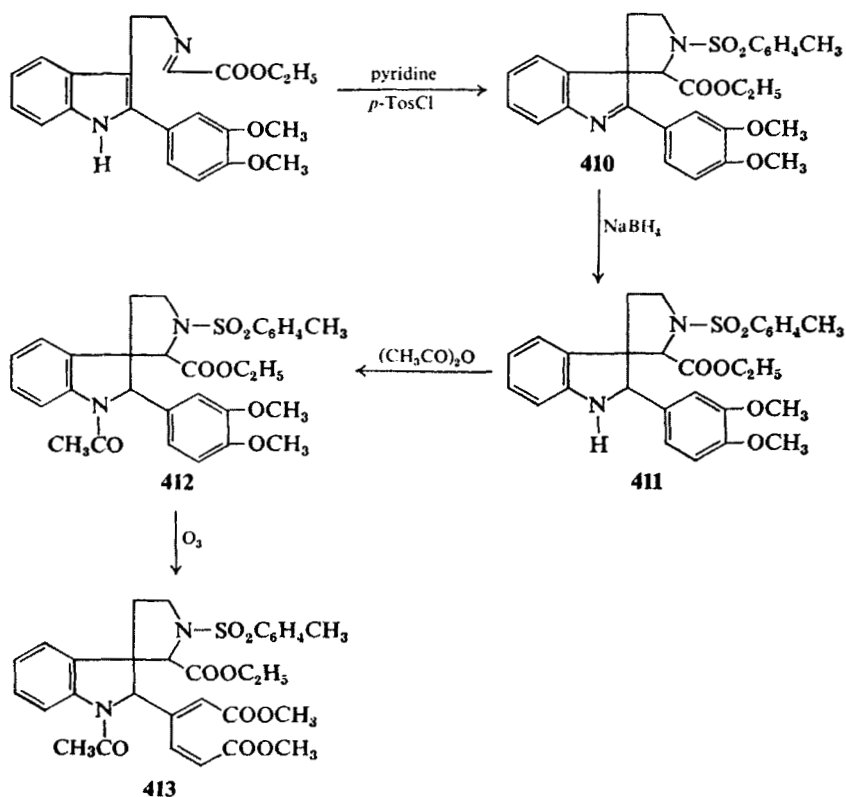
Scheme 73

A route to spiro[indoline-3,3'-pyrrolidines] of formula **405** has been elaborated by Weisbach et al.⁵⁹⁶ and is depicted in Scheme 73. The synthesis of a spiro[indoline-3,4'-piperidine] (**94**) by Fischer cyclization has already been mentioned (Section IV.B.1, Scheme 13).

Other representatives of this class of compounds are **406** and **407**²⁸⁴ and **409**,²⁷⁰ prepared by LiAlH_4 reduction of the spiro-oxindoles, viz. **408** (Eq. 64).

Several spirocyclic indoline derivatives (**410–413**) are intermediates in the Woodward total synthesis of strychnine⁶⁰⁷ (Scheme 74).





Scheme 74

10. Naturally Occurring Indolylalkylamines

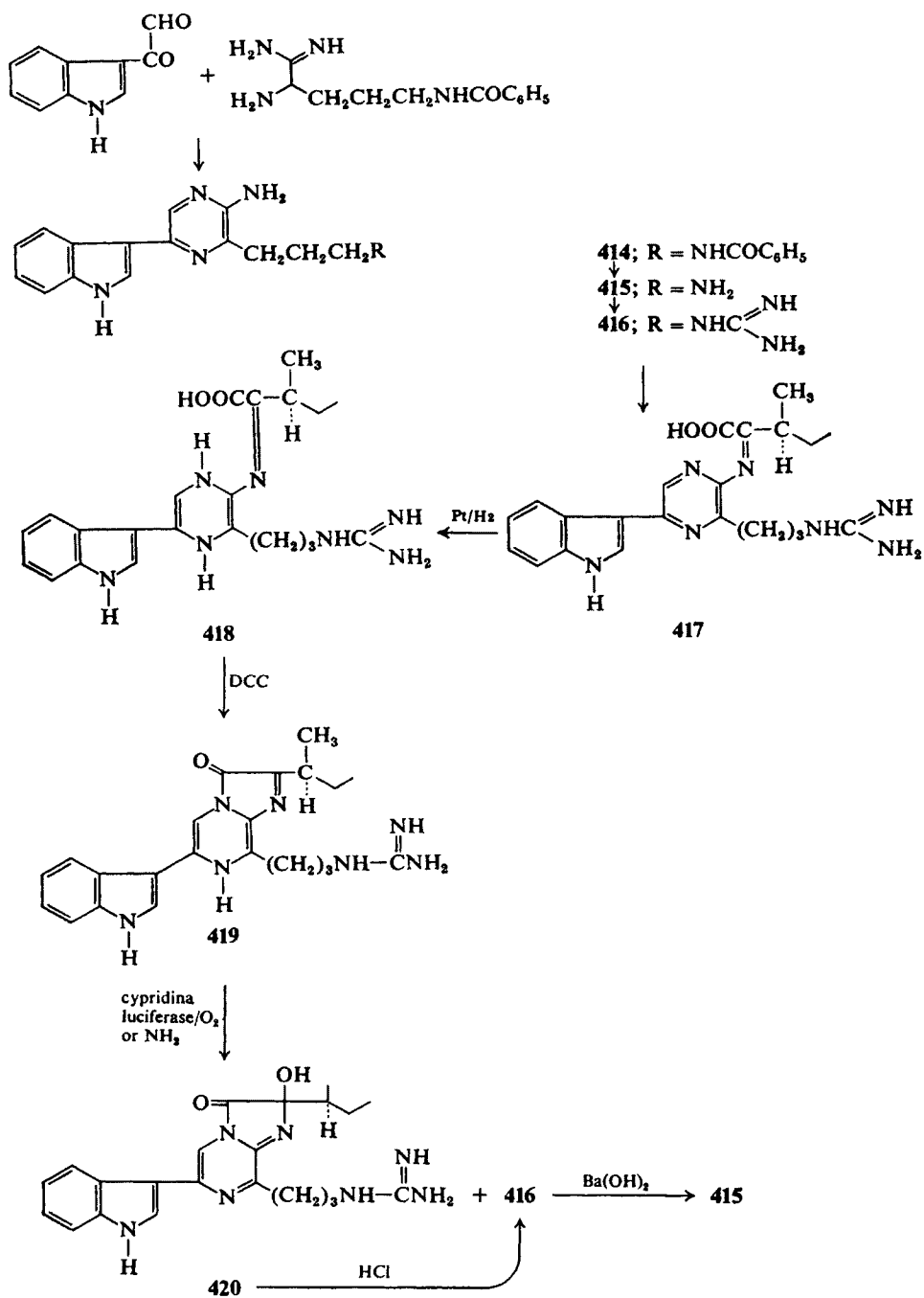
The literature on the natural occurrence of indolylalkylamines has been reviewed to 1960 by Boit.^{63b} More recent work on this subject is reported in the following papers on the isolation of gramine from *phalaris arundinacea*⁹⁹; *N*-methyltryptamine from *Piptadenia peregrina* Benth.³²⁷ and *acacia Maidenii* F. Muell.¹⁵¹; *N,N*-dimethyltryptamine from *Phalaris tuberosa*,⁹⁹ *Desmodium pulchellum* Benth. ex Baker,¹⁷¹ *Acacia maidenii* F. Muell,¹⁵¹ and *Acacia citrina*⁵⁶⁸; *N,N*-dimethyltryptamine-*N*-oxide from *Acacia citrina*⁵⁶⁸ and *Acacia porphyria*⁵⁶⁸; 3-aminomethylindole from barley³⁶⁶; 3-methylaminomethylindole from barley³⁶⁶; 5-hydroxytryptamine from *Paneolus sphinctrinus*,⁵⁶⁹ *Leptodactylus* species,¹³³ *Acacia citrina*,⁵⁶⁸ and *Acacia porphyria*⁵⁶⁸; 5-hydroxy-*N*-methyltryptamine from *Leptodactylus* species,¹³³

Acacia citrina,⁵⁶⁸ and *Acacia porphyria*⁵⁶⁸; 5-hydroxy-*N,N*-dimethyltryptamine from *Desmodium pulchellum* Benth. ex Baker,¹⁷¹ *Acacia citrina*,⁵⁶⁸ and *Acacia porphyria*⁵⁶⁸; 5-hydroxy-*N,N*-dimethyltryptamine-*N*-oxide from *Acacia citrina*⁵⁶⁸ and *Acacia porphyria*⁵⁶⁸; 5-methoxy-*N*-methyltryptamine from *Piptadenia peregrina* Benth.³²⁷; 5-methoxy-*N,N*-dimethyltryptamine from *Phalaris tuberosa*,⁹⁹ *Desmodium pulchellum* Benth. ex Baker,¹⁷¹ *Piptadenia peregrina* Benth.,³²⁷ *Acacia citrina*,⁵⁶⁸ and *Acacia porphyria*⁵⁶⁸; 5-methoxy-*N,N*-dimethyltryptamine-*N*-oxide from *Desmodium pulchellum* Benth. ex Baker¹⁷²; bufotenidine from *Leptodactylus* species¹³³; bufoviridine (dihydrobufothionine) from *Bufo viridis*¹³²; 1-methoxy-*N,N*-dimethyltryptamine (lespadamine) from *Lespedeza bicolor* var. *japonica*³⁶¹; 4-hydroxy-*N,N*-dimethyltryptamine (psilocine) from *Psilocybe baeocystis*⁴² and *Psilocybe cyanescens*⁴¹; 4-phosphoryloxy-*N,N*-dimethyltryptamine (psilocybine) from *Conocybe cyanopus*,⁴¹ *Psilocybe cyanescens*,⁴¹ and *Psilocybe semilanceata* Fr.²³⁸; 4-phosphoryloxy-*N*-methyltryptamine (baeocystine) from *Psilocybe baeocystis*^{334, 335}; 4-phosphoryloxytryptamine (norbaeocystine) from *Psilocybe baeocystis*³³⁵; 1,5-dimethoxy-3-dimethylaminomethylindole (1,5-dimethoxygramine) from *Gymnacranthera paniculata* (A.DC.) Warb. var. *zippeliana* (Miq.) J. Sinclair²⁷⁴; and 6-hydroxytryptamine (?) from heart of crab *Carcinus maenas*³⁰¹; elucidation of structure of 5-methoxy-acetyltryptamine (melatonin) see Ref. 330.

11. *Cypridina Luciferin**

The structure of cypridina luciferin, the substance responsible for the bioluminescence of *Cypridina hilgendorffii*, has been elucidated and a procedure for its synthesis developed by Kishi et al.,^{176b, 303, 304} The synthesis and some degradation reactions are outlined in Scheme 75. Cypridina etioluciferin (**416**), which has been prepared by the procedure shown in the scheme, is condensed with (+)-*d*- α -oxo- β -methylvaleric acid, the resulting azomethine **417** reduced with platinum and hydrogen to **418**, and the latter cyclized to cypridina luciferin (**419**) with DDC. The oxidation of **419** to a mixture of cypridina oxyluciferin (**420**) and **416** with cypridina luciferase and oxygen proceeds with emission of light. Compound **420** is also formed with ammonia but no luminescence occurs under this condition. The action of hydrochloric acid on **420** leads to etioluciferin (**416**) which is hydrolyzed to etioluciferamine (**415**) with barium hydroxide. Recently Inoue et al.^{256a} published an improved synthetic procedure that involves condensation of etioluciferin (**416**) with α -oxo- β -methylvaleraldehyde in the presence of a small amount of hydrochloric acid to give luciferin (**419**) directly.

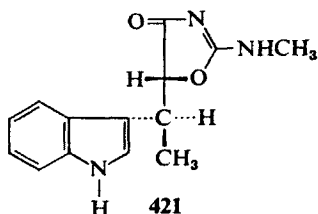
* *Addition in proof.* A revised structure for cypridina oxyluciferin has recently been proposed by S. Sugiura, S. Inoue and T. Goto, *J. Pharm. Soc. Japan*, **90**, 711 (1970).



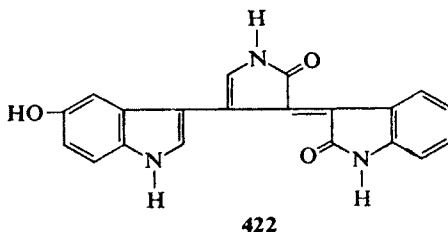
Scheme 75

12. *Indolmycine**

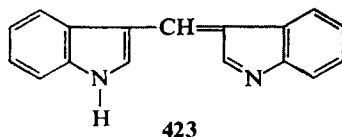
The structure of indolmycine (**421**), an antibiotic produced by *Streptomyces* species, has been established by Schach v. Wittenau and Els.⁴⁶⁶ The synthesis of **421** has been realized by the same authors⁴⁶⁷ and recently by Preobrazhenskaya et al.⁴¹⁹

13. *Violaceine*

Violaceine, the violet pigment of *Chromobacterium violaceum*, has been assigned structure **422**.³¹

14. *Urorosein*

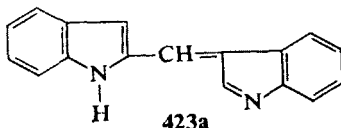
For Urorosein, which results from the action of acid on 3-formylindole, Harley-Mason and Bu'lock²⁰⁷ have proposed structure **423** (as the free base). This is supported by the course of the reduction of uroresoin with



* *Addition in proof.* The absolute configuration of indolmycin has been established as 5S,6R- by T. H. Chan and R. K. Hill [*J. Org. Chem.*, **35**, 3519 (1970)].

LiAlH_4 which leads to di-(3-indolyl)methane.⁵²⁸ In the light of this result the alternative structure assigned to urosein by Fearson and Boggust¹⁴⁴ seems to be untenable.

Dobeneck et al.^{108a} disagreed with the formulation of the title compound as **423**, and they have provided further evidence that urosein is a salt of the chromophore **423a**.^{108b}

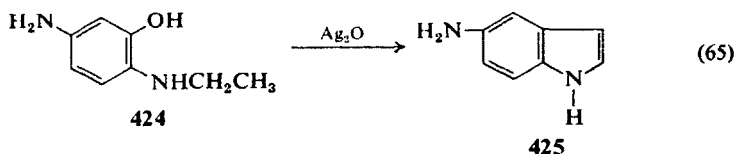


VI. Preparation of Indoles with Basic Function in the Six-Membered Ring

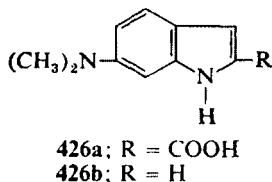
A. 4-, 5-, 6-, and 7-Aminoindoles*

1. By Ring Closure

Oxidative cyclization of **424** with silver oxide leads to 5-aminoindole (**425**) (Eq. 65).²⁰⁸



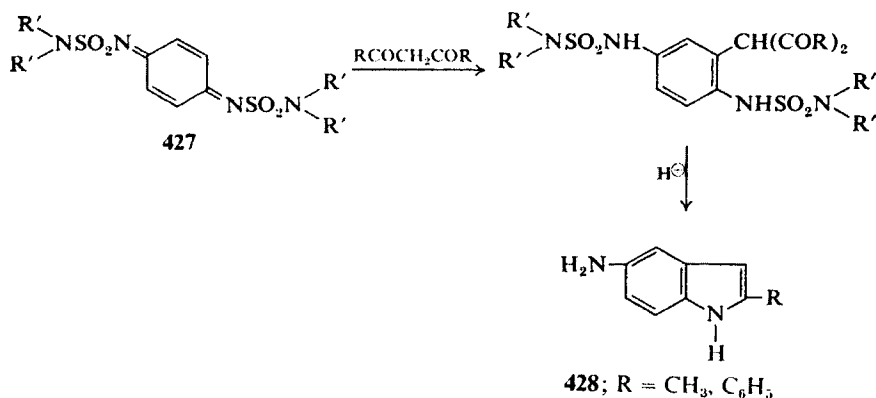
6-Dimethylaminoindole-2-carboxylic acid (**426a**), prepared by the indole synthesis of Reissert, forms 6-dimethylaminoindole (**426b**) by decarboxylation.^{321, 324}



4-Dimethylaminoindole has been obtained in an analogous manner.⁵⁶⁷ Adams et al.⁹⁻¹¹ synthesized 5-aminoindoles **428** by the method outlined in

* *Addition in proof.* Oxidative amination of 5-hydroxyindoles in position 7 (A. N. Grinev, N. V. Arkangel'skaya, and G. Ya. Uretskaya, *Pharmac. Chem. J. USSR*, **1969**, 683).

Scheme 76. In a similar manner Domschke et al.¹¹³ prepared 5-dimethylsulfamoylaminoindoles by reaction of **427** with enamines.

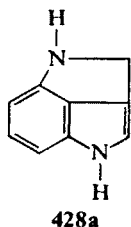


Scheme 76

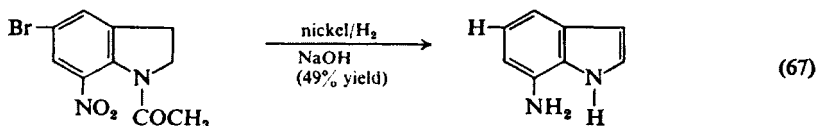
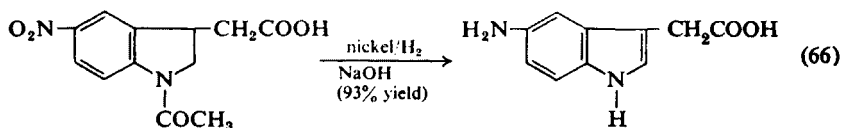
2. From Nitroindoles and Nitroindolines

Nitroindoles, nitrotryptamines, and derivatives of nitroindole-carboxylic acids and nitroindole acetic acids have been reduced to the corresponding amino compounds by means of sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$)^{37, 72, 350, 483} (the method failed in the reduction of 4-nitrotryptamine³⁵⁰), stannous chloride⁷¹ (the method failed in the reduction of 6-nitroindole⁷¹), nickel and hydrogen,^{72, 229, 379} nickel and hydrazine,^{72, 585} palladium and hydrazine,¹⁸¹ palladium and hydrogen,¹⁵⁹ palladium and hydrogen in methanolic hydrochloric acid,¹⁷⁰ and platinum and hydrogen.³⁵⁰ In the reduction of 6-nitroindolyl-3-acetonitrile with nickel and hydrogen, 30% of 6-aminoindolyl-3-acetonitrile has been isolated.⁷⁰ Hiremath and Siddappa²³⁰ reported that this reaction leads to 6-aminotryptamine. According to Berti et al.,⁵³ its course depends on the reaction conditions. In the catalytic hydrogenation (Pt or Pd) of nitrogramines, Berti et al.⁵³ and DeGraw et al.¹⁸² observed no deamination of the side chain (compare, however, Section II.1.5) and obtained aminogramines in good yield. According to Papayan et al.,^{385a} treatment of a methanolic solution of 6-nitrogramine with sulfur in the presence of sodium hydroxide leads to 6-aminogramine, whereas 4-nitrogramine is transformed by this procedure into the tricyclic compound **428a**.

The reduction of nitroindolines to aminoindolines has been effected with nickel and hydrazine,⁵⁴¹ stannous chloride,^{65, 539} palladium and hydrogen,^{249, 255} platinum and hydrogen,³⁰² and nickel and hydrogen.²⁷³ Dehydrogenation of aminoindolines to aminoindoles has been successful using

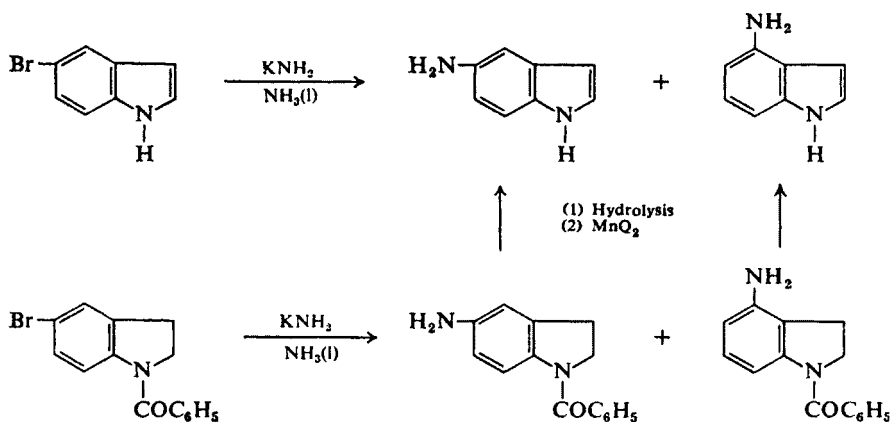


chloranil,⁵⁴⁰ palladium on charcoal,²⁷³ or manganese dioxide.²⁸¹ Shaking nitroindolines with Raney nickel in aqueous sodium hydroxide led to aminoindoles²⁷³ (Eqs. 66 and 67).



3. From Haloindoles

4- and 6-Haloindolyl-2-carboxylic acids are converted into 4- and 6-aminoindoles respectively, on heating with ammonia at 200°. ^{407, 591} In the presence of cuprous chloride this exchange reaction occurs with 4-bromoindole

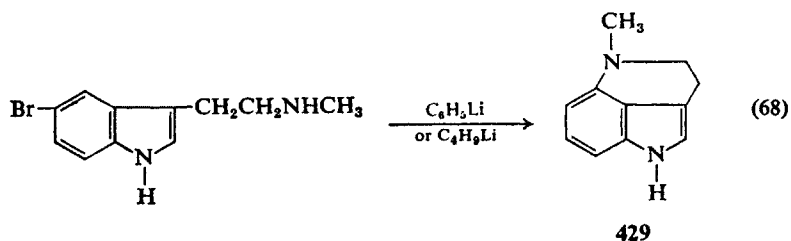


Scheme 77

at 165°; higher temperatures are required with 4-chloroindole.⁵⁶⁷ 4-Amino-1-benzylindole has been isolated as a by-product in the reaction of 4-bromoindole with benzyl chloride/sodium amide in liquid ammonia.⁴⁰⁶

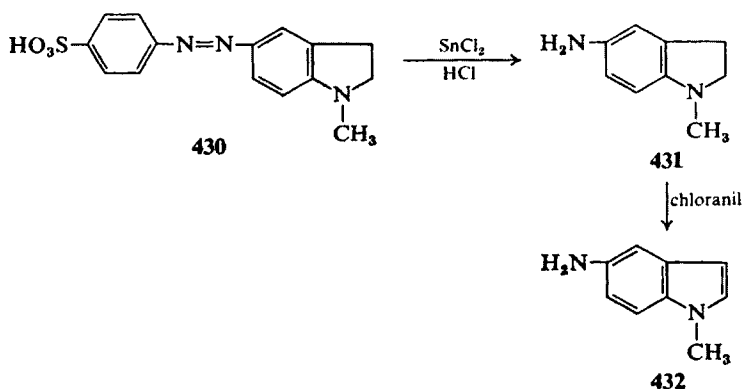
The reaction of 5-bromoindole and 1-benzoyl-5-bromoindoline with potassium amide in liquid ammonia leads to a mixture of the corresponding 4- and 5-amino compounds via an aryne intermediate²⁸¹ (Scheme 77).

An interesting intramolecular modification of this reaction leads to the tricyclic compound **429** (Eq. 68).



4. 5-Aminoindoles from 5-Azoindolines

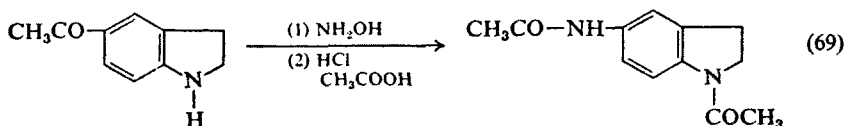
Coupling 1-methylindoline with diazotized sulfanilic acid leads to **430** which can be reduced to 5-amino-1-methylindoline (**431**). Dehydrogenation of its phthaloyl derivative with chloranil yields 5-amino-1-methylindole (**432**) (Scheme 78).⁵⁴⁰ In an analogous manner, 5-amino-1-benzylindoline has been prepared by Teuber et al.^{544a}



Scheme 78

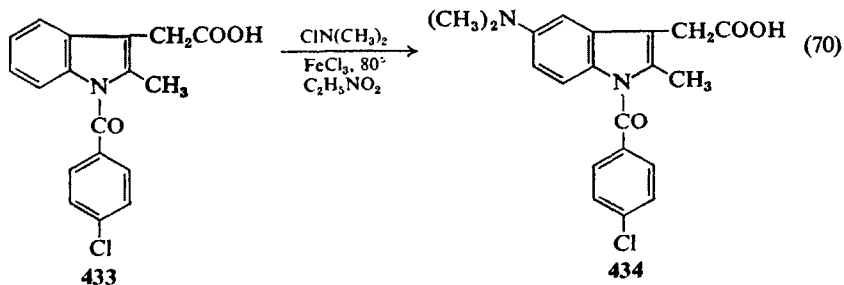
5. 5-Aminoindolines by Beckmann Rearrangement of 5-Acetylindolines

The oximes of 5-acetylindolines form 5-acetaminoindolines when subjected to a Beckmann rearrangement⁵⁴² (Eq. 69).



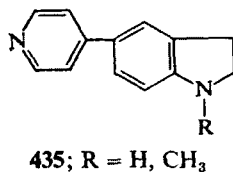
6. Direct Amination of Indoles in the 5-Position

Direct amination of 1-*p*-chlorobenzoyl-2-methylindolyl-3-acetic acid (**433**) with dimethylchloroamine to the 5-dimethylamino compound **434** has been described in a patent³⁵⁵ (Eq. 70).



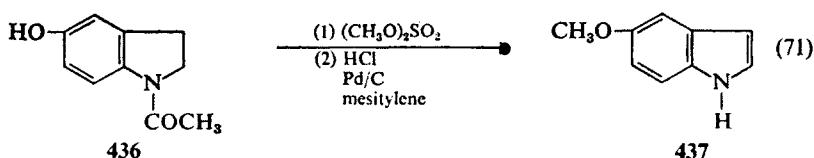
7. Introduction of a Pyridyl Radical in the 5-Position of Indolines

Indolines form the 5-pyridyl derivatives **435** on reaction with benzoylpyridinium chloride in the presence of AlCl_3 .³¹³



8. Alkylation of Aminoindoles and Reactions of Indolyl Diazonium Salts (see also the Addenda)

Methylation of 6-aminoindole with dimethylsulfate/sodium hydroxide led to 6-dimethylaminoindole.⁵⁷² DeGraw¹⁸¹ obtained 5-dimethylaminoindole by quaternization of 5-aminoindole with dimethylsulfate followed by treatment of the quaternary salt with sodium propoxide. The preparation of *N,N*-bis(2-chloroethyl)aminoindoles from aminoindoles has been described by DeGraw and Goodman.¹⁸³⁻¹⁸⁶ The Sandmeyer reaction with 1-acetyl- and 1-methylindolyl diazonium salts has been used for the preparation of 5-fluoroindolines,²⁵⁵ 5-chloroindolines,²⁵⁵ 5-bromoindolines,⁵⁴⁰ 5-iodoindolines,²⁵⁰ 6-fluoroindolines,²⁵⁵ and 7-iodoindolines.^{180, 378} In addition, diazotized 1-acetyl-5-aminoindoline forms 1-acetyl-5-hydroxyindoline (**436**) on warming with an aqueous solution of cupric sulfate. 5-Methoxyindole (**437**) is obtained in 3 steps (Eq. 71) from **436**. The 4-, 6-, and 7-aminoindolines react analogously.^{65, 170, 249}



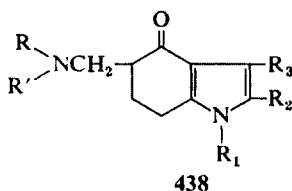
B. Indoles with an Aminomethyl Side Chain in the Six-Membered Ring

1. From Hydroxyindoles by Mannich Reaction

See Section II.G.

2. By Reduction Procedures

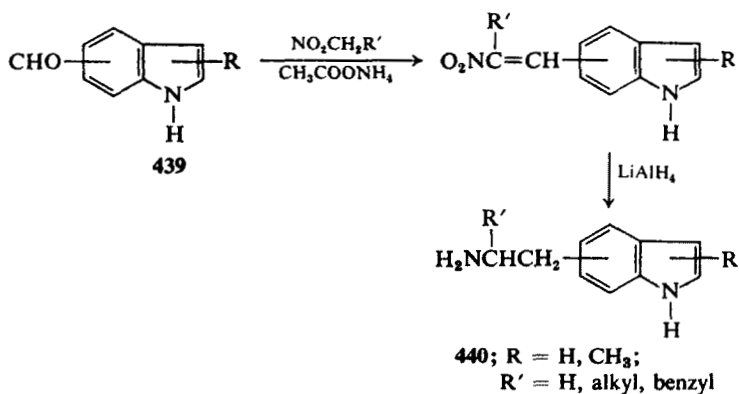
5-, 6-, and 7-Indolylcarboxylic acid amides or hydrazides have been reduced with LiAlH_4 ^{68, 543, 544} to the corresponding aminomethylindoles.



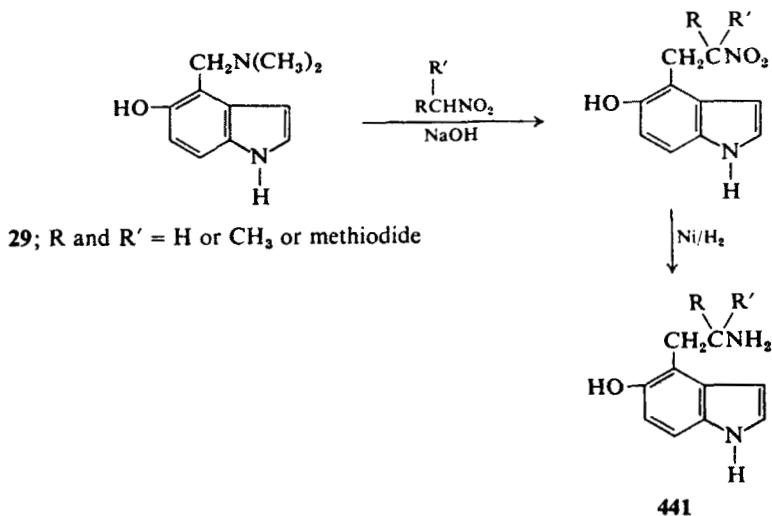
Similar compounds result from the reduction of azomethines of 4-, 5-, 6-, and 7-formylindoles⁴⁵⁷ or 4-, 5-, 6-, and 7-cyanoindoles.⁴⁵⁵ Mannich bases of 4-oxo-4,5,6,7-tetrahydroindoles with the basic side chain in position 5 (**438**) have been prepared by workers at Endo Laboratories^{130, 131} and by Hauptmann and Martin.²¹³

C. Indoles with an Aminoethyl Side Chain in the Six-Membered Ring

Indoles of the general formula **440** are readily accessible by the method outlined in Scheme 79.⁵⁶⁴ The starting formylindoles **439** can be obtained by



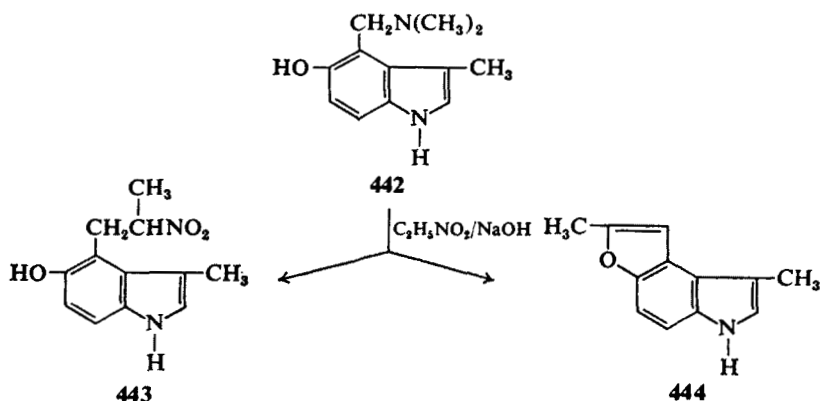
Scheme 79



Scheme 80

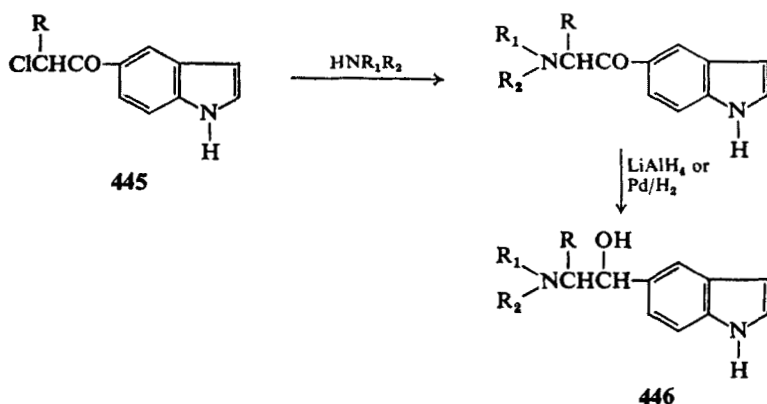
reduction of the corresponding cyanoindoles with sodium hypophosphite and nickel⁵⁶⁴ according to the method described by Backeberg and Staskun.²⁷ The conversion of the Mannich bases **29** into the aminoethyl derivative **441**⁵⁶² is outlined in Scheme 80. The Mannich base from 6-hydroxyindole reacts similarly, yielding compounds with an aminoethyl side chain in position 7.⁵⁶²

In an analogous reaction of the 3-methylindole Mannich base **442** with nitroethane, 30% of the furo[3,2-*e*]indole **444** is formed besides the expected **443** (Scheme 81).⁵⁶²



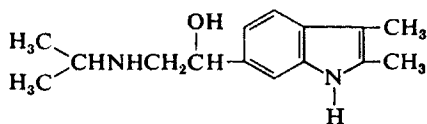
Scheme 81

The reaction of the methiodide of **29** with sodium cyanide leads to 4-cyanomethyl-5-hydroxyindole, which has been reduced to 4-(2-aminoethyl)-5-hydroxyindole (**441**; $\text{R} = \text{R}' = \text{H}$) with nickel/hydrogen.⁵⁶² Julia et al.^{284a} reported on the analogous reduction of 4-cyanomethyl-5-methoxyindole with nickel or LiAlH_4 . Indoles with a 2-amino-1-hydroxyethyl side chain in position 5 (**446**) result from 5-(α -chloroacyl)indoles **445**⁵⁴² by the procedure outlined in Scheme 82.⁵⁶⁴



Scheme 82

The synthesis of **447** from 6-acetyl-2,3-dimethylindole is described in a patent.²⁵¹

**447**

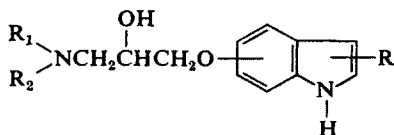
VII. Basic Esters of Indolylcarboxylic Acids

Basic esters of the following carboxylic acids have been described: indolyl-2- and indolyl-3-carboxylic acid,¹²⁸ indolyl-3- and indolyl-4-carboxylic acid,⁷⁵ 1-methyl-3-phenyl-indolyl-2-acetic acid,^{329, 536} indolyl-3-acetic acid,⁵⁶⁰ substituted indolyl-5-carboxylic acid,^{134a, 17a} and substituted indolyl-3-propionic acid.^{385b}

VIII. Basic Ethers of Hydroxyindoles and Mercaptoindoles (see also the Addenda)

Basic ethers of 3-hydroxyindoles^{164, 167, 617} and of 5-hydroxyindoles⁶⁰⁸ have been prepared by alkylation with the appropriate aminoalkyl halides.

Compounds of type **448** result from the alkali-catalyzed condensation of hydroxyindoles with epichlorohydrin and subsequent reaction with primary

**448**; R = H, CH₃

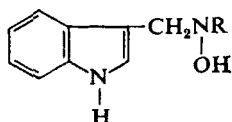
or secondary amines.⁴⁵⁰ 2-Aminoalkylthioindoles have been obtained by alkylation of indoline-2-thiones, viz. by treating them with aziridine.^{83a}

Addenda

Literature published between July 1969 and July 1970 is reviewed in this supplement. Only papers describing new procedures or novel types of compounds are incorporated. The numbering of the paragraph corresponds to the Section numbering in the main part of this Chapter.

Further essential papers appearing before June 1971 have also been mentioned in footnotes of the respective sections.

II.B. The preparation of Mannich bases of the gramine type using hydroxylamines as amine component has been described by Thesing et al.⁶⁶⁰ Alkylhydroxylamines react smoothly to give the expected compounds **449a**, whereas **449b** could not be isolated from the reaction mixture. For the preparation of **449b** from gramine methiodide by amine exchange, see Section V.B.2.d.



449a; R = alkyl

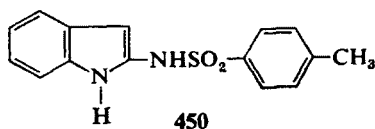
449b; R = phenyl

III.A. Refluxing cinnolines with formic acid and formamide leads to 1-formylaminoindoles (55–74%) which are reduced to 1-methylaminoindoles by means of LiAlH_4 .^{624a} For further work on the Arbuzov cyclization, see Ref. 642a.

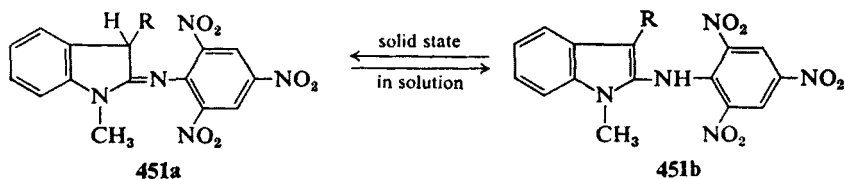
III.B.2. Schubert et al.⁶⁵³ report that in their hands Fischer cyclization to 1-dialkylaminoethylindoles failed.

III.B.3. For examples of the introduction of the dimethylaminopropyl residue in position 1 of compounds of the tryptamine type, see ref. 623.

IV.A. Indole reacts with tosylazide to give **450**,⁶²⁶ whereas the analogous reaction with indolylmagnesium salts is reported to give tars.⁶³⁹ Condensation of 1-methylindoles with picrylazide leads to **451**,⁶²⁷ a substance that exists in the tautomeric forms **451a** and **451b**. For an extension of this study to 1,2,3-trimethylindole, see Ref. 626a.



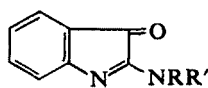
450



451a

451b

Hino et al.⁶⁴⁰ report on the easy autoxidation of 2-aminoindoles to products of formulas **452a** and **452b**.

**452a****452b**

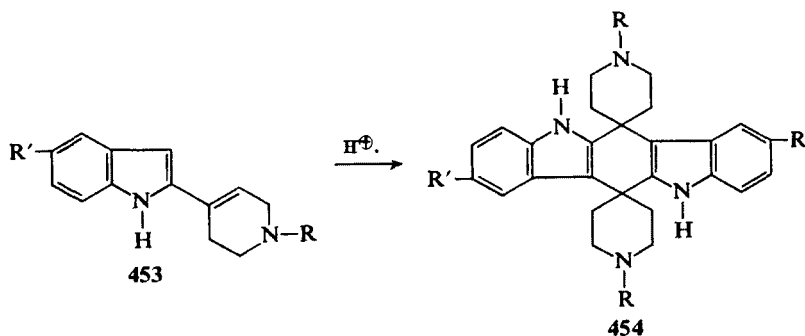
Further examples of the transformation of 2-aminoindole into tricyclic (pyrimido[1,2-*a*]indoles) are described in a patent.⁶⁴³

IV.B.1. Fischer cyclization of the *N*-methylhydrazone of 2-acetylquinoline yields 1-methyl-2-(2-quinolyl)indole.⁶³⁷ For the cyclization of *N*-methyl- and *N*-benzylhydrazones of acetylpyridines to 1-methyl- and 1-benzyl-2-pyridylindoles respectively, thermal indolization was preferred to the usual acid-catalyzed procedure.⁶⁵⁴

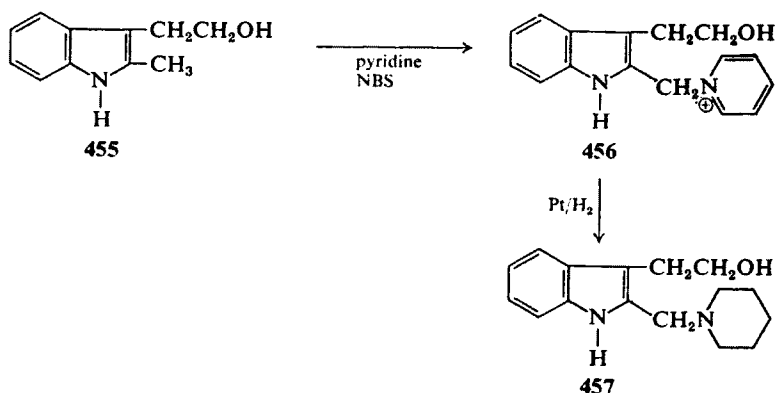
IV.B.6. 2-Cyanoindoles, prepared from indolyl-2-carboxylic acid amides by means of POCl_3 , can be readily reduced with LiAlH_4 to 2-aminomethylindoles.⁶⁵⁹

IV.B.10. The above-mentioned 1-methyl-2-(2-quinolyl)indole has been also obtained by reaction of 1-methylindolyl-2-lithium with quinoline and subsequent dehydrogenation of the intermediary dihydroquinoliny compound.⁶⁵⁵

IV.B.12. For the NaBH_4 reduction of quaternary salts of 2-pyridylindoles to 2-(tetrahydropyridyl)indoles, see also Ref. 654. 2-(Tetrahydropyridyl)indoles of formula **453** dimerize under the influence of acid to products of the presumed structure **454**.⁶⁴⁷

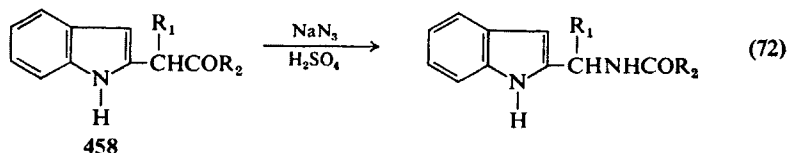


IV.B.13. A piperidinomethyl side chain can also be introduced in position 2 by the following method: a 2-methylindole, viz. **455**, is transformed into the pyridinium salt **456**, which is subsequently reduced to **457** with PtO_2/H_2 .⁶³⁴



Scheme 83

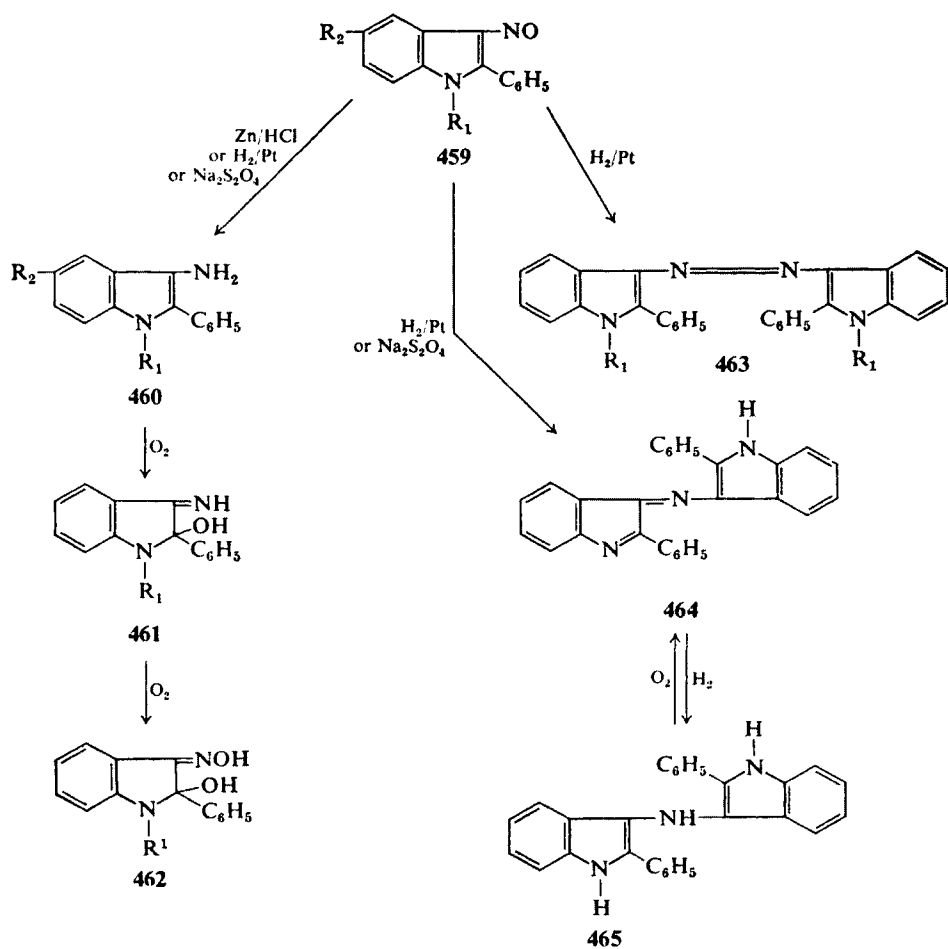
2-Aminomethylindoles are also formed in the Schmidt rearrangement of ketones of formula **458** while Beckmann rearrangement of **458** leads to amides of indolyl-2-acetic acid.⁶⁵⁰ Eq. 72



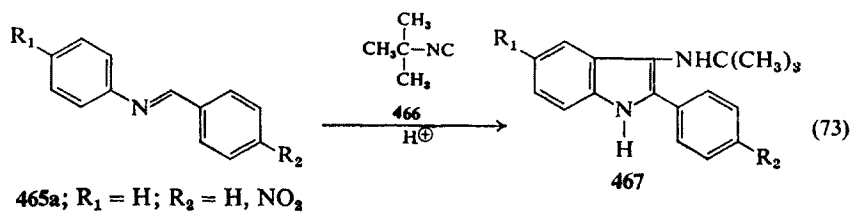
The oxidative rearrangement of 2-aminomethylindoles of type **146** to benzodiazepines **147**⁶¹² has been extended to analogous rearrangements of 2-aminoethyl- and 2-aminopropylindoles yielding 1,5-benzodiazocines and 1,6-benzodiazononines respectively.⁶⁵⁸

V.A. The 3-nitrosoindoles **459** (or the tautomeric 3-isonitroso-indolenines) (Scheme 84) have been reduced to the corresponding 3-aminoindoles **460** by Schmitt et al.^{651, 652} using Pt/H_2 in acetic acid, whereas Huang-Hsinmin and Mann⁶⁴² prefer ethanol as solvent. In the hands of the latter authors, reduction by Zn/HCl ⁶⁴⁵ or $\text{Zn}/\text{CH}_3\text{COOH}$, NH_4SH , and $\text{Na}_2\text{S}_2\text{O}_4$ ⁶⁵² was less satisfactory than catalytic hydrogenation, in which, however, they isolated a small amount of the azo compound **463** as a by-product. Schmitt et al., on the other hand, found a blue dimeric by-product of formula **464**, readily reducible to the leuco compound **465** which is quickly reoxidized to **464** by air. The extreme susceptibility of 3-aminoindoles **460** to autoxidation has been also observed by Huang-Hsinmin and Mann,⁶⁴² who isolated **461** and **462** as oxidation products.

The oxidation of 3-aminoindoles to 3-iminoindolenines (viz. **148a** $\rightarrow$ **148c**) has also been effected with chloranil or nitrobenzene.⁶³¹ Addition of equimolar amounts of an azomethine **465a** to the isonitrile **466** results also in the



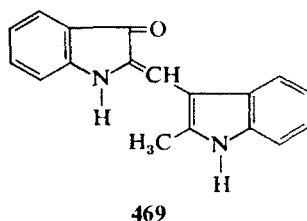
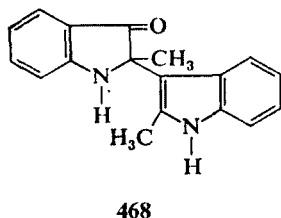
Scheme 84



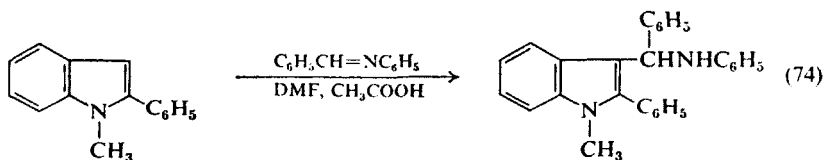
formation of 3-aminoindole derivatives (**467**) (Eq. 73).⁶³² No indoles are formed if the benzylidene derivative of *p*-nitroaniline (**465**; $R_1 = \text{NO}_2$) is used in this reaction.

V.B.2.d. The reaction outlined in Eq. (29) is reported to succeed only in an aprotic solvent such as xylene. Under this condition, also pyrazole is skatylated in position 1.⁶²⁵

V.B.2.g. From the oxidation of 2-methylindole with sodium periodate in aqueous methanol, the indolyl-indoxyl compounds **468** and **469** have been isolated in 33 and 4% yield respectively.⁶³³



V.B.2.h. Another method for the preparation of 3-aminomethylindoles consists in the acid-catalyzed addition of benzalanilines to indoles in which position 1 is substituted (Eq. 74).⁶³⁵

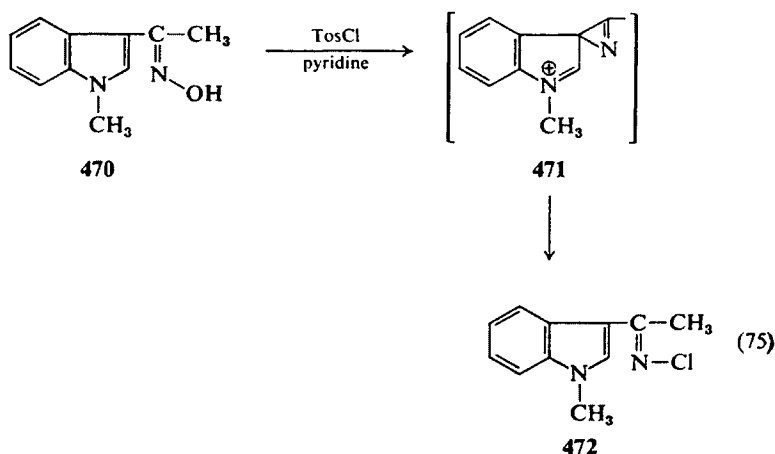


Reaction of the antioxime **470** with tosylchloride/pyridine at -5° led, via a supposed intermediate **471**, to the *N*-chloroimine **472**. The proposed mechanism is supported by the fact that the antioxime from 2-acetyl-1-methylindole did not give an analogous reaction⁶²⁹ (Eq. 75).

V.B.3.a. The mechanism of the cyclization outlined in Eq. (33) is discussed in Ref. 636a.

V.B.3.c. As already reported, reaction of gramine with nitromethane yields predominantly diskatlynitromethane instead of 3-(2-nitroethyl)indole **243** ($R = R' = \text{H}$) (see Eq. 42). The latter compound, however, is obtained in high yield by reaction of gramine methiodide with the magnesium salt of nitroacetic acid (prepared from nitromethane and the so-called magnesium methyl carbonate^{656a}) followed by acidification.^{635a} Under carefully controlled

conditions, reduction of **258** with NaBH_4 , usually leading to the tetrahydropyridyl derivatives, can be stopped at the dihydro stage (working in a strong alkaline two-phase liquid mixture of water, methanol, and ether).^{635b}



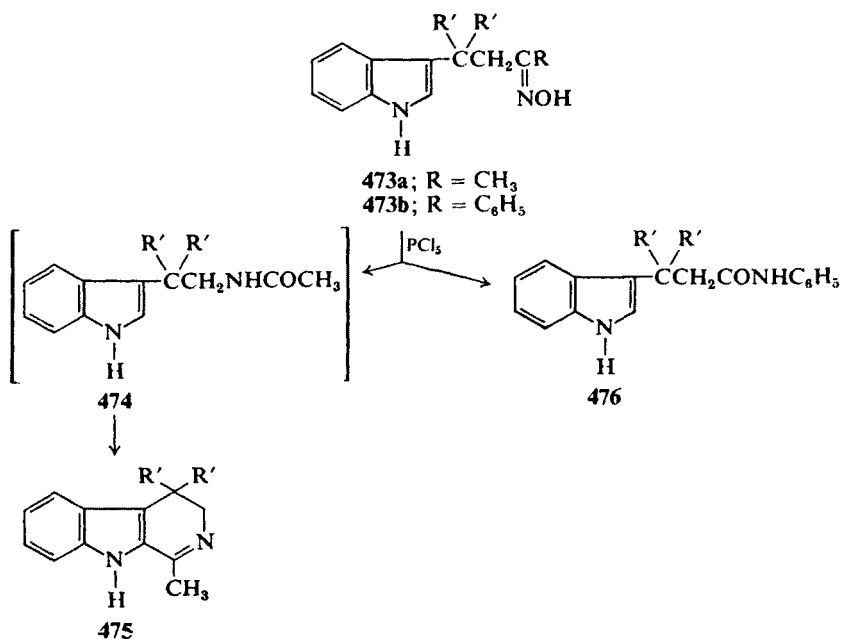
V.B.3.c. and V.B.3.d. According to a patent, reduction of 3-nitroethyl- and 3-nitrovinylindoles to tryptamines with LiAlH_4 also succeeds if position 1 of the indole nucleus is substituted by an aroyl- or heteroaroyl residue (no attack of this group).⁶⁴⁶

V.B.3.f. Oxalyl chloride, which normally substitutes indole on the most nucleophilic position 3, attacks 4,6-dimethoxyindole in position 7 (twice activated by *o*- and *p*-methoxy group) instead of position 3.^{628a} It is to be noted that reaction of indolylmagnesium bromide with oxalic esters does not lead to 3-indolylglyoxylic ester but to the 1-isomer at low temperature or to the 2-isomer at elevated temperature.^{644a}

V.B.3.g. For the reduction of 3-aminopropionylindoles to hydroxy-tryptamines with threo- and erythro-configuration, see Ref. 648.

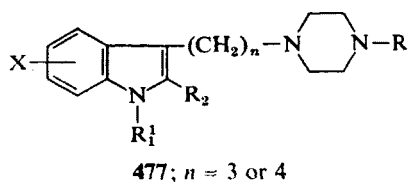
V.B.3.k. According to Ref. 655a, *N*-disubstituted tryptamines are obtained in high yield on boiling a solution of tryptophols in benzene or xylene with secondary amines and a nickel catalyst.

V.B.3.s. Tryptamines by Beckmann Rearrangement of 3-(3-Oxobutyl)-indoles. With PCl_5 the oximes **473a** undergo Beckmann rearrangement to acetyltryptamines **474** which cyclize under these conditions to the corresponding 3,4-dihydro- β -carbolines **475**. Analogous treatment of oximes **473b** yields anilides of the corresponding 3-indolylpropionic acid (**476**) (Scheme 85).⁶⁴⁴

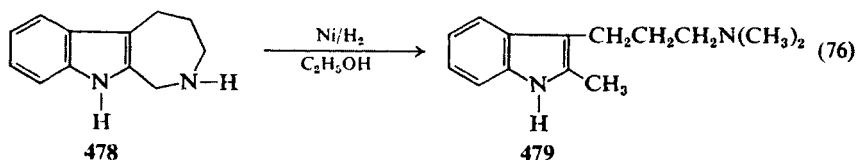


Scheme 85

V.B.5. A large number of examples of Fischer cyclizations to homo- and bishomotryptamines of type **477** are described in a patent.⁶⁵⁶

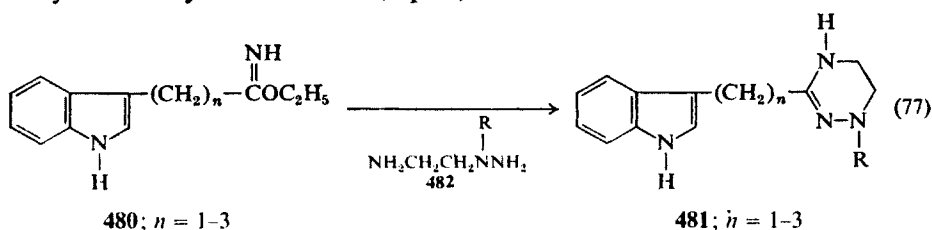


Homotryptamines **479** result from the hydrogenation of azepino[3,4-*a*]-indoles **478** with nickel in ethanol⁶³⁶ (Eq. 76).

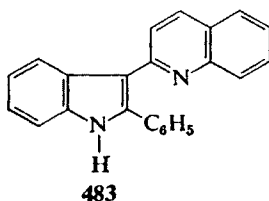


V.B.7. Reaction of dimethyltryptamine-*N*-oxide with SO₂/formic acid results in demethylation and subsequent cyclization to 2-methyl-1,2,3,4-tetrahydro- β -carboline.⁶²⁸

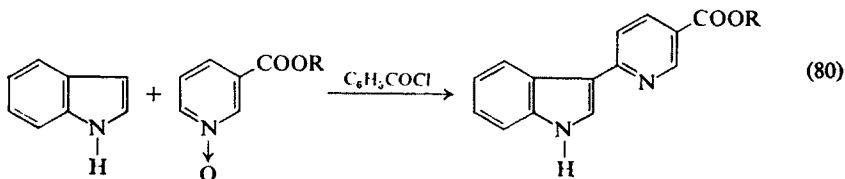
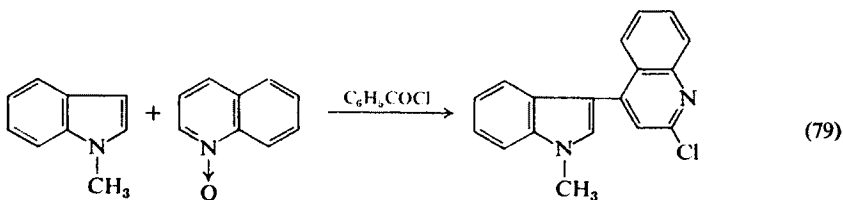
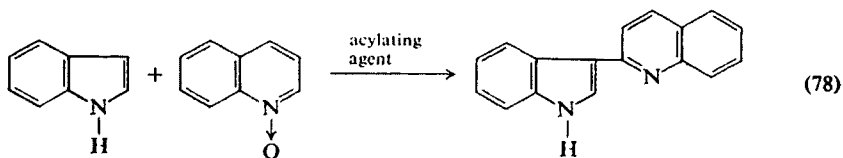
The iminoether **480** yields the triazinylalkylindoles **481** on warming with hydrazinoethylamines **482**^{633a} (Eq. 77).



V.B.8. 2-Phenyl-3-(2-quinolyl)indole (**483**) has been prepared by Fischer cyclization of the appropriate phenylhydrazone with ZnCl_2 .⁶³⁷



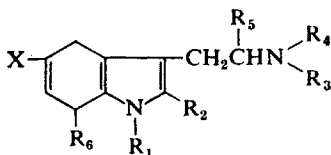
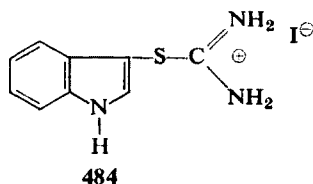
Several condensations of indoles with pyridine- and quinoline-*N*-oxides in the presence of acylating agents are given in Eqs. (78),^{630, 637} (79),⁶³⁷ and (80).^{637*}



* Addition in proof. For further application of such reactions see also H. Hamana and I. Kumadaki, *Chem. Pharm. Bull.*, (Tokyo), **18**, 1742 (1970).

Condensations of indoles with nitrophenazine-*N*-oxide have been described by Pietra et al.⁶⁴⁹

The reaction of indole with thiourea in the presence of iodine/potassium iodide leads to the isothiuronium salt **484**.⁶³⁸



485; X = H, OCH₃; R₁-R₆ = H, lower alkyl

V.B.9. A number of Birch reductions of tryptamines to 4,7-dihydro-tryptamines of the general formula **485** have been described in a patent.⁶²⁴ For a discussion of the reactions depicted in Scheme 72, see Ref. 628b.*

VI.A.8. As already reported, 5-iodoindoline can be prepared by the Sandmeyer reaction of 1-acetyl-5-aminoindoline.²⁵⁰ According to a patent,⁶⁵⁷ an analogous reaction also succeeds in the indole series: diazotization of 1-acetyl-5-aminoindole and treatment of the diazonium salt formed with an aqueous solution of KI led to 1-acetyl-5-iodoindole in 57% yield.

VIII. For further examples of the preparation of basic ethers of 2-mercaptoindoles, see Ref. 641.†

Appendix of Tables

General Remarks

The tables list compounds in which the indole nucleus does not carry substituents other than the basic side chain, or those substituted by alkyl, halogen, trifluoromethyl, or silyl groups. All hydroxy-, alkoxy-, alkylthio-, nitro-, cyano-, acyl- and carbalkoxyindoles have been omitted, since they are summarized in the appropriate chapters. Compounds, however, in which the basic side chain contains further functional groups, such as OH, COOH, COOR, and CN, are taken in account, except for the α -amino acids

* *Addition in proof.* See also W. A. Remers, G. J. Gibbs, Ch. Pidacks and M. J. Weiss *J. Org. Chem.*, **36**, 279 (1971),

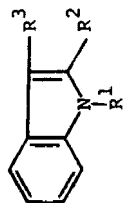
† *Addition in proof.* See also J. Bourdais, *Chimie Thérapeutic*, **5**, 409 (1970).

(tryptophan type) which are collected in a later volume. The compounds are classified by the position of the side chain and the distance of the basic center from the nucleus as follows:

Crystallization Solvents

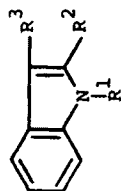
ac	acetone	h	hexane
c	chloroform	ip	isopropanol
cyh	cyclohexane	l	ligroine
b	benzene	m	methanol
bu	butanol	p	petroleum ether
d	dioxane	py	pyridine
dmf	dimethylformamide	t	toluene
e	ethanol	thf	tetrahydrofuran
ea	ethyl acetate	w	water
et	diethyl ether	x	xylene

Table 1. 1-Aminoindoles



R ¹	R ²	R ³		m.p., °C	ref.
NH ₂	H	CH ₃	C ₉ H ₁₀ N ₂ HCl	59-60 (p) 146-154 (w) 123-125 (w)	54, 55, 202 54 202
NHCHO	H	H	C ₉ H ₈ N ₂ O	141-142 (et/w)	624a
NHCHO	H	CH ₃	C ₁₀ H ₁₀ N ₂ O	170-171 (et/w)	624a
NHCHO	CH ₃	CH ₃	C ₁₁ H ₁₂ N ₂ O	186-187 (et/w)	624a
NH ₂	CH ₃	CH ₃	C ₁₀ H ₁₂ N ₂	73-74 (p)	202
NHCH ₃	H	CH ₃	C ₁₀ H ₁₂ N ₂	b.p. 73-75 (0.2 mm)	624a
NH ₂	H	C ₆ H ₅	C ₁₄ H ₁₂ N ₂	101-102 104	202 24
N=CHC ₆ H ₅	H	H	C ₁₅ H ₁₂ N ₂	108	24
NH ₂	CH ₃	C ₆ H ₅	C ₁₅ H ₁₄ N ₂	111-112 (p)	202
N(CH ₃) ₂	H	C ₆ H ₅	C ₁₆ H ₁₆ N ₂	76-77 (h) b.p. 140-147 (0.35 mm.)	356 356
NCH ₃ COC ₆ H ₅	H	CH ₃	C ₁₇ H ₁₆ N ₂ O	111-112 (et/w)	624a
N(CH ₃) ₂	CH ₃	C ₆ H ₅	C ₁₇ H ₁₈ N ₂	91-92	356
NHC ₆ H ₅	H	C ₆ H ₅	C ₂₀ H ₁₆ N ₂	140	594

Table 2. 1-Indolyl-C-N Derivatives



R ¹	R ²	R ³		m.p., °C	ref.
CH ₂ N(CH ₃) ₂	H	H	C ₁₁ H ₁₄ N ₂	-	521
				b.p. 86-87 (0.4 mm.)	521
				b.p. 130 (6 mm.)	521
			picrate methiodide	133 222-227 (dec)	521
CH ₂ N(CH ₃) ₂	H	CH ₃	C ₁₂ H ₁₆ N ₂	-	522
				b.p. 146-150 (9 mm.)	522
				150-151 (m)	522
			picrate methiodide	210-220 (dec) (m)	522
α-pyridyl	H	H	C ₁₃ H ₁₀ N ₂ picrate	101-104 (e)	416
	H	H	C ₁₃ H ₁₆ N ₂ picrate	-	521
				b.p. 98-102 (0.06 mm.)	521
				123	521
			picrate		521
	H	H	C ₁₃ H ₁₆ N ₂ O picrate	-	521
				b.p. 156-158 (0.5 mm.)	521
				175-177	521
			picrate		521

Table 2 (cont.)

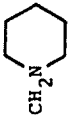
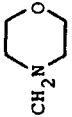
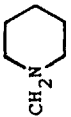
$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	C_2H_5	$\text{C}_{13}\text{H}_{18}\text{N}_2$ picrate	204-205 (m)	523
$\text{CH}_2\text{N}(\text{CH}_3)_2$	CH_3	CH_3	$\text{C}_{13}\text{H}_{18}\text{N}_2$	82 (p)	523
	H	H	$\text{C}_{14}\text{H}_{18}\text{N}_2$ picrate	- b.p. 118-120 (0.3 mm.) 137-138	521 521 521
	H	CH_3	$\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$ picrate	192-193 (m)	523
$\text{CH}_2\text{N}(\text{CH}_3)_2$	CH_3	C_2H_5	$\text{C}_{14}\text{H}_{20}\text{N}_2$ picrate	186-187 (e)	523
	H	CH_3	$\text{C}_{15}\text{H}_{20}\text{N}_2$ picrate	162-165 (m)	523
$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{CH}_2\text{CH}_2\text{OCOCH}_3$	$\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$ HCl	- 162 (m/et)	122 122
$\text{CH}_2\text{NH-CO-C}_6\text{H}_5$	H	H	$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$	130-131 (t)	219
$\text{CH}_2\text{NH-CO-C}_6\text{H}_5$	H	CH_3	$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$	170 (x)	219

Table 2 (cont.)

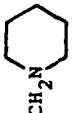
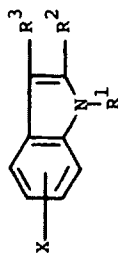
$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{CH}_2\text{C}_6\text{H}_5$	$\text{C}_{18}\text{H}_{20}\text{N}_2$ HBr picrate methiodide	- 157(e) 96-97(e) 225-235(e)	547 547 547 547
$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{CH}_2\text{CH}_2\text{OCOC}_6\text{H}_5$	$\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$ HCl methiodide	- 142-143 188-190	122 122 122
	H	$\text{CH}_2\text{CH}_2\text{OCOC}_6\text{H}_5$	$\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$ HCl methiodide	- 147-149(m) 154-156	122 122 122

Table 3. 1-Indolyl-C-C-N Derivatives



R ¹	R ²	R ³	X	m.p., °C	ref.
	H	CH ₃	H	-	506
	H	H	H	236-237 (e)	506
	H	H	H	-	124
	H	H	H	188	124
	H	C ₂ H ₅	H	90-100	506
	H	H	H	258-260 (ip)	506
	H	H	H	-	406
	H	H	H	140	406

Table 3 (cont.)

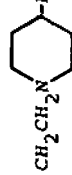
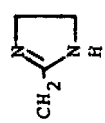
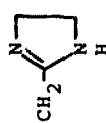
	H	H	H	$C_{17}H_{25}N_3$ di-HCl	- 264-266 (ip)	505a 505a
	C_6H_5	H	5,6-di-Cl	$C_{18}H_{15}Cl_2N_3$	-	163
"	4-ClC ₆ H ₄	H	5-Cl	$C_{18}H_{15}Cl_2N_3$	268-270 (e)	163
"	C_6H_5	H	5-Cl	$C_{18}H_{16}ClN_3$	240-241	163
"	4-ClC ₆ H ₄	H	H	$C_{18}H_{16}ClN_3$	220-223	163
"	C_6H_5	H	H	$C_{18}H_{17}N_3$	181-182 (e)	163
$CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	$C_{18}H_{20}N_2$ HCl	64-66 (p) 223-224	162 162
$CH_2CH_2N(CH_3)_2$	H	C_6H_5	H	$C_{18}H_{20}N_2$ HCl	- 204-205	117 117
	4-ClC ₆ H ₄	H	5-CH ₃	$C_{19}H_{18}ClN_3$	270-272 (m)	163
"	4-CH ₃ C ₆ H ₄	H	5-Cl	$C_{19}H_{18}ClN_3$	264-265 (m)	163

Table 3 (cont.)

	4-CH ₃ C ₆ H ₄	H	C ₁₉ H ₁₉ N ₃	210-212 (m)	163
"	C ₆ H ₅	CH ₃	C ₁₉ H ₁₉ N ₃	154 (m)	163
"	C ₆ H ₅	H	5-CH ₃	226-228 (m)	163
CH ₃ CHCH ₂ N(CH ₃) ₂	C ₆ H ₅	H	C ₁₉ H ₂₂ N ₂	-	117
				b.p. 165-168 (0.05 mm.)	117
	C ₆ H ₅	H	5,6-di-CH ₃	222-223 (m)	163
"	3,4-di-CH ₃ -C ₆ H ₃	H	C ₂₀ H ₂₁ N ₃	205-206 (m)	163
"	4-CH ₃ C ₆ H ₄	H	5-CH ₃	246-247 (m)	163
"	4-C ₂ H ₅ C ₆ H ₄	H	C ₂₀ H ₂₁ N ₃	196-197 (m)	163
CH ₃ CHCH ₂ N(CH ₃) ₂	C ₆ H ₅	CH ₃	C ₂₀ H ₂₄ N ₂	-	117
				b.p. 168-170 (0.05 mm.)	117
CH ₃ CHCH ₂ N(CH ₃) ₂	CH ₃	C ₆ H ₅	C ₂₀ H ₂₄ N ₂	-	117
				b.p. 170-172 (0.05 mm.)	117

Table 3 (cont.)

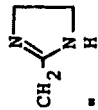
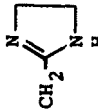
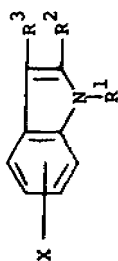
	H	H	C ₂₁ H ₂₁ N ₃	217-218	163
•	CH ₃	H	C ₂₁ H ₂₃ N ₃		163
CH ₂ CH ₂ N(C ₂ H ₅) ₂	C ₆ H ₅	H	C ₂₁ H ₂₆ N ₂	-	117
	H	H	C ₂₂ H ₁₉ N ₂	b.p. 175-177 (0.05 mm.)	117
•				206-208 (m)	163
2-(5,6,7,8-tetrahydronaphthyl)	H	H	C ₂₂ H ₂₃ N ₃	199-200 (m)	163
C ₆ H ₅	C ₆ H ₅	H	C ₂₆ H ₂₆ N ₂	118 (b)	262
CH ₂ CH ₂ N(C ₂ H ₅) ₂	C ₆ H ₅	H	C ₂₆ H ₂₈ N ₂ HCl	- 259 (e)	262 262

Table 4. 1-Indolyl-1-C-C-C-N and 1-Indolyl-1-(C)₃-N Derivatives



R ¹	R ²	R ³	X		m.p., °C	ref.
(CH ₂) ₃ NH ₂	H	H	5-Br	C ₁₁ H ₁₃ BrN ₂ oxalate	- 213(dec)	35 35
(CH ₂) ₃ NH ₂	H	H	7-Br	C ₁₁ H ₁₃ BrN ₂ oxalate	- 207(dec)	35 35
(CH ₂) ₃ NH ₂	H	H	4-Cl	C ₁₁ H ₁₃ ClN ₂ oxalate	- 201(dec)	35 35
(CH ₂) ₃ NH ₂	H	H	5-Cl	C ₁₁ H ₁₃ ClN ₂ oxalate	- 204(dec)	35 35
(CH ₂) ₃ NH ₂	H	H	7-Cl	C ₁₁ H ₁₃ ClN ₂ oxalate	- 200(dec)	35 35
(CH ₂) ₃ NH ₂	H	H	H	C ₁₁ H ₁₄ N ₂ oxalate picrate	- 209(e/w) 166-167	35 35 35

Table 4 (cont.)

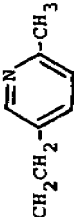
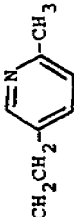
$(\text{CH}_2)_3\text{NH}_2$	H	H	5-CH ₃	C ₁₂ H ₁₆ N ₂ oxalate	- 207	35 35
	H	H	H	C ₁₅ H ₁₄ N ₂ HCl phenyletho- bromide	41-45 206-208 151-153	258,192 258,192 257,194
"	H	CH ₃	H	C ₁₆ H ₁₆ N ₂ HCl	- 211-212(ip)	195 195,258
	H	H	H	C ₁₆ H ₁₆ N ₂	66(h)	584
	H	H	H	C ₁₆ H ₂₂ N ₂ O	90-91(b)	505
	CH ₃	H	H	C ₁₇ H ₁₈ N ₂ sulfate HCl methiodide	79-80(l) 200-201(w) 120(e/et) 272-273(m)	583,311 583 583 583
"	H	CH ₃	H	C ₁₇ H ₁₈ N ₂ sulfate methiodide	70-71(l) 197-198(w) 185-186(m)	583 583 583

Table 4 (cont.)

$(\text{CH}_2)_3\text{N} \begin{array}{c} \diagup \\ \text{CONH}_2 \end{array}$	H	H	H	$\text{C}_{17}\text{H}_{23}\text{N}_3\text{O}$	127-128 (ea)	505, 505a
$(\text{CH}_2)_3\text{N} \begin{array}{c} \diagup \\ \text{C}_8\text{H}_{15}\text{N}_2\text{O} \end{array}$	H	H	H	$\text{C}_{17}\text{H}_{24}\text{N}_2\text{HCl}$	-	504
$(\text{CH}_2)_3\text{N} \begin{array}{c} \diagup \\ \text{C}_8\text{H}_{15}\text{N}_2\text{O} \end{array}$	H	H	H	$\text{C}_{17}\text{H}_{24}\text{N}_2\text{HCl}$	155-158	504
$(\text{CH}_2)_3\text{N} \begin{array}{c} \diagup \\ \text{C}_8\text{H}_{15}\text{N}_2\text{O} \end{array}$	H	H	H	$\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}$	86-87 (ea)	505, 505a
$\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_3$	CH_3	CH_3	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ sulfate methiodide	70.5 (l) 179-180 (w) 245-246 (m)	583 583 583
"	CH_3	H	5- CH_3	$\text{C}_{18}\text{H}_{20}\text{N}_2$ sulfate	55-56 (l) 212-215	583 583
"	H	C_2H_5	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ sulfate methiodide	63-64 (l) 165-167 (w) 169-170 (m)	583 583 583
$(\text{CH}_2)_3\text{N} \begin{array}{c} \diagup \\ \text{COOCH}_3 \end{array}$	H	H	H	$\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{HCl}$	- 131-132 (m)	505, 505a 505, 505a

Table 4 (cont.)

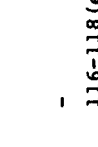
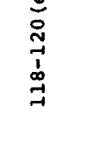
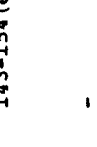
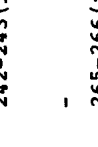
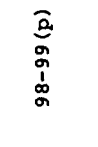
	H	H	H	C ₁₈ H ₂₄ N ₂ O ₂ HCl	- 116-118(e)	505, 505a 505, 505a
	H	H	H	C ₁₈ H ₂₅ N ₃ O	118-120(ea)	505a
	H	H	H	C ₁₈ H ₂₅ N ₃ O	104-106(ip)	505, 505a
	H	H	H	C ₁₈ H ₂₆ N ₂ HCl	- 143-154(ea)	504 504
	H	H	H	C ₁₈ H ₂₆ N ₂ O HCl	- 242-243(ip)	505 505
	H	H	H	C ₁₈ H ₂₇ N ₃ di-HCl	- 265-266(ip)	505 505
	CH ₃	CH ₂ CH ₂ Cl	H	C ₁₉ H ₂₁ ClN ₂	98-99(p)	311

Table 4 (cont.)

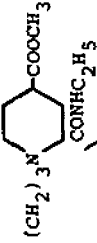
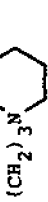
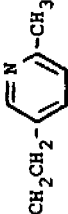
$\text{C}_{16}\text{H}_{15}$ $\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	H	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ hydrogen-oxalate	71-73 (p)	161a
$\text{CH}_2\text{CH}_2\text{-}$ 	CH_3	CH_3	5- CH_3	$\text{C}_{19}\text{H}_{22}\text{N}_2$ sulfate methiodide	169-71 (ip) 90-91 (l) 183-185 (w) 227-229 (m)	161a 583 583 583
$(\text{CH}_2)_3\text{N-}$ 	CH_3	H	H	$\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2$ HCl	- 170-175	505a 505a
$(\text{CH}_2)_3\text{N-}$ 	H	H	H	$\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}$	71-73 (ea)	505, 505a
$(\text{CH}_2)_3\text{N-}$ 	H	H	H	$\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}$	106-107 (h)	505, 505a
$(\text{CH}_2)_3\text{N-}$ 	H	H	H	$\text{C}_{19}\text{H}_{28}\text{N}_2$ HCl	- 180-181 (ip)	504 504
$(\text{CH}_2)_3\text{N-}$ 	H	H	H	$\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}$ HCl	- 180-182 (ip)	505 505
$\text{CH}_2\text{CH}_2\text{-}$ 	CH_3	C_3H_7	H	$\text{C}_{20}\text{H}_{24}\text{N}_2$ sulfate methiodide	47 (l) 167-169 (w) 198 (m)	583 583 583

Table 4 (cont.)

	H	H	H	C ₂₁ H ₂₅ N ₃	97-98 (m)	504a
	H	H	H	C ₂₁ H ₃₀ N ₂ HCl	- 207-209 (ip)	504 504
	H	H	H	C ₂₁ H ₃₂ N ₂ O 2,3,4,5,6, pentachloro- benzochloride	-	505
	H	H	H	C ₂₁ H ₃₃ N ₃ di-HCl	183-184 (ip)	505
	H	H	H	C ₂₃ H ₂₂ N ₂ sulfate methiodide	- 219-220 (ip)	505, 505a 505, 505a
	CH ₃	C ₆ H ₅	H	C ₂₃ H ₂₈ N ₂ HCl	118-119 (l) 229-230 (w) 250-252 (m)	583 583 583
	H	H	H	C ₂₃ H ₂₈ N ₂ HCl	- 161-162 (m)	257 257, 194
	H	H	H	C ₂₃ H ₂₈ N ₂ HCl	- 154-159 (ip)	504 504

Table 4 (cont.)

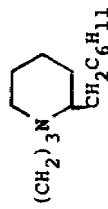
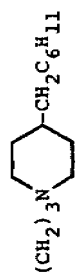
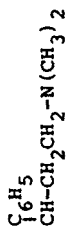
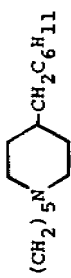
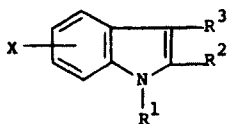
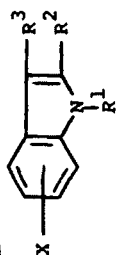
	H	H	H	C ₂₃ H ₃₄ N ₂ HCl	-	505a 505a
					152-154(ip)	
	H	H	H	C ₂₃ H ₃₄ N ₂ HCl maleate	-	505a 505a 505a
					208-210(ip) 133-135(ip)	
"	CH ₃	H	H	C ₂₄ H ₃₆ N ₂	-	505a
					b.p. 180-184(0.00075 mm.)	505a
	H	C ₆ H ₅	H	C ₂₅ H ₂₆ N ₂ hydrogen-oxalate	-	161a
					216-218(m)	161a
	H	H	H	C ₂₅ H ₃₈ N ₂ HCl	-	505a 505a
					169-172(e)	

Table 5. 2-Aminoindoles



R ¹	R ²	R ³	X		m.p. °C	ref.
H	NH ₂	H	H	C ₈ H ₈ N ₂	-	429
				HCl	222-224 (e)	429
CH ₃	NH ₂	H	H	C ₉ H ₁₀ N ₂	-	88a
				HI	260 (dec)	88a
				HCl	260 (e)	298
H	NHCOCH ₃	H	H	C ₁₀ H ₁₀ N ₂ O	142	422
C ₂ H ₅	NH ₂	H	H	C ₁₀ H ₁₂ N ₂	-	88a
				HI	260 (e)	88a
CH ₃	NHCOCH ₃	H	H	C ₁₁ H ₁₂ N ₂ O	154-155 (e)	298
H	N(COCH ₃) ₂	H	H	C ₁₂ H ₁₂ N ₂ O ₂	167	422
H	NHCH ₂ COOC ₂ H ₅	H	H	C ₁₂ H ₁₄ N ₂ O ₂	-	88a
				HBr	260 (dec) (e)	88a
CH ₂ C ₆ H ₅	NH ₂	H	H	C ₁₅ H ₁₄ N ₂	-	88a
				HCl	260 (dec) (e)	88a
H	NHCOOCH ₂ C ₆ H ₅	H	4-Br	C ₁₆ H ₁₃ BrN ₂ O ₂	116-117	176a
H	NHCOOCH ₂ C ₆ H ₅	H	5-Br	C ₁₆ H ₁₃ BrN ₂ O ₂	157-158	176a
H	NHCOOCH ₂ C ₆ H ₅	H	6-Br	C ₁₆ H ₁₃ BrN ₂ O ₂	136-137	176a
H	NHCOOCH ₂ C ₆ H ₅	H	7-Br	C ₁₆ H ₁₃ BrN ₂ O ₂	125-125	176a
H	NHCOOCH ₂ C ₆ H ₅	H	5-Cl	C ₁₆ H ₁₃ ClN ₂ O ₂	142-144	176a
H	NHCOOCH ₂ C ₆ H ₅	H	6-Cl	C ₁₆ H ₁₃ ClN ₂ O ₂	140-142	176a
H	NHCOOCH ₂ C ₆ H ₅	H	H	C ₁₆ H ₁₄ N ₂ O ₂	142-143 (p)	176a, 429
H	NHCOOCH ₂ C ₆ H ₅	H	4-CH ₃	C ₁₇ H ₁₆ N ₂ O ₂	119-120	176a
H	NHCOOCH ₂ C ₆ H ₅	H	5-CH ₃	C ₁₇ H ₁₆ N ₂ O ₂	154-155	176a
H	NHCOOCH ₂ C ₆ H ₅	H	6-CH ₃	C ₁₇ H ₁₆ N ₂ O ₂	125-126	176a

Table 6. 2-Indolyl-C-N Derivatives



R ¹	R ²	R ³	X	m.p., °C	ref.
H	CH ₂ NH ₂	H	H	69-71	371
H	CH ₂ N(CH ₃) ₂	H	H	-	310
				b.p. 143-145 (6 mm.)	310
				182-184	310, 613
				154-155	310, 488
H		H	H	180-81 (ac)	276
CH ₃	CH ₂ N(CH ₃) ₂	H	H	-	488
				b.p. 105 (11 mm.)	488
				212 (dec)	488
H	CH ₂ N(CH ₃) ₂	CH ₃	H	65-66 (p)	524
				210 (e)	524
				180 (dec)	524

Table 6 (cont.)

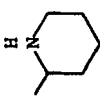
H	$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	6- CH_3	$\text{C}_{12}\text{H}_{16}\text{N}_2$ methiodide	-	488
H	α -pyridyl	H	H	$\text{C}_{13}\text{H}_{10}\text{N}_2$ methobromide methiodide	115-125(dec) 155-57 275 238	488 432, 511 429b, 432 418
H		H	H	$\text{C}_{13}\text{H}_{16}\text{N}_2$	128-129 (et)	110
H		H	H	$\text{C}_{13}\text{H}_{16}\text{N}_2$ picrate	- 195	613 613
H		H	H	$\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$ picrate	- 190	613 613
H	$\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	H	$\text{C}_{13}\text{H}_{18}\text{N}_2$ picrate	- 198	613 613
CH_3	$\text{CH}_2\text{N}(\text{CH}_3)_2$	CH_3	H	$\text{C}_{13}\text{H}_{18}\text{N}_2$ picrate methosulfate	- b.p. 102-103(0.005 mm.) 163(w) 158(e)	547 547 547
CH_3	α -pyridyl	H	H	$\text{C}_{14}\text{H}_{12}\text{N}_2$	90-91 (p)	64

Table 6 (cont.)

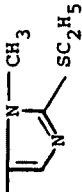
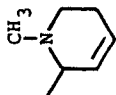
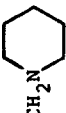
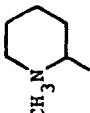
H	α -pyridyl	CH ₃	H	C ₁₄ H ₁₂ N ₂ HCl picrate methiodide methobromide	103-104 250-260(w) 206-207(e) 205-206 248-250	293, 432 429b 293 293 429b, 432
H		CH ₂ OH	H	C ₁₄ H ₁₂ N ₂ O	154(b)	511
H		H	H	C ₁₄ H ₁₅ N ₃ S	150-53(c)	276
H		H	H	C ₁₄ H ₁₆ N ₂ HCl	81 235-236(m)	432 432
H		H	H	C ₁₄ H ₁₈ N ₂ hemihydrate picrate	80-83 176	488 613
H		H	H	C ₁₄ H ₁₈ N ₂ picrate	76-78(h) 154 244-246	110 511 429b, 432

Table 6 (cont.)

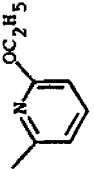
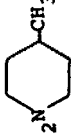
H	CH ₂ N(C ₂ H ₅) ₂	CH ₃	H	C ₁₄ H ₂₀ N ₂	-	291
H	CH ₂ NH ₂	C ₆ H ₅	5-Cl	C ₁₅ H ₁₃ ClN ₂ HCl	b.p. 146-148 (0.5 mm.)	291
H	α-pyridyl	C ₂ H ₅	5-Cl	C ₁₅ H ₁₃ ClN ₂ methobromide	124-125 (e) 222-224 (e)	612 612
H	α-pyridyl	C ₂ H ₅	6-Cl	C ₁₅ H ₁₃ ClN ₂ methobromide	144 214	429b, 432 429b, 432
H		C ₂ H ₅		C ₁₅ H ₁₃ ClN ₂ methobromide	128 221-222	432 432
H		H	H	C ₁₅ H ₁₄ N ₂	107 (e)	75a
H	α-pyridyl	C ₂ H ₅	H	C ₁₅ H ₁₄ N ₂ methobromide ethobromide	105 75-76 (e) 215 196	429b, 432 293 429b, 432 432
H	α-pyridyl	CH ₂ CH ₂ OH	H	C ₁₅ H ₁₄ N ₂ O picrate	107-110 (ac) 239 (e)	84 84
H		H	H	C ₁₅ H ₁₄ N ₂ O	119-120 (e)	75a
H		H	H	C ₁₅ H ₂₀ N ₂ maleate	170-173 (e)	69a

Table 6 (cont.)

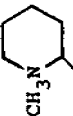
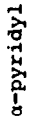
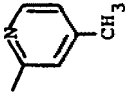
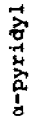
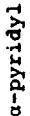
H		C ₂ H ₅	H	C ₁₅ H ₂₀ N ₂ HCl	78-80 230-235	432 432
CH ₃		H	H	C ₁₅ H ₂₀ N ₂	82-83(e)	488
H		CH ₃	H	C ₁₅ H ₂₀ N ₂ HCl	- 142-144	429b, 432 429b, 432
CH ₃		C ₆ H ₅	5-Cl	C ₁₆ H ₁₅ ClN ₂ HCl	- 243(e)	612 612
CH ₃		C ₂ H ₅	H	C ₁₆ H ₁₆ N ₂	67-68	429b
H		C ₂ H ₅	H	C ₁₆ H ₁₆ N ₂ methobromide	135 170	429b, 430 432
H		CH(CH ₃) ₂	H	C ₁₆ H ₁₆ N ₂ methobromide	128 230	432, 429b 432, 429b
H		n-C ₃ H ₇	H	C ₁₆ H ₁₆ N ₂ methobromide	127 154-155	429b, 432 429b, 432

Table 6 (cont.)

H		C ₂ H ₅	H	C ₁₆ H ₂₀ N ₂ HCl	81 235-236 (m)	429b 429b
H		CH=CH ₂	H	C ₁₆ H ₂₀ N ₂ methiodide	- 200 (m)	110 110
H		C ₂ H ₅	H	C ₁₆ H ₂₀ N ₂ O	174	429b
H		C ₂ H ₅	5-Cl	C ₁₆ H ₂₁ ClN ₂ HCl	- 248-250	429b, 432 429b, 432
H		C ₂ H ₅	6-Cl	C ₁₆ H ₂₁ ClN ₂	180/242-243	432
H		CH ₃	H	C ₁₆ H ₂₂ N ₂ HCl	- 235-240	429b 429b
H		C ₂ H ₅	H	C ₁₆ H ₂₂ N ₂ HCl fumarate picrate methiodide	- 213-125 190-192 187 189-190	429b, 432 429b 429b 110

Table 6 (cont.)

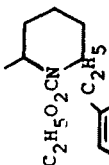
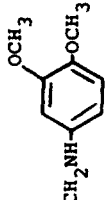
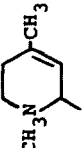
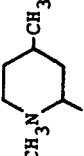
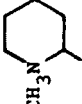
H		H	H	$C_{16}H_{22}N_2O_2$	149-151 (b)	110
H		C_2H_5	H	$C_{17}H_{18}N_2$ HCl picrate	- b.p. 160-170 (0.2 mm.) 183 (m) 177 (e)	23 23 23 23
H		H	H	$C_{17}H_{18}N_2O_2$	181-183 (dec)	371
H		C_2H_5	H	$C_{17}H_{22}N_2$ HCl	- 239-241 (m)	429b, 432 429b
H		C_2H_5	H	$C_{17}H_{24}N_2$ HCl	- 228	429b, 432 429b, 432
CH ₃		C_2H_5	H	$C_{17}H_{24}N_2$ picrate	- 205-207	429b, 432 429b, 432
H	"	n-C ₃ H ₇	H	$C_{17}H_{24}N_2$ HCl methobromide	- 170-71 154-55	429, 432 429b, 432 429b

Table 6 (cont.)

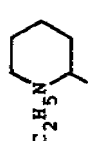
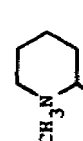
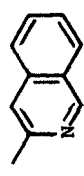
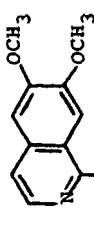
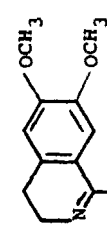
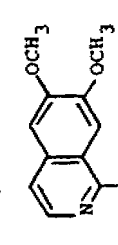
H		C_2H_5	H	$C_{17}H_{24}N_2$ HCl	- 207-12	429b, 432 429b, 432
H		$CH(CH_3)_2$	H	$C_{17}H_{24}N_2$ HCl	- 253-258	429b 429b
CH_3		H	H	$C_{18}H_{14}N_2$	121-123 (e)	64
H		H	H	$C_{19}H_{16}N_2O_2$ methiodide	222 (e) 239 (dec)	510 510
H		H	H	$C_{19}H_{18}N_2O_2$	149 (m)	510
H		CH_2CH_2Br	H	$C_{21}H_{19}BrN_2$ HBr	- 190 (dec)	510 510

Table 6 (cont.)

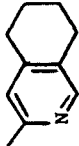
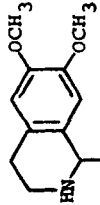
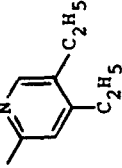
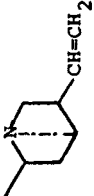
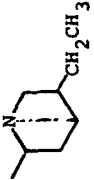
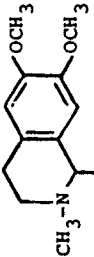
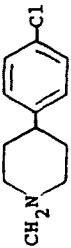
H		C ₂ H ₅	H	C ₁₉ H ₂₀ N ₂ HCl picrate	167 233-36 220-21	295 295 295
H		H	H	C ₁₉ H ₂₀ N ₂ O ₂ methiodide	132-34 216	510 510
H		C ₂ H ₅	H	C ₁₉ H ₂₂ N ₂ picrate HCl	116-17(p) 110-11 218-21 205(b/t)	433 325 325 295
H		CH ₂ CH ₂ OH	H	C ₁₉ H ₂₄ N ₂ O hydrogen- tartrate	196(e)	85
H		CH ₂ CH ₂ OH	H	C ₁₉ H ₂₆ N ₂ O HCl nitrate	162-163 225-27 232-34	381,382,383 381,382 381,382
H		H	H	C ₂₀ H ₂₂ N ₂ O ₂	187-188(ea)	510
H		H	H	C ₂₀ H ₂₁ ClN ₂ maleate	120-22(e)	69a

Table 6 (cont.)

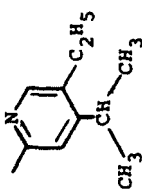
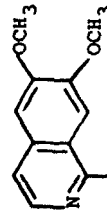
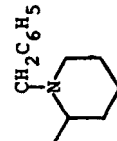
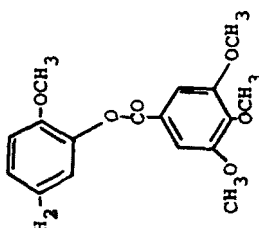
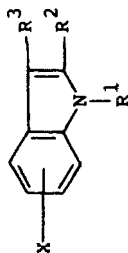
H		C ₂ H ₅	H	C ₂₀ H ₂₄ N ₂ HCl picrate	103-04 (p) 221-23 (m) 211-13 (dmf)	418 418 418
H		CH ₂ CH ₂ OH	H	C ₂₁ H ₂₀ N ₂ O ₃ picrate HCl	212-14 (e) 230 (e) 228 (e)	510 510 510
H		C ₂ H ₅	H	C ₂₂ H ₂₆ N ₂ picrate HCl	- 225-30 245-50	432, 429b 432, 429b 432, 429b
H		H	H	C ₂₇ H ₂₈ N ₂ O ₆	167-69	371

Table 7. 2-Indolyl-C-C-N Derivatives *



R ¹	R ²	R ³	X	m.p., °C	ref.
H	CH ₂ CH ₂ NH ₂	H	H	99-100	210
CH ₃	CH ₂ CH ₂ NH ₂	H	H	-	98
				178-180 (w)	98
H	CH ₂ -C ^{NH} =C ^{OC₂H₅}	H	H	-	469
				156-158	469
H	CH ₂ CH ₂ NHCH ₃	CH ₃	H	-	120
				203-04 (e)	120
H	CH ₂ -C ^{NH₂} (CH ₃) ₂	H	H	127-128 (b)	308
				187-188	308
				191-192	308

*For further compounds see: C. J. Cattanaach, A. Cohen and B. Heath-Brown, J. Chem. Soc., (C) 1971, 359.

Table 7 (cont.)

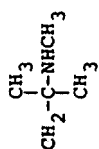
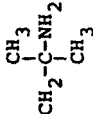
H	β -pyridyl	H	H	$C_{13}H_{10}N_2$ bromo- benzylate quat. salts	170-75(e) 233-35(e)	248 248 193
H		H	H	$C_{13}H_{16}N_2$	178-90(subl)	248
CH ₃	CH ₂ CH ₂ N(CH ₃) ₂	H	H	$C_{13}H_{18}N_2$ hydrogen- oxalate	- 165-66(m)	161a 161a
H	CH ₂ CH ₂ N(CH ₃) ₂	CH ₃	H	$C_{13}H_{18}N_2$ HCl	- 214-15(e)	120 120
H		H	H	$C_{13}H_{18}N_2$ HCl	109-110 181-82	307 307
H		H	5-CH ₃	$C_{13}H_{18}N_2$	-	307
H	β -pyridyl	CH ₃	5-Cl	$C_{14}H_{11}ClN_2$ HCl	- 233-234	165 165

Table 7 (cont.)

H	3-pyridyl	CH ₃	H	C ₁₄ H ₁₂ N ₂ HCl methane- sulfonate	164-65 245-47 158	165 165 165
H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2-\text{C}-\text{NHCOCH}_3 \\ \\ \text{CH}_3 \end{array}$	H	H	C ₁₄ H ₁₈ N ₂ O	126-127	308
CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \end{array}$	CH ₃	H	C ₁₄ H ₂₀ N ₂ HI picrate methosulfate	- b.p. 113-114 (0.007 mm.) 203-204 179 204	554 554 554 554
H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2-\text{C}-\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_3 \end{array}$	H	H	C ₁₄ H ₂₀ N ₂ methiodide	- 191-192 (w)	308 308
H	6-purinylyl	H	H	C ₁₅ H ₁₄ N ₆	285-286 (e)	168
CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2-\text{C}-\text{NHCOCH}_3 \\ \\ \text{CH}_3 \end{array}$	H	H	C ₁₅ H ₂₀ N ₂ O	122-123	307

Table 7 (cont.)

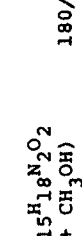
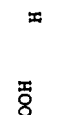
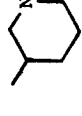
H		H	H	$C_{15}H_{18}N_2O_2$ (+ CH_3OH)	180/220	248
H		H	H	$C_{17}H_{22}N_2O_2$	105-106 (b)	21
H		H	H	$C_{17}H_{22}N_2O_2$	107-08 (h)	248
CH_3		CH_3	H	$C_{17}H_{24}N_2$ HI picrate	45-50 240 (e) 184-85 (e)	554 554 554
C_6H_5		H	H	$C_{18}H_{20}N_2$ hydrogen- oxalate	-	161a
H		C_6H_5	H	$C_{18}H_{20}N_2$ HCl	153-54 (ip)	161a
CH_3		C_6H_5	H	$C_{19}H_{22}N_2$ HCl methiodide	- 239-40 (e) 247-49 (e)	120 120 536 536 536

Table 7 (cont.)

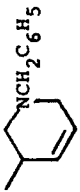
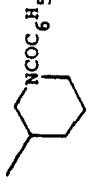
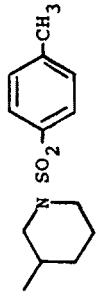
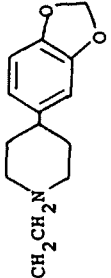
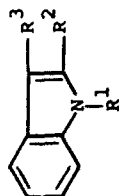
H		H	H	$C_{20}H_{20}N_2$	166-67 (mc)	248
H		H	H	$C_{20}H_{20}N_2O$	207-08 (e)	248
H		H	H	$C_{20}H_{22}N_2O_2S$	192-93 (e)	248
$CH_2C_6H_5$	$CH_2CH_2N(CH_3)_2$	CH_3	H	$C_{20}H_{24}N_2$ picrate HCl	- 146-47 (e) 201 (e)	554 554 554
CH_3	$CH_2CH_2N(C_2H_5)_2$	C_6H_5	H	$C_{21}H_{26}N_2$ HCl	-	536
H		H	H	methiodide $C_{22}H_{22}N_2O_2$ maleate	203-04 (et) 203-09 (ac) 150-153 (m)	536 536 69a

Table 8. 2-Indolyl-C-C-C-N and 2-Indolyl-(C)₃-N Derivatives



R ¹	R ²	R ³		m.p., °C	ref.
H	γ-pyridyl	H	C ₁₃ H ₁₀ N ₂ methiodide	-	38
H	γ'-pyridyl	CH ₃	C ₁₄ H ₁₂ N ₂ HCl	263-65(w) - 244-45(m)	38 165 165
H		H	C ₁₄ H ₁₆ N ₂	175-76(w)	38
H		H	C ₁₄ H ₁₈ N ₂	180	38
H	γ-pyridyl	C ₂ H ₅	C ₁₅ H ₁₄ N ₂ methobromide ethobromide	151 315-20 200-03	429a, 432 429a, 432 429b
CH ₃	COCH ₂ CH ₂ N(CH ₃) ₂	H	C ₁₄ H ₁₈ N ₂ O HCl	194-195(e)	69b

Table 8 (cont.)

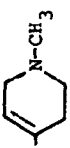
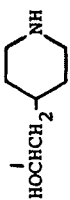
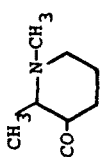
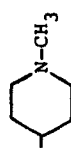
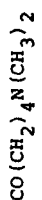
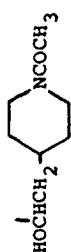
CH ₃		H	C ₁₅ H ₁₈ N ₂	68-70 (t)	38
H		H	C ₁₅ H ₁₈ N ₂ O	173-174 (b)	513
H		H	C ₁₅ H ₂₀ N ₂ O	184-185 (m)	513
H		H	C ₁₆ H ₂₀ N ₂ O methiodide	167-68 (et) 225-26 (m)	110 110
H		C ₂ H ₅	C ₁₆ H ₂₂ N ₂	138 (h)	429b, 432
H		CH=CH ₂	C ₁₇ H ₂₂ N ₂ O	70-71	110
H		H	C ₁₇ H ₂₂ N ₂ O ₂	152-153 (b)	513

Table 8 (cont.)

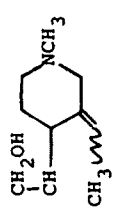
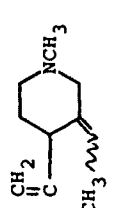
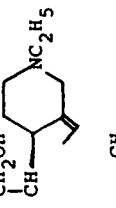
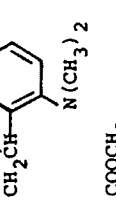
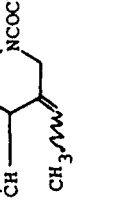
H		H	$C_{18}H_{25}N_2O$	131-134 196-198	590 590
H		CH ₃	$C_{19}H_{24}N_2$	100-05(p)	590
H		H	$C_{19}H_{28}N_2O$	134-37	590
H		H	$C_{20}H_{24}N_2$ picrate	- 175-76	485 485
H		CH ₂ OCH ₃	$C_{22}H_{28}N_2O_4$	142-45 183-185	590 590

Table 8 (cont.)

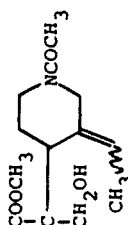
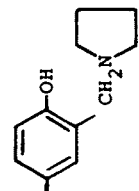
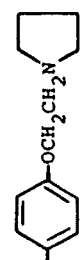
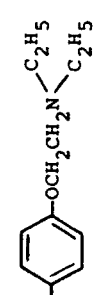
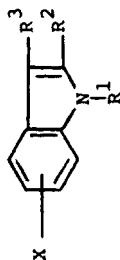
H		CH ₂ OCH ₃	C ₂₃ H ₃₀ N ₂ O ₅	-	590
H		C ₆ H ₅	C ₂₅ H ₂₄ N ₂ O	116 (e)	262
H		C ₆ H ₅	C ₂₆ H ₂₆ N ₂ O	159-60 (b)	262
H		C ₆ H ₅	C ₂₆ H ₂₈ N ₂ O	124 (b)	262

Table 9. 3-Aminoindoles



R ¹	R ²	R ³	X	m.p., °C	ref.
H	H	NH ₂	H	-	341
				117	341
H	CH ₃	NH ₂	H	128	471a
				112-13	587
H	H	NHCOCH ₃	H	162-63	341
				168(subl)	471a
H	CH ₃	N=C(CH ₃) ₂	H	91(p)	471a
				119(e/w)	424a
H	H	NHCH(CH ₃) ₂	H	214	471a
H	C ₆ H ₅	NH ₂	5-Cl		

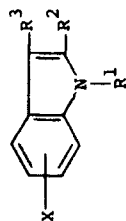
Table 9 (cont.)

H	C ₆ H ₅	NH ₂	H	C ₁₄ H ₁₂ N ₂	180	471a
CH ₃	H		H	C ₁₄ H ₁₈ N ₂	174-76	428
H	2-CH ₃ C ₆ H ₄	NH ₂	H	C ₁₅ H ₁₄ N ₂	135	471a
CH ₃	C ₆ H ₅	NH ₂	H	C ₁₅ H ₁₄ N ₂ acetate	81-84	58
H	4-CH ₃ OC ₆ H ₄	NH ₂	H	C ₁₅ H ₁₄ N ₂ O	172-173(e/w)	58
COCH ₃	H		H	C ₁₅ H ₁₈ N ₂ O HCl	150-151	389
H	C ₆ H ₅	N=C(CH ₃) ₂	H	C ₁₇ H ₁₆ N ₂	90(e)	424a
H	C ₆ H ₅	NH-CH(CH ₃) ₂	H	C ₁₇ H ₁₈ N ₂	235-40(e)	424a
4-ClC ₆ H ₄ CH ₂	CH ₃	N(CH ₃) ₂	H	C ₁₈ H ₁₉ ClN ₂	107(cyh)	471a
C ₆ H ₅ CH ₂	CH ₃	N(CH ₃) ₂	H	C ₁₈ H ₂₀ N ₂	94(cyh)	471a
4-ClC ₆ H ₄ CH ₂	CH ₃		H	C ₂₀ H ₂₁ ClN ₂ O	97(e)	613
					86	613
					109	613

Table 9 (cont.)

$C_6H_5CH_2$	CH_3		H	$C_{20}H_{22}N_2O$	94	613
$4-ClC_6H_4CH_2$	CH_3	$N(C_2H_5)_2$	H	$C_{20}H_{23}ClN_2$	69	613
$C_6H_5CH_2$	CH_3	$N(C_2H_5)_2$	H	$C_{20}H_{24}N_2$	74	613
$4-ClC_6H_4CH_2$	CH_3		H	$C_{21}H_{23}ClN_2$	76	613
Addenda:						
C_2H_5	C_6H_5	NH_2	H	$C_{16}H_{16}N_2$		
				HCl	242-44 (e)	642
C_6H_5	C_6H_5	NH_2	H	$C_{20}H_{16}N_2$	50-53	
				HCl	223-25 (e)	642

Table 10. 3-Indolyl-C-N Derivatives



R ¹	R ²	R ³	X	m.p., °C	Ref.
H	H	CH ₂ NH ₂	H	84 (x) 104-107 (b)	423 177
CH ₃	H	CH ₂ NH ₂	H	- 170	177 177
H	H	CH ₂ NHCH ₃	H	- 126/150-65	369 369
H	CH ₃	CH ₂ NH ₂	H	125-26 (e)	79
H	H	CH ₂ NH-C(=NH) NH ₂	H	- 152-163	506a 506
H	H	CH ₂ NH-C(=NH) NH ₂	H	- 156-59 (ip)	486 486
H	H	CH ₂ NH-C(=NH) NH ₂	H	280 (e/w)	145a
H	H	CH ₂ NH-C(=NH) NH ₂	5-Br	162	212

Table 10 (cont.)

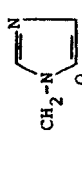
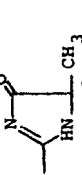
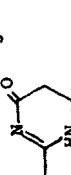
H	H	$\text{CH}_2\text{N}(\text{CH}_3)_2$	4-Cl	$\text{C}_{11}\text{H}_{13}\text{ClN}_2$	147-48 (ac)	206
H	H	"	5-Cl	$\text{C}_{11}\text{H}_{13}\text{ClN}_2$	150	424, 446
H	H	"	6-Cl	$\text{C}_{11}\text{H}_{13}\text{ClN}_2$	129-31 (e/w) 132 (e)	516 446
H	H	"	5-F	$\text{C}_{11}\text{H}_{13}\text{FN}_2$	145-46 150	424 239
H	H	"	6-F	$\text{C}_{11}\text{H}_{13}\text{FN}_2$	138 (e)	50
H	H	"	5-I	$\text{C}_{11}\text{H}_{13}\text{IN}_2$	157-58 (m/w) 159 (m)	420 211
H	H	$\text{CH}_2\text{NHNHCOCH}_3$	H	$\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}$	148 (ea)	520
H	H	$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2$ picrate methiodide	134 141 168-69 (m)	317, 603 317, 603 169
H	H	$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}\cdot\text{H}_2\text{O}$	135-36 121-22	225 225
H	H		H	$\text{C}_{12}\text{H}_{11}\text{N}_3$	180	104
H	H		H	$\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$	265 (e)	145a
H	H		H	$\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$	312	306a

Table 10 (cont.)

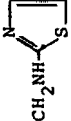
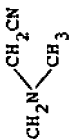
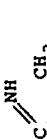
H	H		H	C ₁₂ H ₁₁ N ₃ S	140	589
H	H		H	7-Cl	-	453
				C ₁₂ H ₁₃ ClN ₂ hydrogen-oxalate	129-30 (e/w)	453
H	H		H	C ₁₂ H ₁₃ N ₃ hydrogen-oxalate	-	369
H	H		H	C ₁₂ H ₁₃ N ₃ picrate	130-31	369
H	H		H	C ₁₂ H ₁₃ N ₃ O ₂	115-18 (b) 242-43 (e)	266 266
H	H		H	C ₁₂ H ₁₃ N ₃ O ₂	280 (e/w)	145a
H	H		H	C ₁₂ H ₁₃ N ₃ O ₂	300	306a
H	H		H	C ₁₂ H ₁₄ N ₂	138-140	453
H	H		H	C ₁₂ H ₁₄ N ₂	141-43	620
H	CH ₃		5-Br	C ₁₂ H ₁₅ BrN ₂ HCl	143-45 (m) 170-173	94, 142 424

Table 10 (cont.)

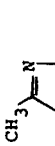
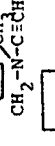
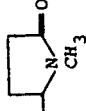
H	CH ₃	CH ₂ N(CH ₃) ₂	5-Cl	C ₁₂ H ₁₅ ClN ₂ HCl	157-59 (m) 177-79 (e)	94, 142 94, 142
H	CH ₃	"	5-F	C ₁₂ H ₁₅ FN ₂	146-147	424
CH ₃	H	"	H	C ₁₂ H ₁₆ N ₂ picrate HCl methiodide	b.p. 94-96 (0.2 mm.) 145-146 198-99 (et) 193	489 491 489
H	CH ₃	"	H	C ₁₂ H ₁₆ N ₂	158-160 (t) 116-117	94 445
H	H	"	4-CH ₃	C ₁₂ H ₁₆ N ₂	128-29	445
H	H	"	5-CH ₃	C ₁₂ H ₁₆ N ₂	138-39 133	424 445
H	H	"	6-CH ₃	C ₁₂ H ₁₆ N ₂	117	445
H	H	"	7-CH ₃	C ₁₂ H ₁₆ N ₂	114 115-17 (b) 119-22	445 239 581
H	H	α-pyridyl	H	C ₁₃ H ₁₀ N ₂	150-54 (b)	416
H	H		H	C ₁₃ H ₁₃ N ₃	170	104
H	H		H	C ₁₃ H ₁₄ N ₂ Oxalate	130-131 156-58 146-48	369 369 582
H	H		H	C ₁₃ H ₁₄ N ₂ O		582

Table 10 (cont.)

H	H		5-Br	$C_{13}H_{15}BrN_2$	139-41 (ac)	620
H	H	"	4-Cl	$C_{13}H_{15}ClN_2$	157-58 (ac)	620
H	H	"	5-Cl	$C_{13}H_{15}ClN_2$	143-45 (et)	620
H	H	"	5-F	$C_{13}H_{15}FN_2$	142-44 (ac)	620
CH ₃	H		H	$C_{13}H_{16}N_2$	140-150 (e)	453
H	H	"	4-CH ₃	$C_{13}H_{16}N_2$	165-70	453
H	H	"	5-CH ₃	$C_{13}H_{16}N_2$ hydrogen-oxalate	-	453
H	H	"	6-CH ₃	$C_{13}H_{16}N_2$ hydrogen-oxalate	150/160 (e)	453
H	H	"	7-CH ₃	$C_{13}H_{16}N_2$ hydrogen-oxalate	-	453
H	H	"			142/160 (e)	453
CH ₃	H		H	$C_{13}H_{16}N_2$ HCl	104-107	453
					140-150	453
					-	620
					215-16 (m)	620

Table 10 (cont.)

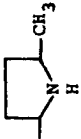
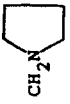
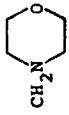
H	H		H	$C_{13}H_{16}N_2$	95-97	620
H	H		H	$C_{13}H_{16}N_2$ HCl	- 225-26 (m)	620 620
H	H		H	$C_{13}H_{16}N_2$	121-22	534, 549 599a
H	H		H	$C_{13}H_{16}N_2$	127-28 (m/w) 125	203 290a
H	H		H	$C_{13}H_{16}N_2O$	121 (m)	16, 444
H	H	$CH_2N(C_2H_5)_2$	4-Cl	$C_{13}H_{17}ClN_2$	130	446
H	H	$CH_2N(C_2H_5)_2$	6-Cl	$C_{13}H_{17}ClN_2$	96 (p)	446
H	H	$CH_2N(C_2H_5)_2$	H	$C_{13}H_{18}N_2$ picrate	103-04 (b) 165 (d) 124 (m)	16 317 317

Table 10 (cont.)

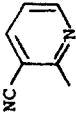
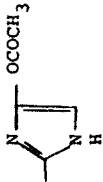
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CHNHCH}(\text{CH}_3)_2 \end{array}$	H	$\text{C}_{13}\text{H}_{18}\text{N}_2$	109-110 113-117 137	419 494 396
CH_3	H	$\text{CH}_2\text{N}(\text{CH}_3)_2$	7- CH_3	$\text{C}_{13}\text{H}_{18}\text{N}_2$ picrate	- 142(e)	97 97
H	CH_3	"	5- CH_3	$\text{C}_{13}\text{H}_{18}\text{N}_2$	160	100, 424
CH_3	H	"	6- CH_3	$\text{C}_{13}\text{H}_{18}\text{N}_2$ picrate	- 142(et)	97 97
H	H	$\text{CH}_2\text{NHC}(\text{CH}_3)_3$	H	$\text{C}_{13}\text{H}_{18}\text{N}_2$	115-19	494
CH_3	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH-N}(\text{CH}_3)_2 \end{array}$	H	$\text{C}_{13}\text{H}_{18}\text{N}_2$		18
H	H	$\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$	H	$\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2$ picrate	- 87(m)	108a 108a
H	H		H	$\text{C}_{14}\text{H}_9\text{N}_3$	199-200	416
CHO	H		H	$\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_3$	145	306a
H	CH_3	α -pyridyl	H	$\text{C}_{14}\text{H}_{12}\text{N}_2$	137-38(1)	534

Table 10 (cont.)

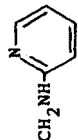
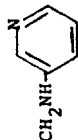
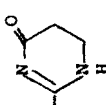
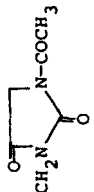
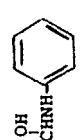
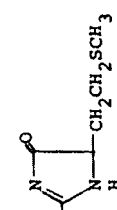
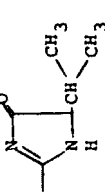
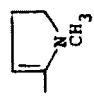
H	H		H	$C_{14}H_{13}N_3$	109	589
H	H		H	$C_{14}H_{13}N_3$	133	589
COCH ₃	H		H	$C_{14}H_{13}N_3O_2$	295	306a
H	H		H	$C_{14}H_{13}N_3O_3$	197-98 (ea)	91
H	H		H	$C_{14}H_{14}N_2O$		343
H	H		H	$C_{14}H_{15}N_2OS$	248 (e)	145a
H	H		H	$C_{14}H_{15}N_3O$	273 (e)	145a
H	H		H	$C_{14}H_{16}N_2$ methiodide	- 205-07	620 620

Table 10 (cont.)

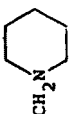
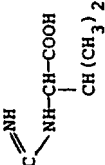
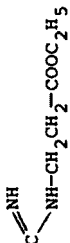
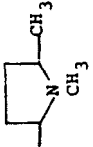
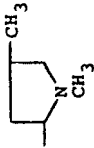
H	H		H	$C_{14}H_{16}N_2O_3$ + 1/2 H ₂ O	213-14	434
H	H		4-Br	$C_{14}H_{17}BrN_2$	190	407
H	H		H	$C_{14}H_{17}N_3O_2$	280(e)	145a
H	H		H	$C_{14}H_{17}N_3O_2$	130	306a
CH ₃	H		H	$C_{14}H_{18}N_2$ picrate	b.p. 142-44 146-47(e)	203 203
H	CH ₃		H	$C_{14}H_{18}N_2$	139-40(e)	100
H	H		H	$C_{14}H_{18}N_2$	151-152(m)	620
H	H		H	$C_{14}H_{18}N_2$ HCl	- 197-200(m)	620 620

Table 10 (cont.)

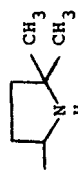
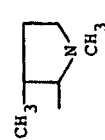
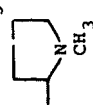
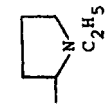
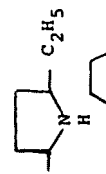
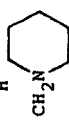
H	H		H	$C_{14}H_{18}N_2$ HCl	- 229-30 (m)	620 620
H	H		H	$C_{14}H_{18}N_2$ HCl	- 211-14 (m)	620 620
CH ₃	H		H	$C_{14}H_{18}N_2$	46-48	620
H	CH ₃	"	H	$C_{14}H_{18}N_2$	122-24 (et)	620
H	H	"	5-CH ₃	$C_{14}H_{18}N_2$	117-118 (et)	620
H	H	"	7-CH ₃	$C_{14}H_{18}N_2$	95-97 (et)	620
H	H		H	$C_{14}H_{18}N_2$ HCl	- 200-02 (e)	620 620
H	H		H	$C_{14}H_{18}N_2$ HCl	- 227-28 (m)	620 620
H	H		H	$C_{14}H_{18}N_2$ picrate	164 158 161 172-73 (e)	290 a 16,372,443 203,221,317 203

Table 10 (cont.)

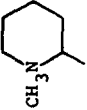
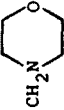
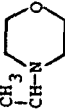
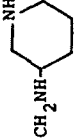
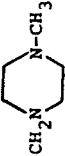
H	CH ₃		H	C ₁₄ H ₁₈ N ₂ picrate- picrate- hydrate	- 180-81 135/175	534 534 534
H	H		H	C ₁₄ H ₁₈ N ₂	156-57 158 160-62	17 534, 599 416
H	CH ₃		H	C ₁₄ H ₁₈ N ₂ O	175-76(e)	66
H	H		H	C ₁₄ H ₁₈ N ₂	115-18(e)	18
H	CH ₃		5-Cl	C ₁₄ H ₁₉ ClN ₂ HCl	104-05(m) 162-64(e)	94, 100 94
H	H		H	C ₁₄ H ₁₉ N ₃ di-HCl	- ca. 150	589 589
H	H		H	C ₁₄ H ₁₉ N ₃	157-60	143
H	CH ₃		H	C ₁₄ H ₂₀ N ₂	104-106	426

Table 10 (cont.)

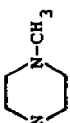
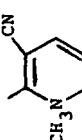
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CHNHC}(\text{CH}_3)_3 \end{array}$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$	70-72	494
H	CH_3	$\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$	89-90 (m)	100
H	H	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\ \\ \text{CH-NH-CH}(\text{CH}_3)_2 \end{array}$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ HCl	- 137-138	394 394, 396
H	H		H	$\text{C}_{14}\text{H}_{20}\text{N}_4$	173	589
H	H	$\text{CH}_2\text{NH}(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	H	$\text{C}_{14}\text{H}_{21}\text{N}_3$ di-HCl	- (+ $\frac{1}{2}\text{H}_2\text{O}$) 163	589 589
H	H	$\text{CH}_2\text{N}(\text{CH}_3)_2$	Si(CH ₃) ₃	$\text{C}_{14}\text{H}_{22}\text{N}_2\text{Si}$	113 (p)	40a
H	H		H	$\text{C}_{15}\text{H}_{13}\text{N}_3$	180-200	416
H	C_6H_5	CH_2NH_2	H	$\text{C}_{15}\text{H}_{14}\text{N}_2$	156-57 (e)	79
H	H	$\text{CH}_2\text{NHC}_6\text{H}_5$	H	$\text{C}_{15}\text{H}_{14}\text{N}_2$	95-96 (m)	545
H	H		H	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$	103-04 (e)	545
H	H	$\text{CH}_2\text{NHSO}_2\text{C}_6\text{H}_5$	H	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$	160-63	336
H	H		H	$\text{C}_{15}\text{H}_{15}\text{N}_3$	116-17 (m)	556

Table 10 (cont.)

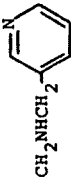
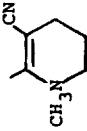
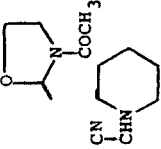
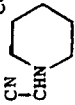
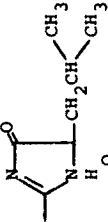
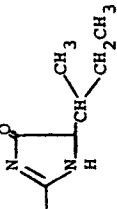
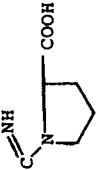
H	H	$\text{CH}_2\text{NHNHC}_6\text{H}_5$	H	$\text{C}_{15}\text{H}_{15}\text{N}_3$ NCOC_6H_5	120-21 (m) 186 (e)	556 556
H	H		H	$\text{C}_{15}\text{H}_{15}\text{N}_3$ dl-HCl	- 220 (dec)	589 589
H	H		H	$\text{C}_{15}\text{H}_{15}\text{N}_3$	200-03	416
COCH_3	H		H	$\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$	157 (ea)	589
H	H		H	$\text{C}_{15}\text{H}_{17}\text{N}_3$	148-50 (b)	266
H	H		H	$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}$	258 (e)	145a
H	H		H	$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}$	248 (e)	145a
H	H		H	$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$	238 (e)	145a

Table 10 (cont.)

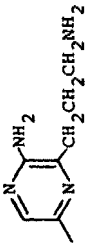
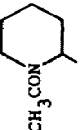
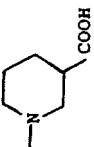
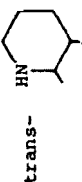
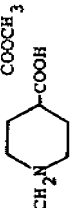
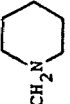
H	H		H	$C_{15}H_{17}N_5$	-	303
H	H	$CH_2N(CH_2CH=CH_2)_2$	H	$C_{15}H_{18}N_2$	77-78 (e)	66
H	H		H	$C_{15}H_{18}N_2$	155-56 (h)	513
H	H		H	$C_{15}H_{18}N_2O$	168-69 (e)	549
H	H		H	$C_{15}H_{18}N_2O_2$	165-66 (dec)	519
H	H		H	$C_{15}H_{18}N_2O_2$	103-04 (h)	599b
H	H		H	$C_{15}H_{18}N_2O_2$	228	519
H	CH_3		5-Cl	$C_{15}H_{19}ClN_2$	161-63 (m) 165-66 (e)	94, 142 100

Table 10 (cont.)

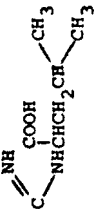
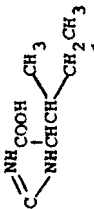
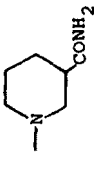
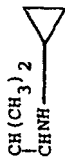
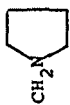
H	H		H	$C_{15}H_{19}N_3O_2$	193 (e/w)	145a
H	H		H	$C_{15}H_{19}N_3O_2$	210 (e/w)	145a
H	H		H	$C_{15}H_{19}N_3$	211-15 (e)	57
H	H		H	$C_{15}H_{19}N_3O$ HCl	- 195	519 519
H	H		H	$C_{15}H_{19}N_3O$ HCl	- 196-97	519 519
H	H		H	$C_{15}H_{20}N_2$ HCl	- 126-28 (m)	394 394
H	H		H	$C_{15}H_{20}N_2$	115	589
H	CH ₃		5-CH ₃	$C_{15}H_{20}N_2$	167-68 (e)	100

Table 10 (cont.)

H	H		H	$C_{15}H_{20}N_2$	140-41(et)	620
H	H		H	$C_{15}H_{20}N_2$	138-40(et)	620
CH ₃	CH ₃		H	$C_{15}H_{20}N_2$ HCl HI	- 198 218(e)	554 554 554
H	CH ₃		H	$C_{15}H_{20}N_2$	157(e)	66
CH ₃	H		H	$C_{15}H_{20}N_2$ picrate	b.p. 130-140 (6 mm.) 174 167	220 220 491
H	H		H	$C_{15}H_{20}N_2$ HCl	100-101 165-70(e)	18 18
H	H		H	$C_{15}H_{20}N_2$	171-73(ac)	16
H	H		H	$C_{15}H_{20}N_2$	150(ac)	17

Table 10 (cont.)

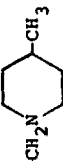
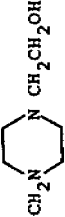
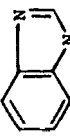
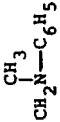
H	H		H	$C_{15}H_{20}N_2$	110(ac)	17
H	H		H	$C_{15}H_{21}N_3$ di-HCl	- 202(dec)	589 589
H	H		H	$C_{15}H_{21}N_3O$	85-95	143
H	H		H	$C_{15}H_{22}N_2$ HCl	74-77 131-33(m)	394, 396 394, 396
H	H	$CH_2NHCH_2CH_2N(C_2H_5)_2$	H	$C_{15}H_{23}N_3$ di-HCl	- 157(dec)	589 589
H	H		H	$C_{16}H_{13}N_3$	215	104
H	H		H	$C_{16}H_{13}N_3S$	186	589
H	H	$CH_2NHCOC_6H_5$	H	$C_{16}H_{14}N_2O$	157(x)	219
H	H		H	$C_{16}H_{16}N_2$	90-91(cyh)	550

Table 10 (cont.)

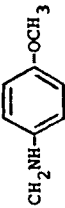
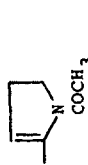
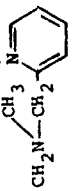
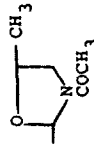
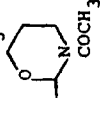
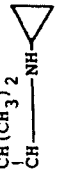
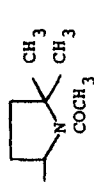
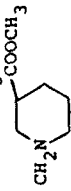
H	H	$\text{CH}_2\text{NHCH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{16}\text{H}_{16}\text{N}_2$	95	589
H	H		H	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}$	110	589
COCH_3	H		H	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$	132-44 (py)	620
H	H		H	$\text{C}_{16}\text{H}_{17}\text{N}_3$ methobromide	- 160 (dec)	372 372
COCH_3	H		H	$\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$	169 (ea)	589
COCH_3	H		H	$\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$	194 (ea)	589
H	H		H	$\text{C}_{16}\text{H}_{20}\text{N}_2$ HCl	- 126-27	396 396
H	H		H	$\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$	203-04 (m)	620
H	H		H	$\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2$ HCl	- 169-70	519 519

Table 10 (cont.)

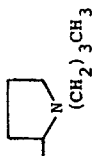
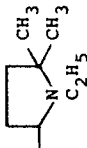
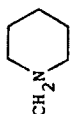
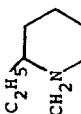
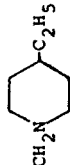
H	H		H	$C_{16}H_{20}N_2O_2$ HCl	- 169-70	519 519
H	H	$CH_2N(CH_3)_2$	$4-CH_2CH=C(CH_3)_2$	$C_{16}H_{22}N_2$	106(b)	407a
H	H		H	$C_{16}H_{22}N_2$ cyclohexyl- sulfamate	- 116-18(e)	620 620
H	H		H	$C_{16}H_{22}N_2$	82-85(p)	620
H	CH ₃		5-CH ₃	$C_{16}H_{22}N_2$	173-74(e)	100
H	H		H	$C_{16}H_{22}N_2$	161(ac)	17
H	H		H	$C_{16}H_{22}N_2$	121-22(ac)	16

Table 10 (cont.)

H	H		H	$C_{16}H_{22}N_2$	104-06 (p)	16
H	H		H	$C_{16}H_{22}N_2$	113-14 (b)	16
H	H		4-CH ₂ -C(CH ₃) ₂ -O-CH ₃	$C_{16}H_{22}N_2O_2$	142-43 (m)	410
H	H		H	$C_{16}H_{21}N_3O_2$ HCl	- 176 (w)	145a 145a
H	H		H	$C_{16}H_{24}N_2$ HCl	- 128-30	394, 396 394, 396
H	H		5-CH ₃	$C_{16}H_{24}N_2$ HCl	- 132-34	394, 396 394, 396
H	H		H	$C_{16}H_{24}N_2O$ HCl	- 133-34	394, 396 394, 396
H	H		H	$C_{16}H_{24}N_2S$ HCl	- 133-35	394 394

Table 10 (cont.)

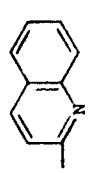
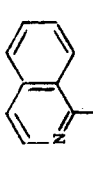
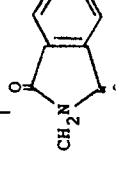
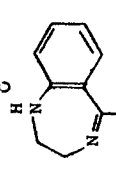
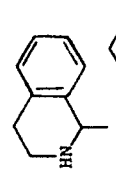
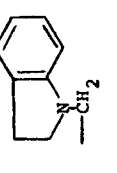
H	H		H	C ₁₇ H ₁₂ N ₂ picrate	120 (e) 245	107 107
H	H		H	C ₁₇ H ₁₂ N ₂ HCl	197-98 (b) 194	95 95
H	H		H	C ₁₇ H ₁₂ N ₂ O ₂	180 (e) 182-83 (e)	221 26
H	H		H	C ₁₇ H ₁₅ N ₃ HCl methiodide	223-25 (e) 180-85 255-63 (m)	162a 438 438 162a
H	H		H	C ₁₇ H ₁₆ N ₂ HCl	- 233 (e)	549 549
H	H		H	C ₁₇ H ₁₆ N ₂	87 (e)	549
H	C ₆ H ₅	CH ₂ N(CH ₃) ₂	7-Cl	C ₁₇ H ₁₇ ClN ₂	98	231

Table 10 (cont.)

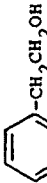
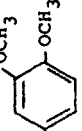
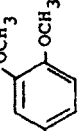
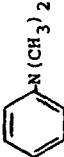
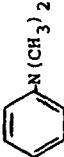
H	C ₆ H ₅	CH ₂ N(CH ₃) ₂	5-Cl	C ₁₇ H ₁₇ ClN ₂	160	231
H	C ₆ H ₅	"	H	C ₁₇ H ₁₈ N ₂	126-27(e/w) 128-29(e)	287 100
H	H	CH ₂ NHCH ₂ CH ₂ C ₆ H ₅	H	C ₁₇ H ₁₈ N ₂ HCl	- 169(dec)	589 589
H	H	 CH ₂ NHCH-C ₆ H ₅	H	C ₁₇ H ₁₈ N ₂	101	589
H	C ₆ H ₅	CH ₂ N(CH ₃) ₂	H	C ₁₇ H ₁₈ N ₂	124-26(e/w) 128-29(e)	498 100
H	H	 CH ₂ NHCH ₂ CH-C ₆ H ₅	H	C ₁₇ H ₁₈ N ₂ O	148	589
H	H	 CH ₂ NH- 	H	C ₁₇ H ₁₈ N ₂ O	96	589
H	H	 CH ₂ NH- 	H	C ₁₇ H ₁₈ N ₂ O ₂	106	589
H	H	 CH ₂ NH- 	H	C ₁₇ H ₁₉ N ₃	131	589
H	H	 CH ₂ NH- 	H	C ₁₇ H ₂₂ N ₂ O ₂ HCl	- 150-151	519 519

Table 10 (cont.)

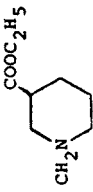
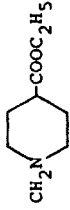
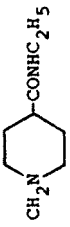
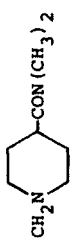
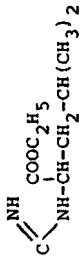
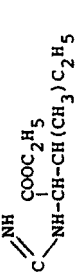
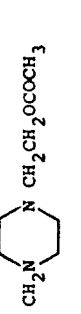
H	H		H	$C_{17}H_{22}N_2O_2$	83-84 (b)	16
H	H		H	$C_{17}H_{22}N_2O_2$	113-115 (p)	16
H	H		H	$C_{17}H_{23}N_3O$ HCl	- 188-89	519 519
H	H		H	$C_{17}H_{23}N_3O$ HCl	- 166-67	519 519
H	H		H	$C_{17}H_{23}N_3O_2$ HCl	- 165 (ac)	145a 145a
H	H		H	$C_{17}H_{23}N_3O_2$ HCl	- 170 (ac)	145a 145a
H	H		H	$C_{17}H_{23}N_3O_2$		16
H	H		H	$C_{17}H_{23}N_3O_2$	84-88	143

Table 10 (cont.)

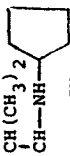
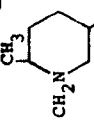
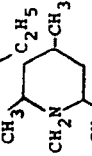
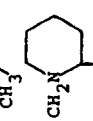
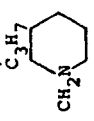
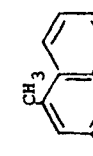
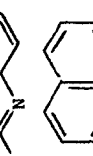
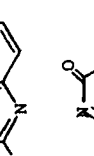
H	H		H	$C_{17}H_{24}N_2$ HCl	- 132-34	396 396
H	H		H	$C_{17}H_{24}N_2$	103-04(p)	16
H	H		H	$C_{17}H_{24}N_2$	111-112(p)	16
H	H		H	$C_{17}H_{24}N_2$	99(p)	17
H	H		5-Si(CH ₃) ₃	$C_{17}H_{26}N_2Si$	126(p)	40a
H	H		H	$C_{18}H_{14}N_2$ HCl	- 179-80	95 95
CH ₃	H		H	$C_{18}H_{14}N_2$ HI	- 285(e/w)	107 107
H	H		H	$C_{18}H_{15}N_3O$	145	306a

Table 10 (cont.)

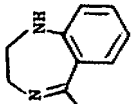
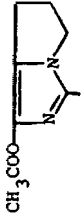
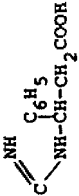
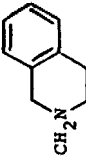
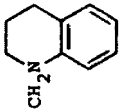
CH ₃	H		H	C ₁₈ H ₁₇ N ₃	144-48	162a
COCH ₃	H		H	C ₁₈ H ₁₇ N ₃ O ₃	200	306a
H	H		H	C ₁₈ H ₁₇ N ₃ O ₂	214	306a
H	H		H	C ₁₈ H ₁₈ N ₂	141(b)	17
H	H		H	C ₁₈ H ₁₈ N ₂	115(b)	17
CH ₂ C ₆ H ₅	H	CH ₂ N(CH ₃) ₂	5-Br	C ₁₈ H ₁₉ BrN ₂ HCl	- 218-20	237 237
CH ₂ C ₆ H ₅	H	"	5-Cl	C ₁₈ H ₁₉ ClN ₂ HCl	- 219-20	237 237
CH ₂ C ₆ H ₅	H	CH ₂ N(CH ₃) ₂	5-F	C ₁₈ H ₁₉ FN ₂ HCl	- 198-99	237 237

Table 10 (cont.)

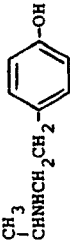
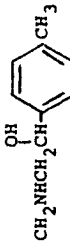
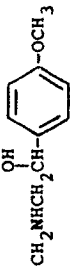
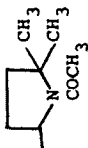
COCH ₃	H		H	C ₁₈ H ₁₉ N ₃ O ₃	228	306a
CH ₂ C ₆ H ₅	H	CH ₂ N(CH ₃) ₂	H	C ₁₈ H ₂₀ N ₂ HCl	- 208(e)	121 121
H	H	CH ₂ NHCH(CH ₃)CH ₂ C ₆ H ₅	H	C ₁₈ H ₂₀ N ₂ HCl	- 155(dec)	589 589
H	H		H	C ₁₈ H ₂₀ N ₂ O HCl	- 170(dec)	589 589
H	H	CH ₂ NHCH(CH ₃)CH ₂ C ₆ H ₅	H	C ₁₈ H ₂₀ N ₂ O	116	589
H	H		H	C ₁₈ H ₂₀ N ₂ O	165	589
H	H		H	C ₁₈ H ₂₀ N ₂ O ₂	149	589
COCH ₃	H		H	C ₁₈ H ₂₂ N ₂ O ₂	189-90(ea)	620

Table 10 (cont.)

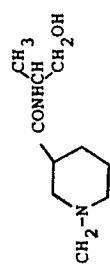
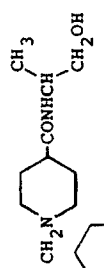
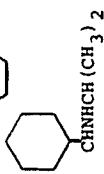
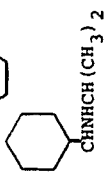
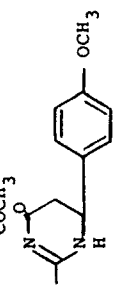
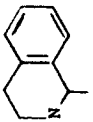
H	H		H	$C_{18}H_{25}N_3O_2$	amorphous	16
H	H		H	$C_{18}H_{25}N_3O_2$	166-67(ac)	16
H	H		H	$C_{18}H_{26}N_2$ HCl	- 130-31	394, 396 396
H	β -naphthyl		H	$C_{19}H_{16}N_2$	165-66	79
COCH ₃	H		H	$C_{19}H_{16}N_3O_3$	179(ea)	589
H	H		H	$C_{19}H_{17}N_3O_2$	300	306a
H	H		H	$C_{19}H_{18}N_2O$	219(ac)	549

Table 10 (cont.)

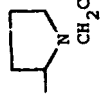
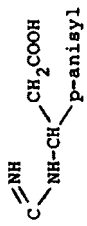
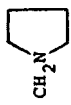
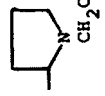
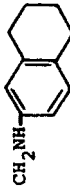
H	H		5-Br	$C_{19}H_{19}BrN_2$ HCl	- 181-186(e)	620 620
H	H	*	5-Cl	$C_{19}H_{19}ClN_2$ HCl	- 174-76(e)	620 620
H	C_6H_5		5-Cl	$C_{19}H_{19}ClN_2O$	165	231
H	C_6H_5	*	7-Cl	$C_{19}H_{19}ClN_2O$	155	231
H	H		H	$C_{19}H_{19}N_3O_3$	197	306a
H	C_6H_5		H	$C_{19}H_{20}N_2$ HCl	- 178(e)	287 287
H	H		H	$C_{19}H_{20}N_2$	92-93	620
H	H		H	$C_{19}H_{20}N_2$	107	589

Table 10 (cont.)

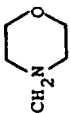
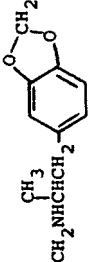
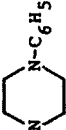
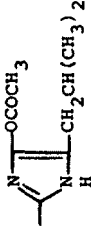
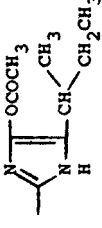
H	C ₆ H ₅		H	C ₁₉ H ₂₀ N ₂ O	144-45 (m)	287
H	H		H	C ₁₉ H ₂₀ N ₂ O ₂ HCl	- 182	589 589
H	C ₆ H ₅	CH ₂ N(C ₂ H ₅) ₂	5-Cl	C ₁₉ H ₂₁ ClN ₂	138	231
H	C ₆ H ₅	CH ₂ N(C ₂ H ₅) ₂	7-Cl	C ₁₉ H ₂₁ ClN ₂	175	231
H	H		H	C ₁₉ H ₂₁ N ₃	183-85 185-87	143 504a
COCH ₃	H		H	C ₁₉ H ₂₁ N ₃ O ₃	233	306a
COCH ₃	H		H	C ₁₉ H ₂₁ N ₃ O ₃	185	306a
H	C ₆ H ₅	CH ₂ N(C ₂ H ₅) ₂	H	C ₁₉ H ₂₂ N ₂ picrate oxalate HCl	- 141 204-05 170 (m)	287 287 287 287

Table 10 (cont.)

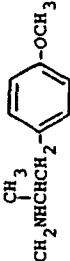
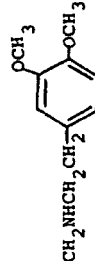
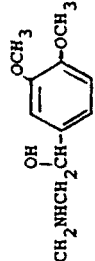
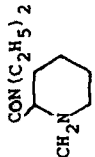
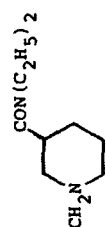
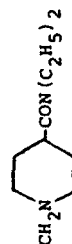
$\text{CH}_2\text{C}_6\text{H}_5$	CH_3	$\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ HCl	- 172 (e)	121 121
H	H		H	$\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ HCl	- 164 (dec)	589 589
H	H		H	$\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ HCl	- 176 (dec)	589 589
H	H		H	$\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$	97	589
H	H		H	$\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}$ HCl	- 169-71	519 519
H	H		H	$\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}$ HCl	- 188-89	351, 519 351, 519
H	H		H	$\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}$ HCl	- 170-72	351, 519 351, 519

Table 10 (cont.)

H	H		H	$C_{19}H_{28}N_2$ HCl	- 130-31 (m)	394, 396 394, 396
H	H		H	$C_{20}H_{13}N_3O_2$	> 300	31
COCH ₃	H		H	$C_{20}H_{17}N_3O_2$	305	306a
CH ₃	H		5,7-di- CH ₃	$C_{20}H_{18}N_2O_2$	190-91	105
H	H		H	$C_{20}H_{19}N_3O_3$	188 (e)	534
H	H		H	$C_{20}H_{20}N_2O$	204 (e)	549
H	C ₆ H ₅		5-Cl	$C_{20}H_{21}ClN_2$	145	231

Table 10 (cont.)

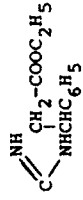
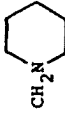
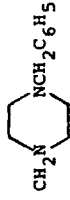
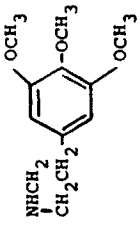
H	C ₆ H ₅		7-Cl	C ₂₀ H ₂₁ ClN ₂	138	231
H	H		H	C ₂₀ H ₂₁ N ₃ O ₂	-	306a
CH ₂ C ₆ H ₅	H		H	C ₂₀ H ₂₂ N ₂ cyclohexyl- sulfamate	- 127-29	620 620
H	H		7-CH ₃	C ₂₀ H ₂₂ N ₂	95-98 (e)	620
H	C ₆ H ₅		H	C ₂₀ H ₂₂ N ₂ acetate HCl	117-118 157-58 (b) 180 (m)	100,287 100 287
H	H		H	C ₂₀ H ₂₃ N ₃	160-63	143
H	H		H	C ₂₀ H ₂₄ N ₃ O ₃ HCl	- 159	589 589

Table 10 (cont.)

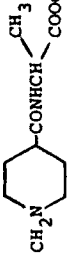
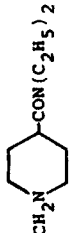
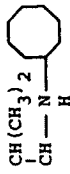
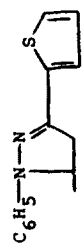
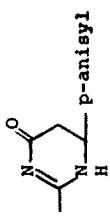
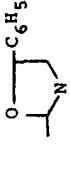
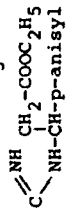
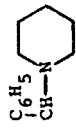
H	H		H	$C_{20}H_{27}N_3O_2$ HCl	- 176-77	519 519
H	CH ₃		H	$C_{20}H_{29}N_3O$	246-47 (m)	351, 519
H	H		H	$C_{20}H_{30}N_2$ HCl	- 121-23	394 394, 396
H	H		H	$C_{21}H_{17}N_3S$	174-75 (e)	567a
COCH ₃	H		H	$C_{21}H_{19}N_3O_4$	288	306a
COCH ₃	H		H	$C_{21}H_{20}N_2O_3$	157 (ea)	589
H	H		H	$C_{21}H_{23}N_3O_3$	-	306a
H	CH ₃		H	$C_{21}H_{24}N_2$	136-37 (t)	18

Table 10 (cont.)

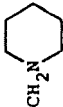
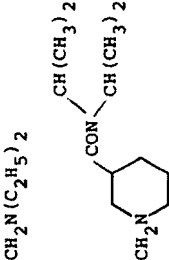
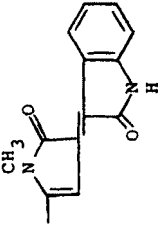
H	C ₆ H ₅		H	C ₂₁ H ₂₄ N ₂ HCl	- 199-01(ip)	287 287
CH ₂ C ₆ H ₅	H		H	C ₂₁ H ₂₄ N ₂ HCl	- 186-87(e)	121 121
CH ₂ C ₆ H ₅	CH ₃		H	C ₂₁ H ₂₆ N ₂ HCl	- 158(e)	121 121
H	H		H	C ₂₁ H ₃₁ N ₃ O HCl	- 177-79(m)	351, 519 351, 519
H	H		H	C ₂₁ H ₃₁ N ₃ O HCl	- 217-18(m)	351, 519 351, 519
CH ₃	H		H	C ₂₂ H ₁₇ N ₂ O ₂	285-90	31

Table 10 (cont.)

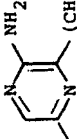
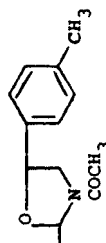
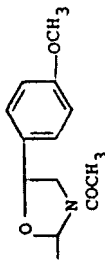
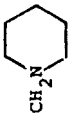
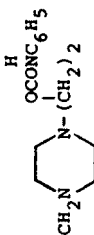
H	H		H	$C_{22}H_{21}N_5O$ picrate nitrate	- 228-29 167-234	303 303 303
COCH ₃	H		H	$C_{22}H_{22}N_2O_3$	157 (ea)	589
COCH ₃	H		H	$C_{22}H_{22}N_2O_4$	105 (ea)	589
H	H		H	$C_{22}H_{25}N_3O$ HCl	- 192-93	519 519
CH ₂ C ₆ H ₅	CH ₃		H	$C_{22}H_{26}N_2$ HCl	- 188 (e)	121
H	H		H	$C_{22}H_{26}N_4O_2$	50-60	143
H	C ₆ H ₅		H	$C_{23}H_{16}N_2$ HCl	- 284-86	95

Table 10 (cont.)

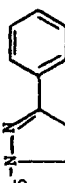
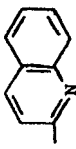
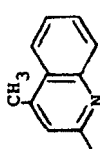
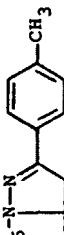
H	H		H	$C_{23}H_{18}BrN_3$	180-81 (e)	567a
H	H		H	$C_{23}H_{18}ClN_3$	160-61 (e)	567a
H	H		H	$C_{23}H_{19}N_3$	176-77 (e)	567a
CH ₃	C_6H_5		H	$C_{24}H_{18}N_2$	145 (p)	95
H	C_6H_5		H	$C_{24}H_{18}N_2$	190 (e/w)	95
H	H		H	$C_{24}H_{21}N_3$	177-78 (e)	567a
H	H		H	$C_{24}H_{21}NO$	156 (e)	567a

Table 10 (cont.)

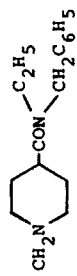
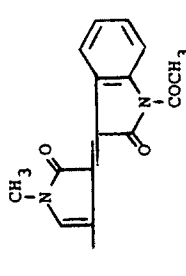
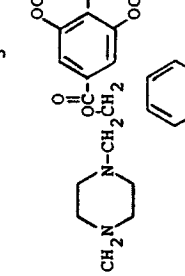
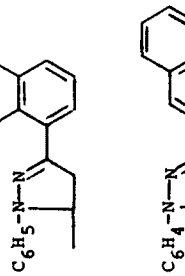
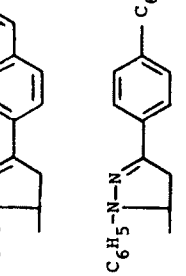
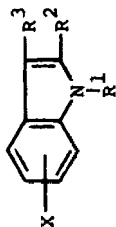
H	H		H	$C_{24}H_{29}N_3O$ HCl	- 196	519 519
COCH ₃	H		H	$C_{25}H_{19}N_3O_4$	275-80 (b)	31
H	H		H	$C_{25}H_{31}N_3O_5$ hydrogen- fumarate	- 130	143 143
H	H		H	$C_{27}H_{21}N_3$	172-73 (e)	567a
H	H		H	$C_{27}H_{21}N_3$	206 (e)	567a
H	H		H	$C_{29}H_{23}N_3$	147 (e)	567a

Table 11. 3-Indolyl-C-C-N Derivatives*



R ¹	R ²	R ³	X	m.p., °C	Ref.
H	H	CH ₂ CH ₂ NH ₂	4,7-Cl ₂	124 (b)	442
H	H	"	6,7-Cl ₂	101 (b)	442
H	H	"	5-Br	-	424
			C ₁₀ H ₁₁ BrN ₂ HCl	290 (dec)	424
H	H	"	4-Cl	178-80 (ip)	442a
			C ₁₀ H ₁₁ ClN ₂		
H	H	"	5-Cl	-	252, 618
			C ₁₀ H ₁₁ ClN ₂ HCl	286-87 297	252, 618 319, 424
H	H	"	6-Cl	113	319
			C ₁₀ H ₁₁ ClN ₂ HCl	224-25 (e) 243-45 (e)	46, 516 516
H	H	"	7-Cl	96	319, 442
			C ₁₀ H ₁₁ ClN ₂		
H	H	"	5-F	-	424
			C ₁₀ H ₁₁ FN ₂ HCl	280-81 (w)	424

*For further compounds: J. L. Archibald, T. Baum, and S. J. Childress, *J. Med. Chem.*, **13**, 138 (1970); M. S. Allen, A. J. Gaskell and J. A. Joule, *J. Chem. Soc., (C)*, **1971**, 736.

Table 11 (cont.)

H	H	$\text{CH}_2\text{CH}_2\text{NH}_2$	6-F	$\text{C}_{10}\text{H}_{11}\text{FN}_2$ picrate	80 264 (m)	323a 323a
H	H	"	5-I	$\text{C}_{10}\text{H}_{11}\text{IN}_2$ HCl picrate	124-25 221-23 238-40 (dec)	420 420 420
H	H	$\text{CH}_2-\text{C} \begin{smallmatrix} \text{NH} \\ \text{NH}_2 \end{smallmatrix}$	H	$\text{C}_{10}\text{H}_{11}\text{N}_3$ maleate	- 177-78	475 475
H	H	$\text{CH}_2\text{CH}_2\text{NH}_2$	H	$\text{C}_{10}\text{H}_{12}\text{N}_2$ picrate HCl	b.p. 148-50 (0.07 mm.) 115 242-43 (m) 247 (e) 248-252 246	573 5,74,77 244 252 12,342 141,372
H	H	$\text{CH}(\text{OH})\text{CH}_2\text{NH}_2$	H	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$ picrate	- 188 (dec)	343 343
H	H	$\text{CH}_2\text{CH}_2\text{NHOH}$	H	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$	113-115 (b)	90
H	CH_3	$\text{CH}_2\text{CH}_2\text{NH}_2$	5-F	$\text{C}_{11}\text{H}_{13}\text{FN}_2$ maleate picrate	- 178-79 (e) 234-35 (m)	86 86 290
H	CH_3	"	6-F	$\text{C}_{11}\text{H}_{13}\text{FN}_2$	104-106 (ea)	290

H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	5,7-Cl ₂	C ₁₁ H ₁₂ Cl ₂ N ₂ HCl	162-65	215
H	CH ₃	CH ₂ CH ₂ NH ₂	5-Br	C ₁₁ H ₁₃ BrN maleate (e)	292-95	215
H	H	CH ₂ CH ₂ NH ₂	5-Br, 7-CH ₃	C ₁₁ H ₁₃ BrN ₂ picrate	186	86
H	H	CH ₂ CH ₂ NH ₂	5-CH ₃ , 7-Br	C ₁₁ H ₁₃ BrN ₂ picrate	220	19
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CH}_2\text{NHCH}_3 \end{array}$	5-Br	C ₁₁ H ₁₃ BrN ₂	238(dec)	19
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	4-Br	C ₁₁ H ₁₃ BrN ₂	93-94	281
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	5-Br	C ₁₁ H ₁₃ BrN ₂	95-103	449a
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	5-Br	C ₁₁ H ₁₃ BrN ₂ HCl	104-05 (b)	518
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CHCH}_2\text{NH}_2 \end{array}$	5-Br	C ₁₁ H ₁₃ BrN ₂ picrate	231-33 (e)	518
H	H	CH ₂ CH ₂ NH ₂	5-Cl, 7-CH ₃	C ₁₁ H ₁₃ ClN ₂ picrate	—	190
H	H	CH ₂ CH ₂ NH ₂	5-Cl, 7-CH ₃	C ₁₁ H ₁₃ ClN ₂ picrate	206-11 (e)	190
H	H	CH ₂ CH ₂ NH ₂	5-Cl, 7-CH ₃	C ₁₁ H ₁₃ ClN ₂ picrate	—	19
H	H	CH ₂ CH ₂ NH ₂	5-Cl, 7-CH ₃	C ₁₁ H ₁₃ ClN ₂ picrate	226(dec)	19

H	H	$\text{CH}_2\text{CH}_2\text{NH}_2$	5-CH ₃ , 7-Cl	C ₁₁ H ₁₃ ClN ₂ picrate	— 243(dec)	19 19
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	4-Cl	C ₁₁ H ₁₃ ClN ₂ HCl	123-25(ea) 269-70(m) 266-67	451 600 254a
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	5-Cl	C ₁₁ H ₁₃ ClN ₂ HCl	102(h) 234-36 240-41(m) 243-45	518 254a 600 518
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	6-Cl	C ₁₁ H ₁₃ ClN ₂ HCl	122-23(b) 218 220-22	215 215, 254a 600
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	7-Cl	C ₁₁ H ₁₃ ClN ₂ HCl	— 255-57	— 386, 600
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CHCH}_2\text{NH}_2 \end{array}$	5-Cl	hydrogen maleinate C ₁₁ H ₁₃ ClN ₂	170-72 99-100(cyh)	451 190
H	CH ₃	$\text{CH}_2\text{CH}_2\text{NH}_2$	5-Cl	C ₁₁ H ₁₃ ClN ₂	—	86
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_3$	5-Cl	maleate C ₁₁ H ₁₃ ClN ₂	186-87(e) 210	86 502b
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	5-Cl	C ₁₁ H ₁₃ ClN ₂ ^O	119-20(b)	90, 436

Table 11 (cont.)

H	H	CH_2CHNH_2 CH_3	5-F	$\text{C}_{11}\text{H}_{13}\text{FN}_2$ HCl	86-87(b) 224-25(e) 233-234(thf)	518 518 290
H	H	CH_2CHNH_2 CH_3	6-F	$\text{C}_{11}\text{H}_{13}\text{FN}_2$	104-06(ea)	290
H	H	CH_2CHNH_2 CH_3	5-F	$\text{C}_{11}\text{H}_{13}\text{FN}_2$ picrate	- 222-24(e)	190 190
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_3$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2$ HCl benzoate oxalate picrate	89-90 176-77 144-45 178-80 178 190 193-95	62,243,244 573,67a 243 502 265 63b,243 151
CH_3	H	$\text{CH}_2\text{CH}_2\text{NH}_2$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2$ picrate HCl	b.p. 108-110(0.1 mm.) 179 199-01	489 2,78,499 489
H	CH_3	"	H	$\text{C}_{11}\text{H}_{14}\text{N}_2$ oxalate picrate	81-83(et) 107 219(e) 218-219	265 179,393 265 377,393
H	H	"	4- CH_3	$\text{C}_{11}\text{H}_{14}\text{N}_2$	118-19(b)	159

Table 11 (cont.)

H	H	$\text{CH}_2\text{CH}_2\text{NH}_2$	5- CH_3	$\text{C}_{11}\text{H}_{14}\text{N}_2$ HCl picrate	96-98 (b) 289-91 243 (e)	12 252, 618 159
H	H	"	6- CH_3	$\text{C}_{11}\text{H}_{14}\text{N}_2$ picrate HCl	141 (b) 253 (dec) 289-91 (m)	159, 319 159 252
H	H	"	7- CH_3	$\text{C}_{11}\text{H}_{14}\text{N}_2$ picrate	120-22 231 236	159 2 159
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2$ picrate HCl acetate	97-100 (ea) 222-23 215-17 144	217, 25 400 252, 618 217
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CHCH}_2\text{NH}_2 \end{array}$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2$ picrate acetate	123-24 224 125	531 3, 124 352, 531
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$ hydrogen- oxalate	68 (b)	90, 436
CH_3	H	$\begin{array}{c} \text{OH} \\ \\ \text{CHCH}_2\text{NH}_2 \end{array}$	H	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$	180-81 -	47 572

Table 11 (cont.)

H	H		H	$C_{11}H_{14}N_2O$ oxalate	b.p. 155-65 (0.035 mm.) 170-71	296
H	H		H	$C_{11}H_{15}N_3$ oxalate	- 181	477 477
H	H		H	$C_{12}H_{10}N_2O$ methiodide	205 (b) 228 (m)	277 277
H	H		H	$C_{12}H_{10}N_3O_2$	214 (e)	14
H	H		H	$C_{12}H_{11}N_3$	129-31	115
H	H	$COCH_2NHCOCH_3$	H	$C_{12}H_{12}N_2O_2$	225 (m)	277
H	H		H	$C_{12}H_{14}N_2$ HCl	102-04 164 (e)	390 278
H	H	$COCH_2N(CH_3)_2$	H	$C_{12}H_{14}N_2O$ picrate methiodide	205-208 209-11 182-84 (e) 222-24	571 21 21 21

Table 11 (cont.)

H	H	$\text{CH}_2-\text{C} \begin{smallmatrix} \text{NH} \\ \text{=C} \end{smallmatrix} \text{OC}_2\text{H}_5$	H	$\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$ HCl	-	475
H	H	$\text{CH}_2\text{CH}_2\text{NHCOCH}_3$	H	$\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$	128(dec)	475
H	H	$\text{CH}_2\text{CH}_2\text{NHCOOCH}_3$	H	$\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$	77(et)	498a
		$\begin{smallmatrix} \text{OH} \\ \\ \text{CHCH}_2\text{NH}_2 \end{smallmatrix}$				
COCH ₃	H		H	$\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$ picrate	53/163 174-76	343 343
H	CH ₃	$\text{CH}_2\text{CH}_2\text{NHCH}_3$	5-Br	$\text{C}_{12}\text{H}_{15}\text{BrN}_2$ maleate	- 153-54	86 86
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_3$	5-CH ₃ , 7-Br	$\text{C}_{12}\text{H}_{15}\text{BrN}_2$ picrate	- 221	19 19
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	5-Br	$\text{C}_{12}\text{H}_{15}\text{BrN}_2$	97-98 185	281 502b
H	H	$(\text{CH}_3)_2\text{CCH}_2\text{NH}_2$	5-Br	$\text{C}_{12}\text{H}_{15}\text{BrN}_2$ picrate	- 222-26(e)	190 190
H	CH ₃	$\text{CH}_2\text{CH}_2\text{NHCH}_3$	5-Cl	$\text{C}_{12}\text{H}_{15}\text{ClN}_2$ maleate	- 157-58(e)	86 86

Table 11 (cont.)

H	H	CH ₂ CH ₂ NHCH ₃	5-Cl, 7-Cl	C ₁₂ H ₁₅ ClN ₂ picrate	- 216	19 19
H	H	"	5-Cl, 7-CH ₃	C ₁₂ H ₁₅ ClN ₂ picrate	- 170	19 19
H	H	CH ₂ CH ₂ N(CH ₃) ₂	4-Cl	C ₁₂ H ₁₅ ClN ₂ HCl	137-38 (cyh) 295-96 (m)	350 600
H	H	"	5-Cl	C ₁₂ H ₁₅ ClN ₂ HCl	195 197-98 (e)	502b 46
H	H	"	6-Cl	C ₁₂ H ₁₅ ClN ₂ HCl	- 196-97 (e)	46
H	H	CH ₂ CH ₂ NHC ₂ H ₅	5-Cl	C ₁₂ H ₁₅ ClN ₂	216	502b
H	H	(CH ₃) ₂ C-CH ₂ NH ₂	5-Cl	C ₁₂ H ₁₅ ClN ₂	107 (cyh)	190
H	H	C ₂ H ₅ CH ₂ CHNH ₂	4-Cl	C ₁₂ H ₁₅ ClN ₂ HCl	- 295-96	254a 254a
H	H	"	5-Cl	C ₁₂ H ₁₅ ClN ₂ HCl	- 238-29 241-42 (m)	254a 600

Table 11 (cont.)

H	H	C_2H_5 CH_2CHNH_2	6-Cl	$\text{C}_{12}\text{H}_{15}\text{ClN}_2$ HCl	- 235-236	254a, 600
H	H	"	7-Cl	$\text{C}_{12}\text{H}_{15}\text{ClN}_2$ HCl	- 226-28 230-32	254a 600
H	H	CH_3 $\text{CH}_2\text{C-NHOH}$ CH_3	5-Cl	$\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{O}$	139-40 (b)	90
H	CH_3	$\text{CH}_2\text{CH}_2\text{NHCH}_3$	5-F	$\text{C}_{12}\text{H}_{15}\text{FN}_2$ maleate	- 146-47 (e)	86 86
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	4-F	$\text{C}_{12}\text{H}_{15}\text{FN}_2$	100-01 (m)	49
H	H	"	5-F	$\text{C}_{12}\text{H}_{15}\text{FN}_2$	145	502b
H	H	"	6-F	$\text{C}_{12}\text{H}_{15}\text{FN}_2$	101-02 (et)	48
H	H	$(\text{CH}_3)_2\text{C-CH}_2\text{NH}_2$	5-F	$\text{C}_{12}\text{H}_{15}\text{FN}_2$	109 (cyh)	190
H	H	C_2H_5 CH_2CHNH_2	6-F	$\text{C}_{12}\text{H}_{15}\text{FN}_2$ HCl	- 211-13 (e)	227, 576
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	5-I	$\text{C}_{12}\text{H}_{15}\text{IN}_2$	90, 92	502b

Table 11 (cont.)

C_2H_5	H	$CH_2CH_2NH_2$	H	$C_{12}H_{16}N_2$ picrate	- 180-81 (b)	124
H	CH_3	"	5- CH_3	$C_{12}H_{16}N_2$ maleate picrate	100-01 184-85 (e) 224-25	179a 86 179a
H	CH_3	"	7- CH_3	$C_{12}H_{16}N_2$ picrate	160-62 220-23	179a 179a
H	H	$CH_2CH_2NHC_2H_5$	H	$C_{12}H_{16}N_2$ picrate HCl	87-88 (et) 186-87 (m) 188-90 (b)	124 124 67a
H	CH_3	$CH_2CH_2NHCH_3$	H	$C_{12}H_{16}N_2$ picrate	82-83 (et) 193-94 (b)	244 244
H	H	$CH_2CH(NHCH_3)$	H	$C_{12}H_{16}N_2$	90-91 (b)	435
CH_3	H	CH_2CHNH_2 $\begin{array}{c} CH_3 \\ \\ CH_2CHNH_2 \end{array}$	H	$C_{12}H_{16}N_2$ picrate HCl	198-200 223-27 (et) 226-28	217 217 518
H	CH_3	"	H	$C_{12}H_{16}N_2$ picrate	- 205-07	179

Table 11 (cont.)

H	H	CH_3 CH_2CHNH_2	4-CH ₃	C ₁₂ H ₁₆ N ₂ (+)-form (-)-form	140-42(b) 137-38(b) 148-150 148-150	215 451 451 451
H	H	"	5-CH ₃	C ₁₂ H ₁₆ N ₂ HCl	- 256-57(m)	252,618
H	H	"	6-CH ₃	C ₁₂ H ₁₆ N ₂	92-93(b)	215
H	H	"	7-CH ₃	C ₁₂ H ₁₆ N ₂ hydrogen- maleate HCl	106-107 108-09 159 215-18	386 215 451 215
H	H	CH ₂ CH ₂ NHCH ₃	7-CH ₃	C ₁₂ H ₁₆ N ₂ picrate	17 194-95(m)	124 124
H	C ₂ H ₅	CH ₂ CH ₂ NH ₂	H	C ₁₂ H ₁₆ N ₂ picrate	- 216-17	326
H	H	CH ₂ CH ₂ NH ₂	6-C ₂ H ₅	C ₁₂ H ₁₆ N ₂ HCl	- 249-51(e)	215
H	H	C_2H_5 CH_2CHNH_2	H	C ₁₂ H ₁₆ N ₂ acetate picrate HCl	99-101(e) 161 165-66 214-15 218-19	217,252 492 217 403 252,618

Table 11 (cont.)

H	H	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{CHCH}_2\text{NH}_2 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2 \\ \text{picrate} \\ \text{HCl} \end{array}$	- 200-01 (e) 202 (e)	284 284
H	H	$\begin{array}{c} \text{CH}_3\text{CH}_3 \\ \\ \text{CH-CH-NH}_2 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2 \\ \text{picrate} \end{array}$	103-06 (b) 100-02 (1) 210-11 (e)	215 532 532
H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2-\text{C}-\text{NH}_2 \\ \\ \text{CH}_3 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2 \\ \text{acetate} \end{array}$	130-31 204	492
H	H	$\begin{array}{c} (\text{CH}_3)_2\text{C-CH}_2\text{NH}_2 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2 \\ \text{picrate} \end{array}$	105-06 228	323, 352 323
H	H	$\begin{array}{c} \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2 \\ \text{picrate} \end{array}$	17 49 71-73 166 170-71 194-95 165-67	124 62, 244, 361 150 361 244, 62 124 67a
H	H	$\begin{array}{c} \text{HOCHCH}_2\text{N}(\text{CH}_3)_2 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2\text{O} \\ \text{picrate} \\ \text{HCl} \end{array}$	75/118-20	571, 579
CH ₃	H	$\begin{array}{c} \text{HOCHCH}_2\text{NHCH}_3 \\ \\ \text{CH}_3 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2\text{O} \\ \text{picrate} \end{array}$	138-140 (ea)	572
H	H	$\begin{array}{c} \text{HOCHCHNHCH}_3 \\ \\ \text{CH}_3 \end{array}$	H	$\begin{array}{c} \text{C}_{12}\text{H}_{16}\text{N}_2\text{O} \\ \text{picrate} \end{array}$	120-30 (b)	335a

Table 11 (cont.)

H	H	HOCHCHNHCH ₃ (thr) 	H	C ₁₂ H ₁₆ N ₂ O	179-81 (ac)	335a
H	H		H	C ₁₂ H ₁₆ N ₂ O	124-26 (b)	90, 436
H	H	CH ₂ CH-NHOH 	H	C ₁₂ H ₁₆ N ₂ O	76-8 (bu)	90
H	H	CH ₂ CH-NHOH 	6-CH ₃	C ₁₂ H ₁₆ N ₂ O	167-69	436
H	H	β-pyridyl 	H	C ₁₃ H ₁₀ N ₂ HCl	166-73 (e) 270-75	258 258
H	H		H	C ₁₃ H ₁₂ N ₂ O ₂	75-76	390
H	H		H	C ₁₃ H ₁₂ N ₂ O ₃	233	466
CH ₂ -C≡CH	H	CH ₂ CH ₂ NH ₂	H	C ₁₃ H ₁₄ N ₂ HCl	- 191-93 (e/w)	263

Table 11 (cont.)

CH ₃	H		H	C ₁₃ H ₁₆ N ₂	170(e)	278
H	H		H	C ₁₃ H ₁₆ N ₂ HCl	111-13(ea) 142(e)	390 278
H	CH ₃	COCH ₂ N(CH ₃) ₂	H	C ₁₃ H ₁₆ N ₂ O	201(e)	448
H	H	CH ₂ CH ₂ N(CH ₃) ₂	5-CH ₃ , 7-Br	C ₁₃ H ₁₇ BrN ₂	117	19
H	H	"	5-Br, 7-CH ₃	C ₁₃ H ₁₇ BrN ₂	154	19
H	CH ₃	"	5-Br	C ₁₃ H ₁₇ BrN ₂ maleate	- 169-70(e)	86
H	H	"	5-CH ₃ , 7-Cl	C ₁₃ H ₁₇ ClN ₂ picrate	- 181	19
H	H	"	5-Cl, 7-CH ₃	C ₁₃ H ₁₇ ClN ₂	155	19
H	CH ₃	"	5-Cl	C ₁₃ H ₁₇ ClN ₂ maleate	- 174-75(e)	86
H	CH ₃	"	5-F	C ₁₃ H ₁₇ FN ₂ maleate	- 165-66(e)	86

Table 11 (cont.)

H	H	CH ₂ CH ₂ NHCH ₂ CH ₂ CH ₃	H	C ₁₃ H ₁₈ N ₂ HCl	-	67a
H	H	CH ₂ CH ₂ N $\begin{smallmatrix} \text{CH}_3 \\ \diagup \\ \text{C}_2\text{H}_5 \end{smallmatrix}$	H	C ₁₃ H ₁₈ N ₂ oxalate	187 (b)	502
H	H	CH ₂ CH ₂ NHCH(CH ₃) ₂	H	C ₁₃ H ₁₈ N ₂ HCl	120	67a
CH(CH ₃) ₂	H	CH ₂ CH ₂ NH ₂	H	C ₁₃ H ₁₈ N ₂	245-46 (b)	159
H	CH ₃	CH ₂ CH ₂ NHCH ₃	5-CH ₃	C ₁₃ H ₁₈ N ₂ maleate	99 (cyh)	86
CH ₃	C ₂ H ₅	CH ₂ CH ₂ NH ₂	H	C ₁₃ H ₁₈ N ₂ methiodide	152-53 (e)	326
H	H	CH ₂ CH ₂ NHC $\begin{smallmatrix} \text{CH}_3 \\ \end{smallmatrix}$ C ₂ H ₅	H	C ₁₃ H ₁₈ N ₂ HCl	b.p. 150 (0.05 mm.) 220-21	326
CH ₃	H	CH ₃ CH ₂ NH ₂	H	C ₁₃ H ₁₈ N ₂ HCl	-	435
H	CH ₃	"	H	C ₁₃ H ₁₈ N ₂ maleate	187-89 (e)	227
H	H	"	7-CH ₃	C ₁₃ H ₁₈ N ₂ HCl	225-26 (m)	227
					-	227
					142 (e)	227
					-	227, 581
					206-07 (m)	

Table 11 (cont.)

H	CH ₃	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₁₃ H ₁₈ N ₂	93-95(e) 97-98(et) 176 127-28(e) 238-39(m)	178 244 178 86 244
H	H	CH ₂ CHN(CH ₃) ₂	H	C ₁₃ H ₁₈ N ₂ picrate maleate methiodide	108(p) 171-72(e)	284 284
H	H	CH ₃ CHCH ₂ N(CH ₃) ₂	H	C ₁₃ H ₁₈ N ₂ dipicrate	107-09 104-05 119	161 284 284
H	H	CH ₂ CH ₂ N(CH ₃) ₂	5-CH ₃	C ₁₃ H ₁₈ N ₂ hydrogen- maleate	99-100 94-95	46 46
H	H	CH ₂ CHNH ₂ CH ₂ CH ₂ CH ₃	H	C ₁₃ H ₁₈ N ₂	158(ea)	217
H	H	CH ₂ CHNH ₂ CH(CH ₃) ₂	H	C ₁₃ H ₁₈ N ₂ picrate	113(b) 191-92(e)	400 400
H	H	CH ₂ CH ₂ CH ₃ CH-CH ₂ NH ₂	H	C ₁₃ H ₁₈ N ₂ acetate picrate	- 136(ea) 248(e)	323, 352 323
H	H	CH(CH ₃) ₂ CH-CH ₂ NH ₂	H	C ₁₃ H ₁₈ N ₂ acetate	116 150 150-60	323 352 323

Table 11 (cont.)

C_2H_5	CH_3	$CH_2CH_2NH_2$	H	$C_{13}H_{18}N_2$ picrate	- b.p. 186-87 (8 mm.) 131-32	179 179
H	H	$HOCHCH_2NHCH(CH_3)_2$	H	$C_{13}H_{18}N_2O$	134-36 (p)	254b
CH_3	H	$HOCHCH_2N(CH_3)_2$	H	$C_{13}H_{18}N_2O$	94-95 (ea)	572
H	H	$CH_2CH_2NH(CH_2)_3OH$	H	$C_{13}H_{18}N_2O$ HCl	b.p. 192-95 (0.05 mm.) 112-15	314 314
H	H	$CH_2CH_2N(CH_3)CH_2CH_2OH$	H	$C_{13}H_{18}N_2O$ picrate	- 140 (e)	421
OCH_3	H	$CH_2CH_2N(CH_3)_2$	B	$C_{13}H_{18}N_2O$ picrate styphnate HCl	- 160-62 (m) 169-70 (m) 163-64 (b)	361 361 361
H	H	CH_2CH_2NHOH CH_3	6- CH_3	$C_{13}H_{18}N_2O$	167-9 (e)	90
CH_3	H	$HOCHCH_2N(CH_3)CH_3$	H	$C_{13}H_{18}N_2O_2$	148-52	574
H	H	$CH_2CH_2N(CH_3)C(=NH)NH_2$ C_2H_5	H	$C_{13}H_{18}N_4$ HCl	- 216-19	397

Table 11 (cont.)

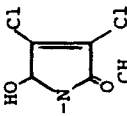
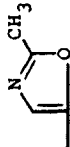
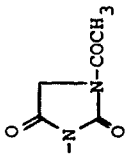
H	H	$\text{CH}_2\text{CH}_2\text{NH}_2$	5-Si(CH ₃) ₃	C ₁₃ H ₂₀ N ₂ Si	103 (p)	40a
H	H		H	C ₁₄ H ₁₀ N ₂ O HCl	- 178-180	431
H	H		H	C ₁₄ H ₁₂ Cl ₂ N ₂ O ₂	167 (et)	606
H	H		H	C ₁₄ H ₁₂ N ₂ picrate methiodide	98-101 (cyn) 104 (p) 121 180-83	188 89 89 188
H	H		H	C ₁₄ H ₁₂ N ₂ O	160-61 (b)	28, 29
COCH ₃	H		H	C ₁₄ H ₁₂ N ₂ O ₂	160 (m)	277
H	H		H	C ₁₄ H ₁₃ N ₃ O ₃	197-98 (ea)	91

Table 11 (cont.)

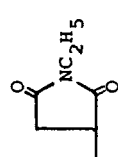
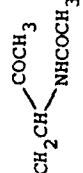
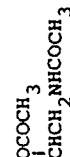
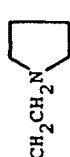
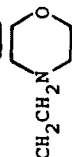
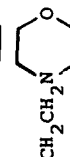
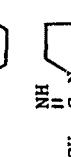
H	H		H	C ₁₄ H ₁₄ N ₂ O ₂	94-96 (et)	390
COCH ₃	H	CH-CH ₂ NHCOCH ₃	H	C ₁₄ H ₁₄ N ₂ O ₃	179 (m)	277
H	H		H	C ₁₄ H ₁₆ N ₂ O ₂ 2,4-dinitro- phenylhydrazone	137 (m/w)	217
H	H		H	C ₁₄ H ₁₆ N ₂ O ₃	265-66 (e)	176
H	H	CHCH ₂ NHCOCH ₃	H		202-04 (ac)	343
H	H		5-Br	C ₁₄ H ₁₇ BrN ₂	109-10	281
H	H		4-F	C ₁₄ H ₁₇ FN ₂ O	158-59 (m)	49
H	H		6-F	C ₁₄ H ₁₇ FN ₂ O picrate	137 (m) 230 (m)	48 48
H	H		H	C ₁₄ H ₁₇ N ₃ HCl	- 270-71 (m)	475

Table 11 (cont.)

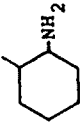
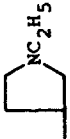
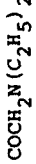
H		H	$C_{14}H_{18}N_2$ picrate	176-77(l) 134-35(e)	404 404
H		H	$C_{14}H_{18}N_2$ HCl	67-68(p) 145(e)	390 278
C_2H_5		H	$C_{14}H_{18}N_2$ HCl	- 157	- 278
CH_3		H	$C_{14}H_{18}N_2$ HCl	- 152	- 278
H		H	$C_{14}H_{18}N_2$ acetate picrate HCl	156-57(b) 189-90 220 78-82(ip)	191,17 188 431 28
CH_3		H	$C_{14}H_{18}N_2$ HCl	- 130(e)	- 279
H		H	$C_{14}H_{18}N_2O$	139-41(ip)	579

Table 11 (cont.)

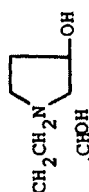
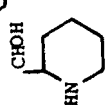
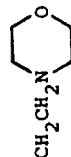
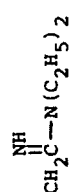
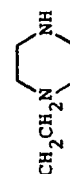
H	H		H	$C_{14}H_{18}N_2O$	144-46	598
H	H		H	$C_{14}H_{18}N_2O$	200-201(ac) 213-14(ip)	28 431
H	H		H	$C_{14}H_{18}N_2O$ picrate	145-47 193-95	372,573 578 372
H	H	$CH_2CH_2N(C_2H_5)_2$	5-Br	$C_{14}H_{19}BrN_2$	84-85	281
H	H	"	5-Cl	$C_{14}H_{19}ClN_2$	240	502b
H	H	"	4-F	$C_{14}H_{19}FN_2$	102(m)	49
H	H	"	6-F	$C_{14}H_{19}FN_2$ picrate HCl	69-70(p) 222-23(ea) 139-40(m)	290 290 48
H	H		H	$C_{14}H_{19}N_3$ HCl	- ca. 260-61(m)	475
H	H		H	$C_{14}H_{19}N_3$	148-52 150-152	143 504a

Table 11 (cont.)

H	H	$\text{CH}_2\text{CH}_2\text{NHP}-\text{(N}\triangle\text{)}_2$	H	$\text{C}_{14}\text{H}_{19}\text{N}_4\text{OP}$	138-139	515
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ HCl	85-88 168-70 170-71	372 372 67a
H	H	$\text{CH}_2\text{CH}_2\text{NH}(\text{CH}_2)_3\text{CH}_3$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ HCl	- 203-05 (b)	67a
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}\begin{matrix} \text{CH}_2\text{CH}_3 \\ \text{CH}_3 \end{matrix}$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ HCl	- 175-77 (b)	67a
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}(\text{CH}_3)_2$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ maleate	- 150-51 (ea)	67a
H	CH_3	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	5- CH_3	$\text{C}_{14}\text{H}_{20}\text{N}_2$ maleate	- 165-66 (e)	86
H	H	$\text{CH}_2\text{CH}-\text{N}(\text{CH}_3)_2$ C_2H_5	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ picrate HCl	- 154-55 (e) 168-72 (e)	284 284
H	H	$\text{C}_2\text{H}_5\text{CHCH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ picrate HCl	73 (et) 143 (e) 175 (e)	284 284 284

Table 11 (cont.)

H	H	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{CH}_2\text{CHNHC}_2\text{H}_5 \\ \\ \text{C}(\text{CH}_3)_3 \end{array}$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ acetate	-	227
H	H	$\begin{array}{c} \text{C}(\text{CH}_3)_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ picrate	142(m) 177(b) 218-19(e)	400 400 400
H	H	$\begin{array}{c} \text{C}(\text{CH}_3)_3 \\ \\ \text{HC-CH}_2\text{NH}_2 \end{array}$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ picrate	171-72(b) 233(e)	531 531
H	H	$(\text{C}_2\text{H}_5)_2\text{C-CH}_2\text{NH}_2$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$	124	352
CH_3	CH_3	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{CH}_2\text{CH-NH}_2 \end{array}$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2$ HCl	-	227
H	CH_3	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{CH}_2\text{CH-NH}_2 \end{array}$	7- CH_3	$\text{C}_{14}\text{H}_{20}\text{N}_2$ acetate	-	581, 227
H	H	$\text{HOCH-CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$	-	579
C_2H_5	H	$\text{HOCH-CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$ pyruvate Cl_3CCOOH HCl	82-83(ea) 113-16 92-96 109-11	572 572 572 572
CH_3	CH_3	"	H	$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$	110-12(ea)	20

Table 11 (cont.)

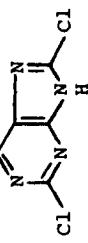
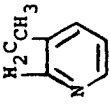
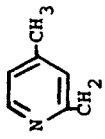
CH ₃	H	HOCH-CH ₂ NHCH(CH ₃) ₂	H	C ₁₄ H ₂₀ N ₂ O	115 (ea)	572
H	H	CH ₂ CH ₂ N(CH ₃)(CH ₂) ₃ OH	H	C ₁₄ H ₂₀ N ₂ O picrate	- 98-100 (e/w)	421
H	H	CH ₂ CH ₂ NCH ₂ C(CH ₃) ₂ OH	H	C ₁₄ H ₂₀ N ₂ O picrate	90-91 (et) 175-77 (e)	421 421
C ₂ H ₅	H	HOCHCH ₂ N(CH ₃)CH ₃	H	C ₁₄ H ₂₀ N ₂ O ₂	74-84 (monohydrate)	574
H	H	CH ₂ CH ₂ NH	H	C ₁₅ H ₁₂ Cl ₂ N ₆	145-46 (e)	331
						
						
H	H		H	C ₁₅ H ₁₄ N ₂ methiodide	135-37 (e/w) 244-47	439 439
H	H		H	C ₁₅ H ₁₄ N ₂ methiodide benzobromide	131-32 237-39 205-206	362, 593 362 362

Table 11 (cont.)

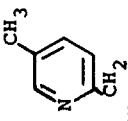
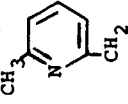
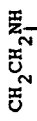
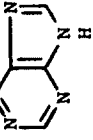
H		H	$C_{15}H_{14}N_2$ methiodide	138-40 (e/w) 232-35	439 439
H		H	$C_{15}H_{14}N_2$ methiodide	147-48 (e/w) 188-90	439 439
H		H	$C_{15}H_{14}N_2O$	136-37 (b)	414, 474
H		H	$C_{15}H_{14}N_2O$	216 (m)	605
H		H	$C_{15}H_{14}N_6$	285-286	168
H		H	$C_{15}H_{16}N_2O$	164 (ac)	605
$CH_2C\equiv CH$		H	$C_{15}H_{16}N_2O$	128 (m)	263

Table 11 (cont.)

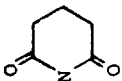
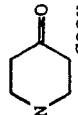
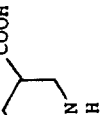
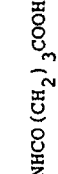
H	H		H	$C_{15}H_{16}N_2O$ picrate HCl	56-57(l) 161(b) 168(ac)	414 414 414
H	H		H	$C_{15}H_{16}N_2O_2$	173-75	362
H	H		H	$C_{15}H_{18}N_2$	152-53	125,412
H	H		H	$C_{15}H_{18}N_2O$	134-35(b)	413
H	H		H	$C_{15}H_{18}N_2O_2$	rac I: 310 rac II: 275	17 17
H	H		H	$C_{15}H_{18}N_2O_3$	135-37(ac)	175
H	CH ₃		5-Br	$C_{15}H_{19}BrN_2$ maleate	- 95-96(e)	86
H	H		5-CH ₃ , 7-Br	$C_{15}H_{19}BrN_2O$	119	19
H	H		5-Br, 7-CH ₃	$C_{15}H_{19}BrN_2O$	136	19

Table 11 (cont.)

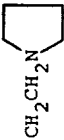
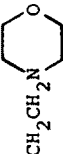
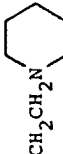
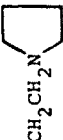
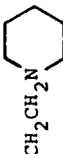
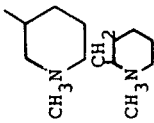
H	CH ₃		5-Cl	C ₁₅ H ₁₉ ClN ₂ maleate	- 105-06 (e)	86
H	H		5-CH ₃ , 7-Cl	C ₁₅ H ₁₉ ClN ₂ O	142-43	19
H	H	"	5-Cl, 7-CH ₃	C ₁₅ H ₁₉ ClN ₂ O	156	19
H	H		4-F	C ₁₅ H ₁₉ FN ₂	181	49
H	H	"	6-F	C ₁₅ H ₁₉ FN ₂ picrate	110 (m) 208-12 (m)	48 48
H	CH ₃		5-F	C ₁₅ H ₁₉ FN ₂ maleate	- 145-46 (e)	86
H	H		H	C ₁₅ H ₂₀ N ₂	149-50 (b) 161-62 (et) 204 228-29 (e)	16, 125 372 421 372 421
CH ₃	H		H	methiodide HCl	- 220 (e)	279
H	H		H	C ₁₅ H ₂₀ N ₂ HCl	113-14 (b) 109-10 (cyh) 223-27 (ip)	17 28 28

Table 11 (cont.)

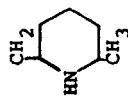
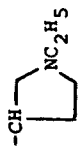
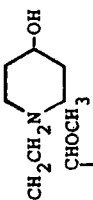
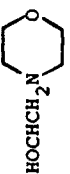
H	H		H	$C_{15}H_{20}N_2$	167-68 (b)	17
CH ₃	H		H	$C_{15}H_{20}N_2$ HCl ethochloride	- 148 235 (e)	278 278
H	H		H	$C_{15}H_{20}N_2O$	164-65 (b)	90
H	H		H	$C_{15}H_{20}N_2O$	138 (w)	122
H	H		H	$C_{15}H_{20}N_2O$	145-47 (ea)	505
H	H		H	$C_{15}H_{20}N_2O$	156-57 (ip)	431
H	CH ₃		H	$C_{15}H_{20}N_2O$ HCl	- 208-09 (ip)	598
CH ₃	H		H	$C_{15}H_{20}N_2O_2$	99-100 (ea)	572

Table 11 (cont.)

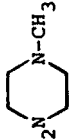
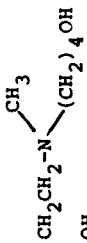
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	5-CH ₃ , 7-Br	$\text{C}_{15}\text{H}_{21}\text{BrN}_2$ picrate	- 165	19
H	H	*	5-CH ₃ , 7-Cl	$\text{C}_{15}\text{H}_{21}\text{ClN}_2$ HCl	- 197	19
H	H		H	$\text{C}_{15}\text{H}_{21}\text{N}_3$ di-HCl benzochloride	- 280-85 227-229	143, 504a 504a
CH ₃	C ₂ H ₅	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{15}\text{H}_{22}\text{N}_2$ picrate methiodide	- 174-75(e) 220-21(e)	326 326
CH ₃	H	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	$\text{C}_{15}\text{H}_{22}\text{N}_2$ HCl	- 203(e)	282
H	CH ₃	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	$\text{C}_{15}\text{H}_{22}\text{N}_2$ HCl	- 207-08(et)	328
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	5, 6, 7- (CH ₃) ₃	$\text{C}_{15}\text{H}_{22}\text{N}_2$ HCl	- 124-25(e)	46
H	H		H	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ picrate	- 111(e)	421
CH ₃	H	$\text{CH}-\text{CH}_2\text{NHC}(\text{CH}_3)_3$	H	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$	124-26(ea)	254b

Table 11 (cont.)

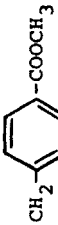
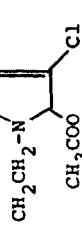
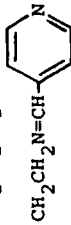
C_2H_5	H	$\begin{array}{c} OH \\ \\ CH-CH_2NHCH(CH_3)_2 \\ \\ OH \end{array}$	H	$C_{15}H_{22}N_2O$	125-26 (ea)	254b
CH_3	H	$\begin{array}{c} CH_3 \\ \\ CH-CH_2NH-C-CH_2OH \\ \\ CH_3 \end{array}$	H	$C_{15}H_{22}N_2O_2$ picrate	- 146 (e)	254b
H	H		5-Br	$C_{16}H_{13}BrN_2O_2$ methiodide	149-50 235	280a 280a
H	H		H	$C_{16}H_{14}Cl_2N_2O_3$	131 (e)	606
H	4-Br C_6H_4	$CH_2CH_2NH_2$	H	$C_{16}H_{15}BrN_2$ HCl	- 224-27 (e)	287
H	C_6H_5	$CH_2CH_2NH_2$	5-Cl	$C_{16}H_{15}ClN_2$ picrate	80 (e) 240	231 231
H	C_6H_5	$CH_2CH_2NH_2$	7-Cl	$C_{16}H_{15}ClN_2$ picrate	142 (e) 220	231 231
H	4-Cl C_6H_4	$CH_2CH_2NH_2$	H	$C_{16}H_{15}ClN_2$	104-106 (c)	596
H	H		H	$C_{16}H_{15}N_3$	180-81	232

Table 11 (cont.)

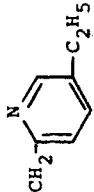
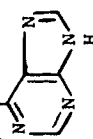
H	C ₆ H ₅	CH ₂ CH ₂ NH ₂	H	C ₁₆ H ₁₆ N ₂ HCl	- 247 (e) 262-64 (m)	287 596
H	H	$\begin{matrix} \text{C}_6\text{H}_5 \\ \\ \text{CH}_2\text{CHNH}_2 \end{matrix}$	H	C ₁₆ H ₁₆ N ₂ picrate HCl	- 213-14 (e) 250-51 252-53	400 400 387
H	H	C ₆ H ₅ CHCH ₂ NH ₂	H	C ₁₆ H ₁₆ N ₂ picrate	130-32 232-33	374 405, 532
H	H	CH ₂ CH ₂ N(CH ₂ C≡CH) ₂	H	C ₁₆ H ₁₆ N ₂ HCl	92-93 (ea) 143-44 (ac)	369 369
H	H		H	C ₁₆ H ₁₆ N ₂ methiodide	104-06 (e) 243-46	439 439
H	CH ₃	CH ₂ CH ₂ N(CH ₂ C(=O)c1cccnc1)	H	C ₁₆ H ₁₆ N ₂ O	277 (m)	605
H	H	CH ₂ CH ₂ NHOSO ₂ C ₆ H ₅	H	C ₁₆ H ₁₆ N ₂ O ₂ S	89 (b)	232a
H	H	$\begin{matrix} \text{CH}_2\text{OH} \\ \\ \text{CH}_2\text{CHNH} \end{matrix}$ 	H	C ₁₆ H ₁₆ N ₆ O	248-49	331

Table 11 (cont.)

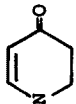
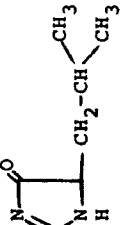
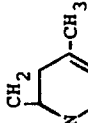
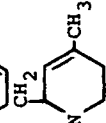
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_2$		H	$\text{C}_{16}\text{H}_{17}\text{N}_3$ picrate	- 166-67 (e)	232
H	CH_3	$\text{CH}_2\text{CH}_2\text{N}$		H	$\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$	206 (ac)	605
COCH_3	H	OCOCH_3 $\text{CHCH}_2\text{NHCOCH}_3$		H	$\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$	68-71 (p)	343
H	H	CH_2		H	$\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}$	98-99	145
H	H	CH_2		H	$\text{C}_{16}\text{H}_{20}\text{N}_2$	183-84 (b)	187
H	H	CH_3		H	$\text{C}_{16}\text{H}_{20}\text{N}_2$	165-67	363
H	H	CH_3		H	$\text{C}_{16}\text{H}_{20}\text{N}_2$	174-76	363

Table 11 (cont..)

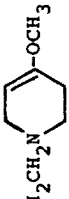
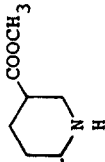
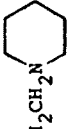
H	H		H	$C_{16}H_{20}N_2O$	138(ac)	605
H	H	$CH_2CH_2NHCO(CH_2)_3COCH_3$	H	$C_{16}H_{20}N_2O_2$	128(ac)	605
H	H		H	$C_{16}H_{20}N_2O_2$	rac I: 132-4 rac II: 146-9	17 17
H	H	$CH_2CH_2NHCOCH_2C(=O)C_2H_5$	H	$C_{16}H_{20}N_2O_2$	105-106(et)	217
H	H		5-CH ₃ , 7-Br	$C_{16}H_{21}BrN_2$ picrate	- 177	19
H	H	"	5-Br, 7-CH ₃	$C_{16}H_{21}BrN_2$ picrate	- 162	19
H	H	"	5-CH ₃ , 7-Cl	$C_{16}H_{21}ClN_2$ picrate	- 199-200	19
H	H	"	5-Cl, 7-CH ₃	$C_{16}H_{21}ClN_2$ picrate	- 175	19

Table 11 (cont.)

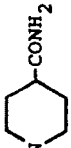
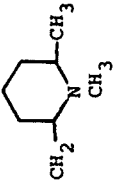
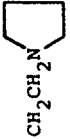
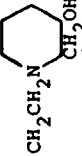
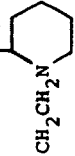
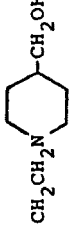
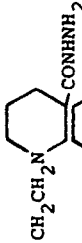
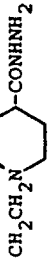
H	H		H	$C_{16}H_{21}N_3O$	183-84 (ea)	505a
H	H	$CH=CHN(C_3H_7)_2$	H	$C_{16}H_{22}N_2$	129-32	102
H	H		H	$C_{16}H_{22}N_2$	100-02 (b)	17
H	CH_3		5- CH_3	$C_{16}H_{22}N_2$ maleate	- 150-51 (e)	86
H	CH_3		H	$C_{16}H_{22}N_2$	149-51	483
H	H		H	$C_{16}H_{22}N_2O$	101-02 (ea)	505
H	H		H	$C_{16}H_{22}N_2O$	160-63 (ea)	505
H	H		H	$C_{16}H_{22}N_4O$	138-40 (c)	505
H	H		H	$C_{16}H_{22}N_4O$	165-66 (c)	505 505a

Table 11 (cont.)

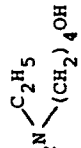
H	H	CH ₂ CH ₂ N(C ₃ H ₇) ₂	5-Br	C ₁₆ H ₂₃ BrN ₂ HCl	- 183	281
H	H	CH ₂ CH ₂ N  NCH ₂ CH ₂ OH	H	C ₁₆ H ₂₃ N ₃ O di-HCl	105-110 265-67	143 143 504a
H	H	CH ₂ CH ₂ N(C ₃ H ₇) ₂	H	C ₁₆ H ₂₄ N ₂ HCl	- 178-79 (b)	67a
H	H	CH ₂ CH ₂ N[CH(CH ₃) ₂] ₂	H	C ₁₆ H ₂₄ N ₂ HCl	- 198-99 (b)	67a
C ₂ H ₅	H	CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₁₆ H ₂₄ N ₂ HCl	- 115-16 (ip)	282
H	H	CH ₂ CH ₂ N 	H	C ₁₆ H ₂₄ N ₂ O	b.p. 195-204 (0.05 mm.)	314
H	H	COCH ₂ NHCOC ₆ H ₅	H	C ₁₇ H ₁₄ N ₂ O ₂	227-30 (e)	21
H	H	CH ₂ CH ₂ N=CH-C ₆ H ₅	H	C ₁₇ H ₁₆ N ₂	118 (p)	264
H	H	CH ₂ CH ₂ NHCOC ₆ H ₅	H	C ₁₇ H ₁₆ N ₂ O	130-32 (b)	232a
H	H	HOCHCH ₂ NH-COC ₆ H ₅	H	C ₁₇ H ₁₆ N ₂ O ₂	116-17 (b)	21

Table 11 (cont.)

H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_2\text{C}_6\text{H}_4\text{Cl-4}$	H	$\text{C}_{17}\text{H}_{17}\text{ClN}_2$ HCl	-	67a
H	H	$\text{CH}_2\text{CH}_2\text{N} \begin{smallmatrix} \text{C}_6\text{H}_5 \\ \text{NHCOCH}_3 \end{smallmatrix}$	H	$\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}$	250-52 (b) 117-18	556
H	$\text{CH}_2\text{C}_6\text{H}_5$	$\text{CH}_2\text{CH}_2\text{NH}_2$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2$	160-62 (e) 156 (e/w)	152 63a
CH_3	C_6H_5	"	H	$\text{C}_{17}\text{H}_{18}\text{N}_2$ picrate	-	20
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2$ HCl	215-17 (e)	67a 573, 578
H	H	$\begin{smallmatrix} \text{CH}_3 & \text{C}_6\text{H}_5 \\ & \\ \text{CH} & - \text{CH} - \text{NH}_2 \end{smallmatrix}$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2$ picrate	241-43 (e) 232-34	402
CH_3	H	$\begin{smallmatrix} \text{C}_6\text{H}_5 \\ \\ \text{CH} - \text{CH}_2\text{NH}_2 \end{smallmatrix}$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2$ picrate	123-24 (l) 204-05 (e)	402
H	CH_3	$\begin{smallmatrix} \text{C}_6\text{H}_5 \\ \\ \text{CH} - \text{CH}_2\text{NH}_2 \end{smallmatrix}$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2$ picrate	-	405
CH_3	C_6H_5	$\text{HOCHCH}_2\text{NH}_2$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$	158-60 130-32 (ea)	377 20
H	$\text{CH}_2\text{C}_6\text{H}_4\text{OH-2}$	$\text{CH}_2\text{CH}_2\text{NH}_2$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$	193 (m)	63a

Table 11 (cont.)

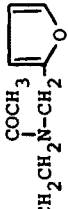
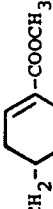
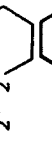
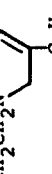
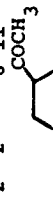
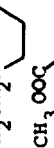
H	$\text{CH}_2\text{C}_6\text{H}_4\text{OH}-4$	$\text{CH}_2\text{CH}_2\text{NH}_2$	H	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$	105-08 (m/w)	63a
H	H		H	$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	102 (ac/w)	414
H	H		5-Br	$\text{C}_{17}\text{H}_{19}\text{BrN}_2\text{O}_2$ picrate	80-82 150	280a 280a
H	H		H	$\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$	133-34 (e)	599
H	H		H	$\text{C}_{17}\text{H}_{22}\text{N}_2$	121-23	412
H	H		H	$\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$ methobromide	- 262-63	372
H	H	$\text{CH}_2\text{CH}_2\text{NHCOC}_6\text{H}_{11}$	H	$\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$	130-32 (e/w)	232a
H	H		H	$\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$	130-31	599
H	H		H	$\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2$	125-27 (ac)	505a

Table 11 (cont.)

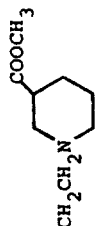
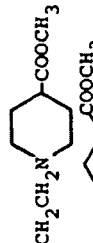
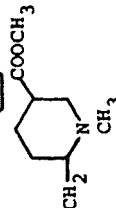
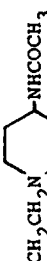
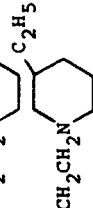
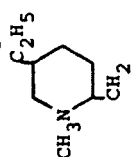
H	H		H	$C_{17}H_{22}N_2O_2$	108-11 (b)	505a
H	H		H	$C_{17}H_{22}N_2O_2$	110-12 (ac)	505a
H	H		H	$C_{17}H_{22}N_2O_2$	103-04 (b)	17
H	H		H	$C_{17}H_{22}N_2O_3$	101-02	362
H	H		H	$C_{17}H_{23}N_3O$	167-69 (ea)	505, 505a
H	H		H	$C_{17}H_{24}N_2$	112-14 (cyh)	599
H	CH ₃		H	$C_{17}H_{24}N_2$ HCl	157-58 (ip) 252-54 (ip)	573 573, 578
H	H		H	$C_{17}H_{24}N_2$ picrate	100-01 (l) 170-72 (c) 188-89 (c)	17 17 17

Table 11 (cont.)

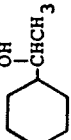
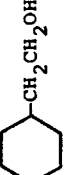
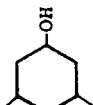
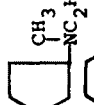
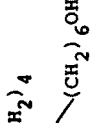
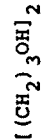
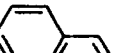
H	H		H	$C_{17}H_{24}N_2O$ HCl	- 177-84 (m)	505
H	H		H	$C_{17}H_{24}N_2O$	116-18 (ea)	505
H	H		H	$C_{17}H_{24}N_2O$	230-25 (ip)	505
H	H		H	$C_{17}H_{25}N_3$ hexamate	- 124-28 (ip)	598
H	H		H	$C_{17}H_{25}N_3$ di-HCl	- 259-62 (e)	505a 505
H	H		H	$C_{17}H_{26}N_2O$ HCl	68(et) 117(ac)	421 421
H	H		H	$C_{17}H_{26}N_2O_2$ HCl	b.p. 232-36 (0.05 mm.) 131-39	314 314
H	H		H	$C_{18}H_{14}N_2$ picrate methiodide	171-72 (e) 163-65 (e) 227-28 (e)	63 63 63

Table 11 (cont.)

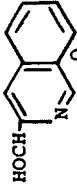
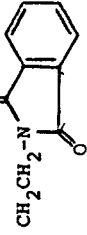
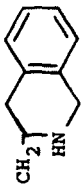
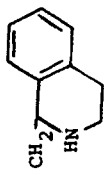
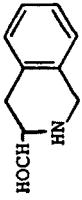
H	H		H	$C_{18}H_{14}N_2O$	159-60 (m/w)	29
H	H		H	$C_{18}H_{14}N_2O_2$	164-65	344
H	H		H	$C_{18}H_{16}N_2O_3$		21
H	H		H	$C_{18}H_{18}N_2$ HCl	- 209-11 (ip)	29
H	H		H	$C_{18}H_{18}N_2$ picrate HCl	139-40 (m) 210-11 (e) 248-50	63 63 63
CH ₃	H		H	$C_{18}H_{18}N_2$	b.p. 160 (1 mm.)	264
H	CH ₃	"	H	$C_{18}H_{18}N_2$	93-94 (p)	264
H	H		H	$C_{18}H_{18}N_2O$	215-16 (ac)	29

Table 11 (cont.)

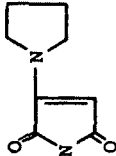
H	H	$\text{CH}_2\text{CH}_2\text{NHCOC}_6\text{H}_5$	H	$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}$	144-45 (e)	232a
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_4\text{Br}-4$	H	$\text{C}_{18}\text{H}_{19}\text{BrN}_2$ methobromide	- 204-05 (e)	201
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_4\text{Cl}-2$	H	$\text{C}_{18}\text{H}_{19}\text{ClN}_2$ methobromide	- 181-84 (e)	201
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_4\text{Cl}-3$	H	$\text{C}_{18}\text{H}_{19}\text{ClN}_2$ methobromide	- 204-07 (m)	201
H	C_6H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	5-Cl	$\text{C}_{18}\text{H}_{19}\text{ClN}_2$ picrate	115 (e) 188	231 231
H	C_6H_5	"	7-Cl	$\text{C}_{18}\text{H}_{19}\text{ClN}_2$ picrate	90 (e) 140	231 231
H	H	$\text{CH}_2\text{CH}_2\text{NHC}(\text{OH})\text{CH}_2\text{CHC}_6\text{H}_5$	5-Cl	$\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}$	129-31 (b)	263
H	H		H	$\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$	212 (mc)	606

Table 11 (cont.)

H	H	CH_3 $\text{CH}_2\text{CH}_2\text{N}-\text{CH}_2\text{C}_6\text{H}_4\text{NO}_2-3$	H	$\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$ methobromide	-	214-17 (ac)	201
H	H	CH_3 $\text{CH}_2\text{CH}_2\text{N}-\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ methobromide	-	202-04 (m)	201
H	H	$\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ HCl	-	215-16 (b) 210-13 (e/w)	67a 421
H	H	CH_3 $\text{CH}_2\text{CH}_2\text{NHCH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ HCl	-	262-63 (b)	67a
H	C_6H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ HCl	124-26 (ea) 174-75 (e)	123 (e)	20 287
H	C_6H_5	$\text{CH}_2\text{CH}_2\text{NHC}_2\text{H}_5$	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$	123 (e)		287
$\text{CH}_2\text{C}_6\text{H}_5$	H	CH_3 CH_2CHNH_2	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ HCl	-	183-85 (e)	518
$\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{CH}_3\text{CH}-\text{CH}_2\text{NH}_2$	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ picrate	-	105	352
CH_3	$\text{CH}_2\text{C}_6\text{H}_5$	$\text{CH}_2\text{CH}_2\text{NH}_2$	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$	126 (e/w)		63a
H	H	$\text{CH}_2\text{C}_6\text{H}_5$ $\text{CH}-\text{CH}-\text{CH}_2\text{NH}_2$ CH_3	H	$\text{C}_{18}\text{H}_{20}\text{N}_2$ picrate	114-15 (b) 205-06 (e)		403 403

Table 11 (cont.)

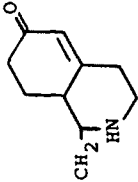
CH ₃	H	C ₆ H ₅ CHCH ₂ NHCH ₃	H	C ₁₈ H ₂₀ N ₂ picrate	- 181	20
CH ₃	CH ₃	C ₆ H ₅ CHCH ₂ NH ₂	H	C ₁₈ H ₂₀ N ₂ HCl	- 259-60	377
H	CH ₃	C ₆ H ₅ CH ₃ CH—CH—NH ₂	H	C ₁₈ H ₂₀ N ₂	183-84	377
CH ₂ CH ₂ C ₆ H ₅	H	CH ₂ CH ₂ NH ₂	H	C ₁₈ H ₂₀ N ₂ HCl	- 128-30 (ea)	283
H	H	HNCH ₂ CH ₂ CH ₂ C ₆ H ₄ OCH ₃ -4	H	C ₁₈ H ₂₀ N ₂ O HCl	- 219-20 (b)	67a
CH ₃	H	HOCHCH ₂ NHCH ₂ C ₆ H ₅	H	C ₁₈ H ₂₀ N ₂ O	111-13 (ea)	572
C ₆ H ₅	H	HOCHCH ₂ N(CH ₃) ₂	H	C ₁₈ H ₂₀ N ₂ O	104-05 (e)	20
H	CH ₂ C ₆ H ₄ OH-4	CH ₂ CH ₂ NHCH ₃	H	C ₁₈ H ₂₀ N ₂ O	191-93	63a
H	4-HOC ₆ H ₄	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₁₈ H ₂₀ N ₂ O	216-17 (e)	20
H	H		H	C ₁₈ H ₂₀ N ₂ O	203-04	365

Table 11 (cont.)

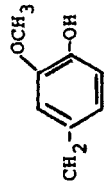
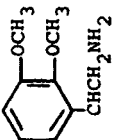
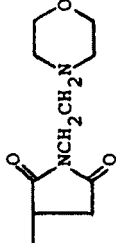
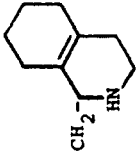
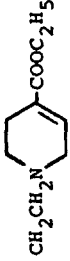
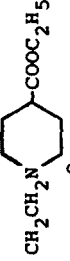
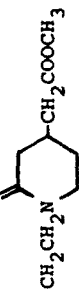
H		H	$C_{18}H_{20}N_2O_2$	181-84	63a
H		H	$C_{18}H_{20}N_2O_2$	192 (e)	447
H		H	$C_{18}H_{21}N_3O_3$ HCl	107-09 (e) 172-75 (m)	390 390
H		H	$C_{18}H_{22}N_2$	160-61	364
H		H	$C_{18}H_{22}N_2O_2$ picrate	- 168-71 (e)	125
H		H	$C_{18}H_{24}N_2O_2$ HBr	- 155-57 185-87	125 125
H		H	$C_{18}H_{22}N_2O_3$	116-17 (b)	140

Table 11 (cont.)

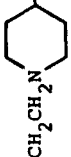
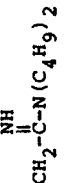
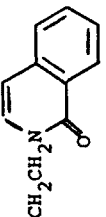
H	H		H	$C_{18}H_{25}N_3O$	166-169 (ea)	505
H	H		H	$C_{18}H_{25}N_3O$ di-HCl	- 257 (m)	390
H	H		H	$C_{18}H_{26}N_2O$	109-14 (ea)	505
H	CH ₃		H	$C_{18}H_{26}N_2O$ HCl	- 256-61	505
H	H		H	$C_{18}H_{27}N_3$ di-HCl	- > 290	505
H	H		H	$C_{18}H_{27}N_3$ HCl	130-31 (ac) 155-57	475 475
H	H		H	$C_{18}H_{28}N_2$ HCl	- 186-88 (b)	67a
H	H		H	$C_{18}H_{28}N_2$ HCl	- 202-04 (b)	67a
H	H		H	$C_{19}H_{16}N_2O$	151-53	69

Table 11 (cont.)

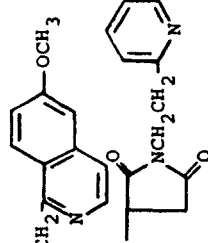
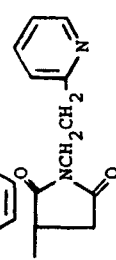
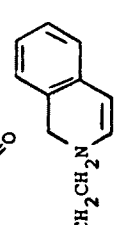
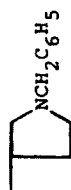
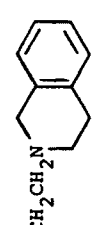
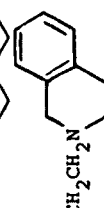
H	H		H	C ₁₉ H ₁₆ N ₂ O methiodide benzobromide	163-64 (ip) 247-49 219-22	622 622 622
H	H		H	C ₁₉ H ₁₇ N ₃ O ₂	151-53 (ea)	390
H	H		H	C ₁₉ H ₁₈ N ₂	100-05 (dec)	247
H	H		H	C ₁₉ H ₂₀ N ₂ HCl	- 144 (e/w)	278
H	H		H	C ₁₉ H ₂₀ N ₂ picrate	- 171 (ac/w)	414
H	H		H	C ₁₉ H ₂₀ N ₂ picrate	121-22 (cyh) 167-69 170-71 (ac/w)	247 482 247
H	H		H	C ₁₉ H ₂₀ N ₂ HCl	- 137 (ac)	29

Table 11 (cont.)

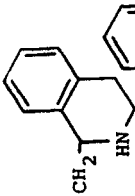
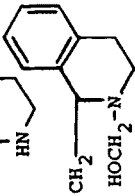
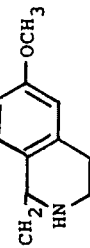
H	H	$\text{CH}_2\text{CH}_2\text{NCOCH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	104-05	232a
CH_3	H	$\text{CH}_2\text{CH}_2\text{NHCOC}_2\text{H}_5$	H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	76-77 (e/w)	232a
H	H	$\text{CH}_2\text{CH}_2\text{NHCOC}_2\text{H}_5$	H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	74-75 (e)	232a
H	H	$\text{COCH}_2\text{NCH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	179-80 (ip)	571, 579
H	H	$(\text{CH}_3)_2\text{C}(\text{CH}_2)\text{NHCOC}_6\text{H}_5$	H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	148	492
H	H	$\text{CH}_2\text{CH}(\text{C}_2\text{H}_5)\text{NHCOC}_6\text{H}_5$	H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	101	492
H	CH_2OH		H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	205-07 (b)	63
H	H		H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	169-70 (m)	63
H	H		H	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$	162-64	365

Table 11 (cont.)

H	H	$\text{CH}_2\text{CH}_2\text{NCH}_2\text{C}_6\text{H}_4\text{Cl}-3$	H	$\text{C}_{19}\text{H}_{21}\text{ClN}_2$ ethobromide	-	188-91 (e)	201
CH ₃	$\text{C}_6\text{H}_4\text{Cl}-2$	$\text{HOCHCH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}$	117-18 (ea)	20	
CH ₃	C_6H_5	$\text{HOCHCH}_2\text{N}(\text{CH}_3)_2$	5-Cl	$\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}$	119-21 (ea)	20	
H	H	$\text{CH}_2\text{CH}_2\text{NCH}_2\text{C}_6\text{H}_5$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ HCl	-	224-25 (e)	573, 578
H	H	$\text{CH}_2\text{CH}_2\text{NCH}_2\text{C}_6\text{H}_4\text{CH}_3-2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ methobromide	-	204-05 (e)	201
H	H	$\text{CH}_2\text{CH}_2\text{NCH}_2\text{C}_6\text{H}_4\text{CH}_3-3$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ methobromide	-	181-82 (ac)	201
H	H	$\text{CH}_2\text{CH}_2\text{NCH}_2\text{C}_6\text{H}_4\text{CH}_3-4$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ methobromide	-	189-92 (e)	201
$\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{CH}_2\text{CH}(\text{NH}_2)\text{C}_6\text{H}_5$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ HCl	-	164-65 (e)	284
$\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{C}_2\text{H}_5\text{CHCH}_2\text{NH}_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ HCl	-	201-02 (e)	284
CH ₃	C_6H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ picrate	-	152-54 (e)	20

Table 11 (cont.)

$\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ picrate	-	613, 620
					212	
CH_3	H	$\text{C}_6\text{H}_5\text{CHCH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ picrate	-	20
				citrate-	199	
				dihydrate	69	20
H	C_6H_5	$\text{CH}_2\text{CH}_2\text{NHC}_3\text{H}_7$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ HCl	75-76(b)	287
					215-18(e)	287
H	C_6H_5	$\text{CH}_2\text{CH}_2\text{NHCH}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ HCl	97-98	287
					238-40(e)	287
$\text{CH}_2\text{C}_6\text{H}_5$	H	$(\text{CH}_3)_2\text{CCH}_2\text{NH}_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$ picrate	-	323, 352
		$\text{C}_6\text{H}_5\text{CH}_3$			184	
CH_3	CH_3	$\text{CH}-\text{CH}-\text{NH}_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2$	123-26	377
H	$4-\text{CH}_3\text{OC}_6\text{H}_4$	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$	173-75(m)	20
CH_3	C_6H_5	$\text{HOCHCH}_2\text{NHC}_3\text{H}_5$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$	89-91(ea)	20
CH_3	C_6H_5	$\text{HOCHCH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$	110-12	20

Table 11 (cont.)

H	H		$C_{19}H_{22}N_2O$	157-58	365
CH ₃	C ₆ H ₅		$C_{19}H_{22}N_2O_2$	182-84 (b)	20
H	CH ₂ -	CH ₂ CH ₂ NH ₂	$C_{19}H_{22}N_2O_2$	179-80 (m)	63a
H	"	CH ₂ CH ₂ NHCH ₃	$C_{19}H_{22}N_2O_2$	174-75 (m)	63a
H	H		$C_{19}H_{22}N_2O_2$	-	478
CH ₃	4-HOC ₆ H ₄	HOCHCH ₂ N(CH ₃) ₂	$C_{19}H_{22}N_2O_2$	171-72 (m)	20
H	H		$C_{19}H_{22}N_2O_2$	ca. 191	476
			tartrate	ca. 100	478
			HCl	242	478

Table 11 (cont.)

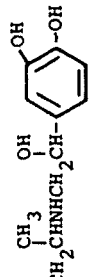
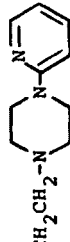
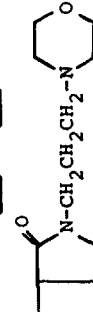
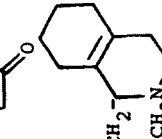
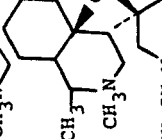
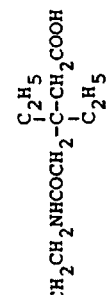
H	H		$C_{19}H_{22}N_2O_3$ tartrate	-	476, 478
H	H		$C_{19}H_{22}N_4$	ca. 65 232-34	504a
H	H		$C_{19}H_{23}N_3O_2$	138-40 (ea)	390
H	H		$C_{19}H_{24}N_2$	148	364
H	H		$C_{19}H_{25}ClN_2$	159-60	364
H	H		$C_{19}H_{26}N_2O$	117-21	36
H	H		$C_{19}H_{26}N_2O_3$	124-25 (ea)	175

Table 11 (cont.)

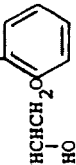
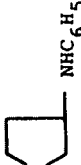
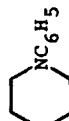
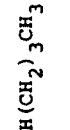
H	4-HOC ₆ H ₄		CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₀ H ₂₂ N ₂ O ₂	218-20 (m)	20
H	4-BrC ₆ H ₄		CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₀ H ₂₃ BrN ₂ ethanesulfonate	124-25 (ac) 192-93	328 328
H	4-ClC ₆ H ₄		CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₀ H ₂₃ ClN ₂ ethanesulfonate	116-17 183-84	328 328
H	H		CH ₂ CH ₂ NHCHCH ₂ OC ₆ H ₄ CH ₃ HO	5-Cl	C ₂₀ H ₂₃ ClN ₂ O ₂	148-50	263
H	H	"	"	5-P	C ₂₀ H ₂₃ FN ₂ O ₂	118-20	263
H	H		CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₀ H ₂₃ N ₃	-	598
H	H		CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₀ H ₂₃ N ₃	133-35 132-36 (ac)	143 504a
H	C ₆ H ₅		CH ₂ CH ₂ NH(CH ₂) ₃ CH ₃	H	C ₂₀ H ₂₄ N ₂ oxalate	- 230 (e)	287
H	C ₆ H ₅		CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₀ H ₂₄ N ₂ ethanesulfonate HCl	125-26 (m) 210-11 (ac) 169-71 (e)	328 328 287

Table 11 (cont.)

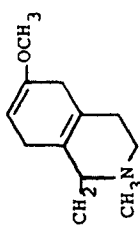
$\text{CH}_2\text{C}_6\text{H}_5$	H	$(\text{CH}_3)_2\text{CHCHCH}_2\text{NH}_2$	H	$\text{C}_{20}\text{H}_{24}\text{N}_2$ picrate	-	323, 352
$\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{CH}_3(\text{CH}_2)_2\text{CHCH}_2\text{NH}_2$	H	$\text{C}_{20}\text{H}_{24}\text{N}_2$ picrate	140-42	323, 352
$\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{20}\text{H}_{24}\text{N}_2$	160	283
H	$\text{CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{OH}-4$	"	H	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	199-200 (e)	20
H	H		H	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	168-69 (m)	365
C_6H_5	C_6H_5	$\text{HOCHCH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	141-42	20
CH_3	C_6H_5	"	5- CH_3	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	118-20	20
CH_3	4- $\text{CH}_3\text{C}_6\text{H}_4$	"	H	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	101-02 (ea)	20
$\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{HOCHCH}_2\text{NHCH}(\text{CH}_3)_2$	H	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	118-19 (ea)	20
CH_3	4- $\text{CH}_3\text{OC}_6\text{H}_4$	$\text{HOCHCH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$	118-20	254b
					131-33	20

Table 11 (cont.)

H	H		H	$C_{20}H_{24}N_2O_2$ tartrate	- ca. 227	478
H	H		H	$C_{20}H_{24}N_2O_2$	113-15	263
H	H		H	$C_{20}H_{24}N_2O_3$	124-26	263
$CH_2C_6H_5$	CH_3	$CH_2CH_2NH_2$	5-OCH ₂ CONHNH ₂	$C_{20}H_{24}N_4O_2$ HCl	131 (b) 233-36 (e)	608 608
$CH_2C_6H_5$	CH_3	"	5-OCH ₂ CH ₂ NH ₂	$C_{20}H_{25}N_3O$ di-HCl	- 249 (e)	608
H	H		H	$C_{20}H_{29}N_3O$	139-40 (ea)	505
H	H		H	$C_{20}H_{30}N_2O$	143-44	505
H	H		H	$C_{21}H_{18}N_2$	166-68 (e)	232

Table 11 (cont.)

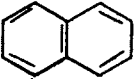
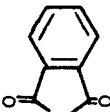
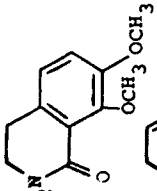
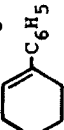
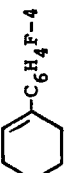
H	H		H	$C_{21}H_{18}N_2$	134-35 (e)	232
H	H		H	$C_{21}H_{20}N_2$	94-95 (h)	232
CH ₃	C ₂ H ₅		H	$C_{21}H_{20}N_2O_2$	141-42 (e)	326
H	H		H	$C_{21}H_{20}N_2O_3$	226-28 (m)	69
H	H		5-Cl	$C_{21}H_{21}ClN_2$	168-70 (b)	598
H	H		H	$C_{21}H_{21}ClN_2O_3$	149-50 (ac)	175
H	H		H	$C_{21}H_{21}FN_2$	157-59 (b)	598

Table 11 (cont.)

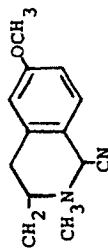
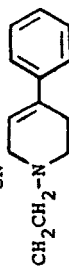
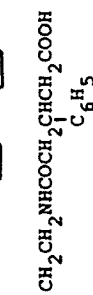
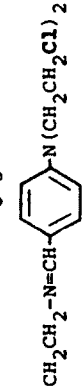
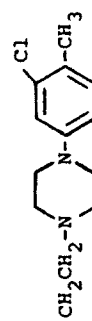
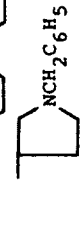
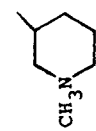
H	H		H	$C_{21}H_{21}N_3O$	153-54 (b)	628
H	H		H	$C_{21}H_{22}N_2$	138-40 (b)	598
H	H		H	$C_{21}H_{22}N_2O_3$	157-59 (ac)	175
H	H		H	$C_{21}H_{23}ClN_3$	113-14 (ea)	126
H	H		H	$C_{21}H_{24}ClN_3$	159-61	504a
C_2H_5	H		H	$C_{21}H_{24}N_2$ HCl	- 147 (m)	278
$CH_2C_6H_5$	H		H	$C_{21}H_{24}N_2$	183 (e)	279

Table 11 (cont.)

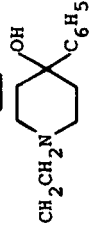
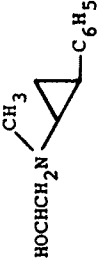
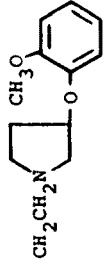
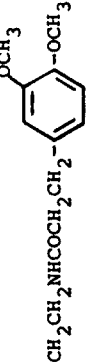
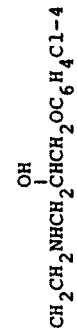
H	C_6H_5		H	$C_{21}H_{24}N_2$ HCl	128-30 (ea) 210 (e)	20 287
CH ₃	H		H	$C_{21}H_{24}N_2$ HCl	- 130 (e)	279
H	H		H	$C_{21}H_{24}N_2O$	137-39 (b)	598
CH ₃	H		H	$C_{21}H_{24}N_2O$	-	598
H	H		H	$C_{21}H_{24}N_2O_2$ HCl	- 50-55	598
H	H		H	$C_{21}H_{24}N_2O_3$	84-86 (e)	292
CH ₃	4-ClC ₆ H ₄		H	$C_{21}H_{25}ClN_2O$	131-32 (e)	20
C ₂ H ₅	H		H	$C_{21}H_{25}ClN_2O_2$	110-12	263

Table 11 (cont.)

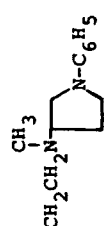
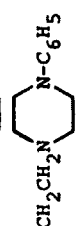
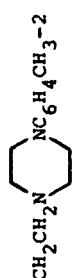
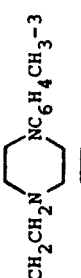
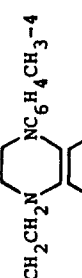
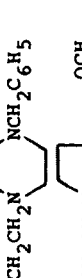
H	H		H	$C_{21}H_{25}N_3$	104-06 (e)	598
CH ₃	H		H	$C_{21}H_{25}N_3$	90-94 94-96	143 504a
H	CH ₃	"	H	$C_{21}H_{25}N_3$	150-53 (w) 154-56	143 504a
H	H	"	6-CH ₃	$C_{21}H_{25}N_3$	170-73 174-75	143 504a
H	H		H	$C_{21}H_{25}N_3$	124-26 (b)	504a
H	H		H	$C_{21}H_{25}N_3$	164-66	504a
H	H		H	$C_{21}H_{25}N_3$	145-50 148-55	143 504a
H	H		H	$C_{21}H_{25}N_3$ methochloride	90-95 227-29 (m)	143 504a
H	H		H	$C_{21}H_{25}N_3O$	94-96 (b)	598

Table 11 (cont.)

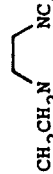
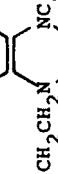
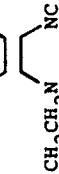
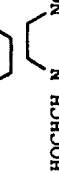
H	H		H	$C_{21}H_{25}N_3O$	110-14 111-14	143 504a
H	H		H	$C_{21}H_{25}N_3O$	146-48	504a
H	H		H	$C_{21}H_{25}N_3O$	130-32	504a
H	CH ₃		H	$C_{21}H_{25}N_3O$	137-40	504a
CH ₂ C ₆ H ₅	H	$C_2H_5CHCH_2N(CH_3)_2$	H	$C_{21}H_{26}N_2$ picrate oxalate	- 133(e) 192-94(e)	284 284
H	4-CH ₃ C ₆ H ₄	$CH_2CH_2N(C_2H_5)_2$	H	$C_{21}H_{26}N_2$ ethanesulfonate	90-92(e) 193-34	328 328
CH ₂ C ₆ H ₅	H	$(C_2H_5)_2C-CH_2NH_2$	H	$C_{21}H_{26}N_2$ benzoate	- 159	- 352
C ₃ H ₇	C ₆ H ₅	$HOCHCH_2N(CH_3)_2$	H	$C_{21}H_{26}N_2O$	86-87(ea)	20
CH ₃	C ₆ H ₅	$HOCHCH_2N(C_2H_5)_2$	H	$C_{21}H_{26}N_2O$	85-87	20
H	4-CH ₃ OC ₆ H ₄	$CH_2CH_2N(C_2H_5)_2$	H	$C_{21}H_{26}N_2O$ ethanesulfonate	110-11 178-79	328 328

Table 11 (cont.)

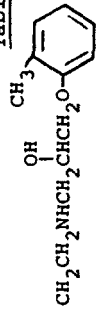
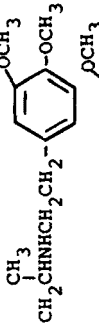
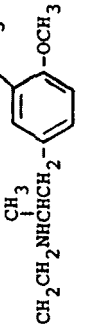
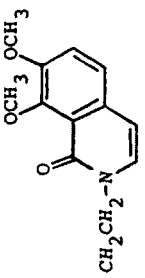
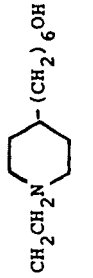
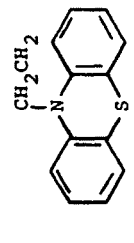
H	H		5-CH ₃	C ₂₁ H ₂₆ N ₂ O ₂	130-32	263
H	H		H	C ₂₁ H ₂₆ N ₂ O ₂ HCl -hydrate	- 152-53 125-28	478 478
H	H		H	C ₂₁ H ₂₆ N ₂ O ₂ HCl oxalate	- ca. 184 ca. 226	476 476
H	H				226-28	69
H	H		H	C ₂₁ H ₃₂ N ₂ O	112-14 (ea)	505
H	H		H	C ₂₂ H ₁₈ N ₂ S	159-62	372

Table 11 (cont.)

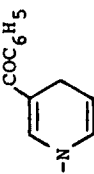
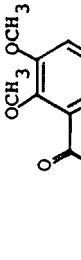
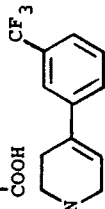
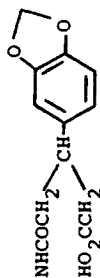
H	4-ClC ₆ H ₄	C ₆ H ₅ CHCH ₂ -NH ₂	H	C ₂₂ H ₁₉ ClN ₂	182-84 (e)	20
H	C ₆ H ₅	4-ClC ₆ H ₄ CHCH ₂ NH ₂	H	C ₂₂ H ₁₉ ClN ₂	188 (e)	20
H	C ₆ H ₅	C ₆ H ₅ CHCH ₂ NH ₂	H	C ₂₂ H ₂₀ N ₂	180-82	377
H	H	C ₆ H ₅ CHCHNH ₂ C ₆ H ₅	H	C ₂₂ H ₂₀ N ₂ picrate	187-88 (b) 216-17 (e)	403
H	H	CH ₂ CH ₂ -N- 	H	C ₂₂ H ₂₀ N ₂ O	250-255	514
H	H	CH ₂ CH ₂ -N- 	H	C ₂₂ H ₂₀ N ₂ O ₅	249-50 (ac)	69
H	H	CH ₂ CH ₂ -N- 	H	C ₂₂ H ₂₁ F ₃ N ₂	152-54 (b)	598
H	H	CH ₂ CH ₂ NHCOCH ₂ -CH- 	H	C ₂₂ H ₂₂ N ₂ O ₅	132-34 (e)	175

Table 11 (cont.)

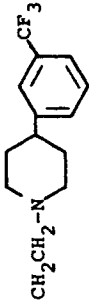
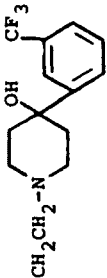
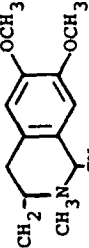
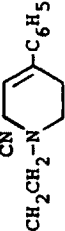
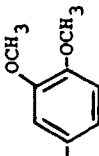
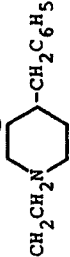
H	H		H	$C_{22}H_{23}F_3N_2$	104-06 (ip)	598
H	H		H	$C_{22}H_{23}F_3N_2O$ HCl	- 244-46 (ip)	598
H	H		H	$C_{22}H_{23}N_3O_2$	149-50	622
CH ₃	H		H	$C_{22}H_{24}N_2$ HCl	- 219-22 (ip)	598
H	CH ₃	"	H	$C_{22}H_{24}N_2$	142-44 (b)	598
H		$CH_2CH_2N=CHCOOC_2H_5$	H	$C_{22}H_{24}N_2O_4$	170-80 (b)	607
H	H		H	$C_{22}H_{26}N_2$ HCl	109-110 (e) 212-13 (e)	287 287
H	H		H	$C_{22}H_{26}N_2$	94-96 (h)	505a

Table 11 (cont.)

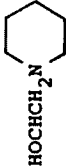
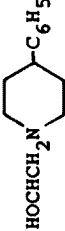
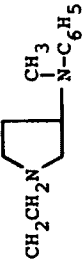
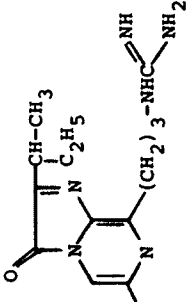
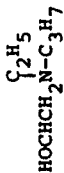
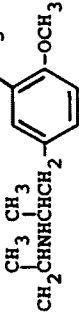
CH ₃	C ₆ H ₅		H	C ₂₂ H ₂₆ N ₂ O	155-56	572
CH ₃	H		H	C ₂₂ H ₂₆ N ₂ O	137-39 (b)	598
H	CH ₃		H	C ₂₂ H ₂₇ N ₃	131-33 (e)	598
H	H		H	C ₂₂ H ₂₇ N ₇ O dl-HBr	- 252-53	256a
CH ₂ CH ₂ C ₆ H ₅	H	CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₂ H ₂₈ N ₂	104-05 (e)	283
CH ₃	C ₆ H ₅		H	C ₂₂ H ₂₈ N ₂ O	64-65 (ea)	20
H	H		H	C ₂₂ H ₂₈ N ₂ O ₂ HCl	- ca. 95	476

Table 11 (cont.)

H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}(\text{OH})\text{CH}_3)\text{O}-\text{C}_6\text{H}_5$	H	$\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$ HCl	- 162-64	263
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{C}_6\text{H}_{11})\text{C}_6\text{H}_{11}$	5-F	$\text{C}_{22}\text{H}_{31}\text{FN}_2$	146-47 (ea) 141-42 (ea)	505 505a
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{C}_6\text{H}_{11})\text{C}_6\text{H}_{11}$	H	$\text{C}_{22}\text{H}_{32}\text{N}_2$	151-53 (ea)	505a
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{C}_6\text{H}_{11})\text{C}_6\text{H}_{11}$	H	$\text{C}_{22}\text{H}_{32}\text{N}_2$	143-44 (h)	505 505a
H	H	$\text{C}_6\text{H}_5\text{CHCH}_2\text{NHCOC}_6\text{H}_5$	H	$\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}$	188 (e)	20
H	C_6H_5	$\text{C}_6\text{H}_5\text{CHCH}_2\text{NHCONH}_2$	H	$\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}$	153-55 (e)	20
CH_3	C_6H_5	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2$	H	$\text{C}_{23}\text{H}_{22}\text{N}_2$ picrate	- 198-99 (m)	20
$\text{CH}_2\text{C}_6\text{H}_5$	H	$\text{CH}_2\text{CH}_2\text{NHC}_6\text{H}_5$	H	$\text{C}_{23}\text{H}_{22}\text{N}_2$ HCl	- 136-38 (b)	282
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}(\text{OH})\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{C}_6\text{H}_5$	H	$\text{C}_{23}\text{H}_{24}\text{N}_2$	193 (ac)	125
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}(\text{OH})\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{C}_6\text{H}_5$	5-Cl	$\text{C}_{23}\text{H}_{25}\text{ClN}_2\text{O}_2$ HCl	- 186-88	263

Table 11 (cont.)

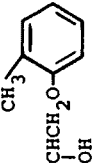
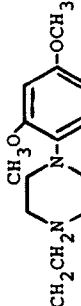
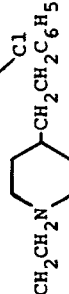
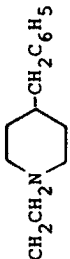
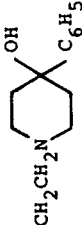
H	CH ₃	CH ₂ CH ₂ N		5-CH ₃	C ₂₃ H ₂₆ N ₂	150-52 (b)	598
CH ₂ C≡CH	H	CH ₂ CH ₂ NHCH ₂ CHCH ₂ O		H	C ₂₃ H ₂₆ N ₂ O ₂	94-96	263
H	H	CH ₂ CH ₂ N		H	C ₂₃ H ₂₇ N ₃	258-63	504a
H	H	CH ₂ CH ₂ NHCOCHNHCOOCH ₂ C ₆ H ₅		H	C ₂₃ H ₂₇ N ₃ O ₃	173-76 (ea)	24a
H	CH ₃	CH ₂ CH ₂ N		H	C ₂₃ H ₂₈ ClN ₃ O ₂	156-57 (m)	505b
H	H	CH ₂ CH ₂ N		H	C ₂₃ H ₂₈ N ₂ HCl HBr	119 233-35 (m) 219-21 (e)	125, 194 194 125
H	CH ₃	CH ₂ CH ₂ N		H	C ₂₃ H ₂₈ N ₂	142-44 (ea)	505a
CH ₃	CH ₃	CH ₂ CH ₂ N		H	C ₂₃ H ₂₈ N ₂ O	96	614

Table 11 (cont.)

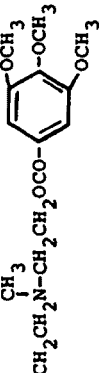
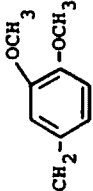
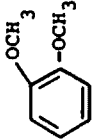
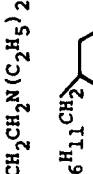
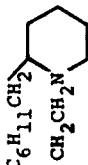
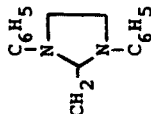
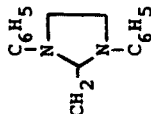
H	H		H	$C_{23}H_{28}N_2O_5$ HCl	- 76-78 (ac)	421
CH ₃	C ₆ H ₅		HOCHCH ₂ N(C ₃ H ₇) ₂	H	$C_{23}H_{30}N_2O$	20
H	CH ₂ - 		CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	$C_{23}H_{30}N_2O_2$ $C_2H_5SO_3H$	328 328
H	CH ₃		$C_6H_{11}CH_2$ CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	$C_{23}H_{34}N_2$	505a
H	H	CH=CHN(CH ₂ C ₆ H ₅) ₂	CH=CHN(CH ₂ C ₆ H ₅) ₂	H	$C_{24}H_{22}N_2$	102
H	H	CH ₂ CH ₂ NHCOCH(C ₆ H ₅) ₂	CH ₂ CH ₂ NHCOCH(C ₆ H ₅) ₂	H	$C_{24}H_{22}N_2O$	122
H	H			H	$C_{24}H_{23}N_3$	409
H	C ₆ H ₅	C ₆ H ₅ CHCH ₂ N(CH ₃) ₂	C ₆ H ₅ CHCH ₂ N(CH ₃) ₂	H	$C_{24}H_{24}N_2$	20

Table 11 (cont.)

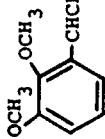
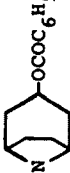
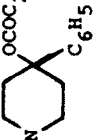
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{C}_6\text{H}_5)_2$	H	$\text{C}_{24}\text{H}_{24}\text{N}_2$ HCl	- 208 214-15 218-20 (e) 83-85 (b)	573, 578 372 67a 20
H	C_6H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{C}_6\text{H}_5)_2$ 	H	$\text{C}_{24}\text{H}_{24}\text{N}_2$		
$\text{CH}_2\text{C}_6\text{H}_4\text{OCH}_3-4$	H	$\text{CH}_2\text{CH}_2\text{NHC}_6\text{H}_5$	H	$\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}$ HCl	151-53 (e)	282
C_6H_5	C_6H_5	$\text{HOCHCH}_2\text{N}(\text{CH}_3)_2$ 	H	$\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}$	148-49 (ea)	20
H	C_6H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	$\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2$	141 (e/w)	447
H	β -naphthyl	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	$\text{C}_{24}\text{H}_{26}\text{N}_2$ $\text{C}_2\text{H}_5\text{SO}_3\text{H}$	114-18 (m) 175-77	328 328
H	H	$\text{CH}_2\text{CH}_2\text{N}$ 	H	$\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_2$ methobromide	- 246-48	372
H	H	$\text{CH}_2\text{CH}_2\text{-N}$ 	H	$\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_2$	142-44 (b)	598

Table 11 (cont.)

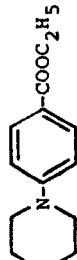
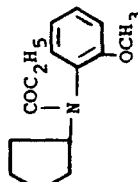
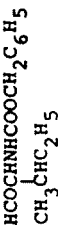
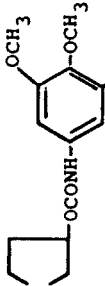
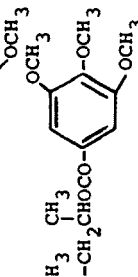
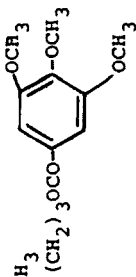
H	CH ₃		H	C ₂₄ H ₂₉ N ₃ O ₂	239-41 (e)	505b
H	H		H	C ₂₄ H ₂₉ N ₃ O ₂	-	598
H	H		H	C ₂₄ H ₂₉ N ₃ O ₃	139-42	24a
H	H		H	C ₂₄ H ₂₉ N ₃ O ₅	-	598
H	H		H	C ₂₄ H ₃₀ N ₂ O ₅ HCl	75-78 (ac)	421
H	H		H	C ₂₄ H ₃₀ N ₂ O ₅ HCl	75-76 (ac)	421

Table 11 (cont.)

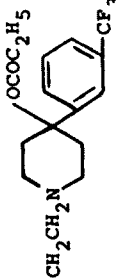
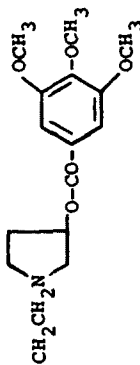
H	C ₆ H ₅	C ₆ H ₅ CHCH ₂ NHCOOC ₂ H ₅	H	C ₂₅ H ₂₄ N ₂ O ₂	138-39 (e/w)	20
CH ₃	C ₆ H ₅	C ₆ H ₅ CHCH ₂ N(CH ₃) ₂	H	C ₂₅ H ₂₆ N ₂	122-24 (e)	20
CH ₃	C ₆ H ₅		H	C ₂₅ H ₂₆ N ₂ sulfate	- 120 (et)	20
CH ₃	H	CH ₂ CH ₂ N(CH ₂ C ₆ H ₅) ₂	H	C ₂₅ H ₂₆ N ₂	123-4 (e)	78
H	4-C ₆ H ₅ OC ₆ H ₄	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₂₅ H ₂₆ N ₂ O	142-43 (m)	20
CH ₃	H	HOCHCH ₂ N(CH ₂ C ₆ H ₅) ₂	H	C ₂₅ H ₂₆ N ₂ O	120-22 (ea)	572
H	H		H	C ₂₅ H ₂₇ F ₃ N ₂ O ₂ HCl	- 68 (ip)	598
H	H	CH ₂ CH ₂ NHCH ₂ CH ₂ N(CH ₂ C ₆ H ₅) ₂	H	C ₂₅ H ₂₇ N ₃ di-HCl	- 171-75	504a
H	CH ₃		H	C ₂₅ H ₃₀ N ₂ O ₅	119-21 (m)	598

Table 11 (cont.)

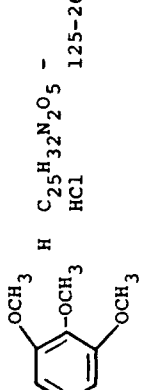
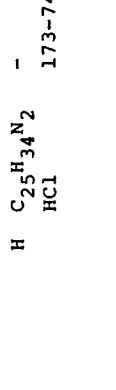
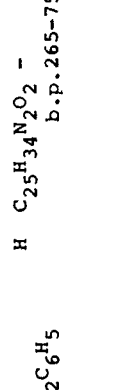
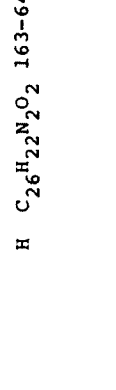
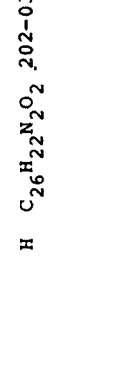
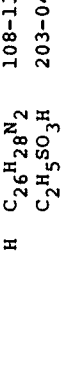
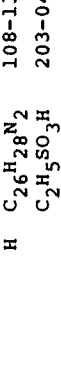
H	H		H	$C_{25}H_{32}N_2O_5$ HCl	- 125-26	421
H	H		H	$C_{25}H_{34}N_2$ HCl	- 173-74	573, 578
H	H		H	$C_{25}H_{34}N_2O_2$ b.p. 265-75 (0.01 mm.)	-	314
CH ₃	CH ₃		H	$C_{26}H_{22}N_2O_2$	163-64	377
H	CH ₃		H	$C_{26}H_{22}N_2O_2$	202-03	377
H			H	$C_{26}H_{28}N_2$ $C_2H_5SO_3H$	108-110 (b) 203-04	328 328

Table 11 (cont.)

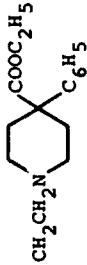
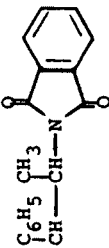
CH ₃	C ₆ H ₅	$\text{HOCHCH}_2\text{N}(\text{CH}_2\text{C}_6\text{H}_5)_2$	H	C ₂₆ H ₂₈ N ₂ O	78-79 (ea)	20
CH ₃	4-C ₆ H ₅ CH ₂ OC ₆ H ₄	$\text{HOCHCH}_2\text{N}(\text{CH}_3)_2$	H	C ₂₆ H ₂₈ N ₂ O ₂	137-39 (b)	20
H	C ₆ H ₅	$\text{CHCH}_2\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$	H	C ₂₆ H ₂₈ N ₂ O ₂	178-79 (m)	20
CH ₃	CH ₃		H	C ₂₆ H ₃₂ N ₂ O ₂	99-100	614
H	H		H	C ₂₆ H ₃₂ N ₂ O ₅	143 (m)	505
H	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)_4\text{OCO}-\text{C}_6\text{H}_3(\text{OCH}_3)_3$	H	C ₂₆ H ₃₄ N ₂ O ₅ HCl	- 140-42	314
CH ₃	CH ₃		H	C ₂₇ H ₂₄ N ₂ O ₂	242-45	377

Table 11 (cont.)

H	C ₆ H ₅		H	C ₂₇ H ₂₇ ClN ₂ O HCl	- 260 (m)	614
H	4-C ₆ H ₅ CH ₂ OC ₆ H ₄		H	C ₂₇ H ₂₈ N ₂ O ₂	159-60 (m)	20
CH ₂ C ₆ H ₅	H		H	C ₂₇ H ₃₀ N ₂ O ₂	78-80	263
H	H		H	C ₂₇ H ₃₆ N ₂ O ₅ HCl	- 115-16 (ac)	421
H	C ₆ H ₅		H	C ₂₈ H ₂₃ ClN ₂	188 (e)	20
CH ₂ C ₆ H ₅	CH ₃		5-OCH ₂ CH ₂ NH ₂	C ₂₈ H ₃₁ N ₃ O di-HCl	- 158-62 (e)	608
C ₁₆ H ₃₃	H		H	C ₂₈ H ₄₈ N ₂ O	48-50	572

Table 11 (cont.)

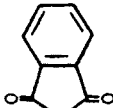
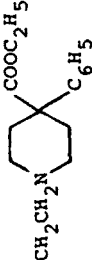
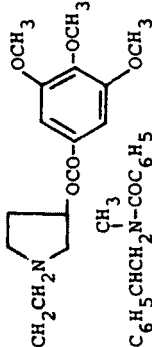
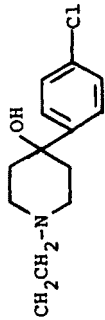
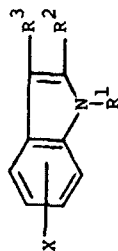
H	C ₆ H ₅	C ₆ H ₅ CHCH ₂ NHCOC ₆ H ₅	H	C ₂₉ H ₂₄ N ₂ O	188-89 (e)	20
H	C ₆ H ₅		H	C ₃₀ H ₂₂ N ₂ O ₂	232-33	377
H	C ₆ H ₅		H	C ₃₀ H ₃₂ N ₂ O ₂ HCl	- 209	614
H	H		H	C ₃₀ H ₃₄ N ₂ O ₅	79-86 (b)	598
CH ₃	C ₆ H ₅	C ₆ H ₅ CHCH ₂ N(CH ₃)COC ₆ H ₅	H	C ₃₁ H ₂₈ N ₂ O	168-69 (e)	20
CH ₃	C ₆ H ₅	C ₆ H ₅ CHCH ₂ N(CH ₃)CH ₂ C ₆ H ₅	H	C ₃₁ H ₃₀ N ₂ picrate	83-85 (e) 148-50	20 20
CH ₃	C ₆ H ₅	HOCHCH ₂ N(CH ₂ C ₆ H ₅) ₂	H	C ₃₁ H ₃₀ N ₂ O	96-98 (e)	20
H	CH ₂ CH ₂ C ₆ H ₅	CH ₂ CH ₂ N(CH ₂ C ₆ H ₅) ₂	H	C ₃₂ H ₃₂ N ₂	88-89 (m)	20
CH ₂ - 	C ₆ H ₅		H	C ₃₄ H ₃₂ Cl ₂ N ₂ O HCl	- 260-62	614

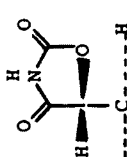
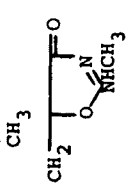
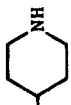
Table 12. 3-Indolyl-C-C-C-N and 3-Indolyl-(C)₃-N Derivatives*



R ¹	R ²	R ³	X		m.p., °C	Ref.
H	H	(CH ₂) ₃ NH ₂	H	C ₁₁ H ₁₄ N ₂ HCl picrate	60-64 169-70 155-56	342 265a, 342 342
H	H	(CH ₂) ₃ NHCHO	H	C ₁₂ H ₁₄ N ₂ O	b.p. 170-90 (0.1 mm.)	124
H	H	CH ₂ CH ₂ -CH-NH ₂ CH ₃	H	C ₁₂ H ₁₆ N ₂ creatinine sulfate	b.p. 159-63 (1.6 mm.) 153-56	504 525
CH ₃	H	(CH ₂) ₃ NH ₂	H	C ₁₂ H ₁₆ N ₂ picrate	- 176(w)	124
H	CH ₃	"	H	C ₁₂ H ₁₆ N ₂	-	180
H	H	"	5-CH ₃	C ₁₂ H ₁₆ N ₂ HCl	b.p. 166-70 (1 mm.) - 256-57 (m)	252
H	H	(CH ₂) ₃ NHCH ₃	H	C ₁₂ H ₁₆ N ₂	87(et)	124

*For further compounds: Chas. Pfizer & Co., Brit. Pat. 1,220,628 (1968).

Table 12 (cont.)

H	H	$(\text{CH}_2)_4\text{NH}_2$	H	$\text{C}_{12}\text{H}_{16}\text{N}_2$ HCl	- 218-19 (m)	252
H	H	4-pyridyl*	H	$\text{C}_{13}\text{H}_{10}\text{N}_2$ HCl methobromide bromobenzylate	203-06 (e) 210-12 220-21 (t) 285 254-56 152-53	258 38 429a 258 38 38
H	H		H	$\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3$	178-80	467
H	H		H	$\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_2$	211 (ea)	419
H	H	$\text{CH}=\text{CHCH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{13}\text{H}_{16}\text{N}_2$	108-12 (b)	527
H	H		H	$\text{C}_{13}\text{H}_{16}\text{N}_2$	214-15	38

*For further 3-(4-pyridyl)indoles and quat. salts thereof: W. J. Fanshawe, V. J. Bauer, S. R. Safir, D. A. Blicke and S. J. Riggi, J. Med. Chem., **13**, 993 (1970).

Table 12 (cont.)

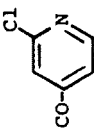
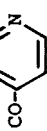
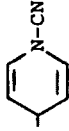
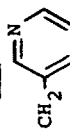
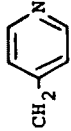
H	H	$\text{COCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$ picrate HCl methiodide	116-18 175-78(e) 179-80(m) 208-09(m)	527, 571, 575 527 527 527
H	H	$(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	H	$\text{C}_{13}\text{H}_{18}\text{N}_2$	92-95	527
H	H	$\text{HOCHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	$\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$	149-51(b)	527, 571, 579
H	H		H	$\text{C}_{14}\text{H}_9\text{ClN}_2\text{O}$	235-36	416
H	H		H	$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}$	235-36	416
H	H		H	$\text{C}_{14}\text{H}_{11}\text{N}_3$	143-44	416
H	H		H	$\text{C}_{14}\text{H}_{12}\text{N}_2$	151-54	188
H	H		H	$\text{C}_{14}\text{H}_{12}\text{N}_2$	108-11(b)	188
CH_3	H	γ -pyridyl	H	$\text{C}_{14}\text{H}_{12}\text{N}_2$	163	429a

Table 12 (cont.)

H	CH ₃		γ -pyridyl	H	C ₁₄ H ₁₂ N ₂	187, 195	429a
H	H			H	C ₁₄ H ₁₂ N ₂	191	429a
H	H		HOCH-	H	C ₁₄ H ₁₂ N ₂ O	157-58 (m)	29
H	H			H	C ₁₄ H ₁₄ N ₂ O ₃	170 169-72	466 467
H	H			H	C ₁₄ H ₁₅ N ₃ O ₂ several diastereomers and racemates	213 242-45 184	419, 467 419, 467 419
H	H			H	C ₁₄ H ₁₆ N ₂	218-20	38
H	H			H	C ₁₄ H ₁₆ N ₂ HCl	- 218-19 (e)	370
H	H			H	C ₁₄ H ₁₈ N ₂	175-76	38

Table 12 (cont.)

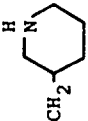
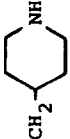
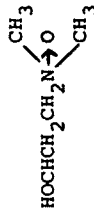
H	H		H	$C_{14}H_{18}N_2$ picrate	- 95-102(w)	188
H	H		H	$C_{14}H_{18}N_2$ HCl	155(m) 171(w) 178-80 253-54 260	29 191, 533 188 29 191
CH ₃	H	$CH=CHCH_2N(CH_3)_2$	H	$C_{14}H_{18}N_2$ trinitrofluorene- complex	-	527
H	H	$CO(CH_2)_4NHCH_3$	H	$C_{14}H_{18}N_2O$	108-13	416
CH ₃	H	$COCH_2CH_2N(CH_3)_2$	H	$C_{14}H_{18}N_2O$ HCl	- 185-86(m) 186-87(m)	575 527
H	H		H	$C_{14}H_{18}N_2O$ picrate methiodide	101-02(ea) 219 174-77(m)	527, 575 527 620
CH ₃	H	$HOCHCH_2CH_2N(CH_3)_2$	H	$C_{14}H_{20}N_2O$	88	527, 574
CH ₃	H		H	$C_{14}H_{20}N_2O_2$	103/140	574

Table 12 (cont.)

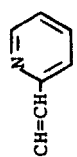
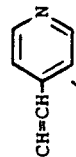
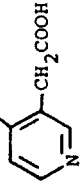
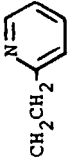
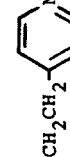
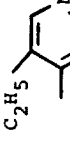
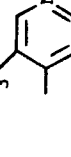
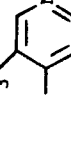
H	H		H	$C_{15}H_{12}N_2$ methiodide	-	437 83 83
H	H		H	ethiodide	260-65 (m) 273 285	193 193
H	H		H	$C_{15}H_{12}N_2$ quat. salts	-	429a
H	H		H	$C_{15}H_{12}N_2O_2$	182-84 (m)	192 258 192, 258 192 193
H	H		H	$C_{15}H_{14}N_2$ HCl methobromide quat. salts	118-20 (ip) 157-59 226-27	192 258 192, 258 192 193
H	H		H	$C_{15}H_{14}N_2$ HCl methobromide quat. salts	149-51 (ip) 260-62 211-13	192 258 192, 258 192 193, 194, 257
H	H		H	$C_{15}H_{14}N_2$	178 (m)	429a
H	CH ₃		H	$C_{15}H_{14}N_2$	197 (m)	429a

Table 12 (cont.)

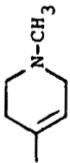
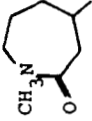
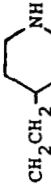
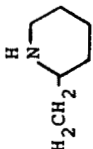
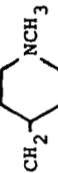
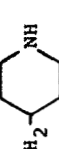
CH ₃	CH ₃	γ-pyridyl	H	C ₁₅ H ₁₄ N ₂	171	429a
CH ₃	H		H	C ₁₅ H ₁₈ N ₂	94-95 (t)	38
H	H		H	C ₁₅ H ₁₈ N ₂ O	149-50 (ea)	226
H	H		H	C ₁₅ H ₂₀ N ₂ HCl	162-63 213-15	194 194, 257
H	H		H	C ₁₅ H ₂₀ N ₂	139-41	194
H	H		H	C ₁₅ H ₂₀ N ₂ HCl	- 224-25 (m)	29
CH ₃	H		H	C ₁₅ H ₂₀ N ₂ HCl	- 203-05 (e)	533
H	H		H	C ₁₅ H ₂₀ N ₂ HCl	- 286-88 (e)	533

Table 12 (cont.)

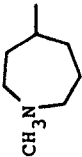
H	H		H	$C_{15}H_{20}N_2$	81-85(et)	226
CH ₃	H		H	$C_{15}H_{20}N_2O$	80-81	527, 575
C ₂ H ₅	H		H	$C_{15}H_{20}N_2O$ methiodide	- 192-94 (m)	527
H	H		H	$C_{16}H_{13}N_3O$ methiodide	- 310	83
CH ₃	H		H	$C_{16}H_{16}N_2$ HCl quat. salts	b.p. 170-85 (0.5 mm.) 159-60	258 192, 258 258 193
CH ₃	H		H	$C_{16}H_{16}N_2$ HCl quat. salts	85-87 (ip) 96-98 (ac) 152-53	258 192, 258 192, 258 193
H	CH ₃	"	H	$C_{16}H_{16}N_2$ HCl	153-54 (ip) 242-43	195, 258 195, 258
H	H		H	$C_{16}H_{16}N_2$	126-27 (m)	550, 551

Table 12 (cont.)

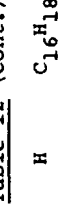
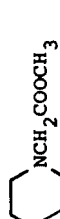
H	H		H	$C_{16}H_{18}N_2O_2$	178-80 (w)	38
H	H		H	$C_{16}H_{20}N_2O_2$	120-21 (w)	38
CH ₃	H		H	$C_{16}H_{22}N_2$ HCl	65-66 200-01 (ip)	194, 257 194, 257
H	CH ₃		H	$C_{16}H_{22}N_2$	212-15 (e)	43
H	CH ₃		H	$C_{16}H_{22}N_2$	260-62 (e)	43
H	H		H	$C_{16}H_{22}N_2$ HCl methiodide	138-40 (b) 170-73 246-48 (m)	17, 192 192 437
H	H		H	$C_{16}H_{22}N_2$ HCl	172-73 (e) 206-08	192 258 192, 258

Table 12 (cont.)

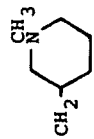
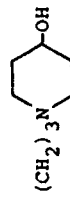
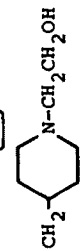
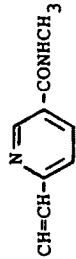
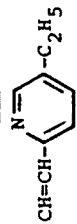
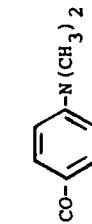
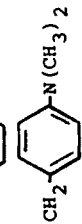
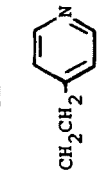
CH ₃	H		H	C ₁₆ H ₂₂ N ₂	112-14 (cyh)	188
H	H		H	C ₁₆ H ₂₂ N ₂ O	195-98 (ea)	505
H	H		H	C ₁₆ H ₂₂ N ₂ O	114-15 (b)	533
H	H		H	C ₁₇ H ₁₅ N ₃ O methiodide	- 308	83
H	H		H	C ₁₇ H ₁₆ N ₂ methiodide ethiodide	294 248	83 83
H	H		H	C ₁₇ H ₁₆ N ₂ O	212-13 (e)	551
H	H		H	C ₁₇ H ₁₈ N ₂ HI methiodide	143-44 189-90 (w) 206-07 (w)	550, 551, 556 551 551
C ₂ H ₅	H		H	C ₁₇ H ₁₈ N ₂ HCl	45-50 167-69	195, 258 195, 258

Table 12 (cont.)

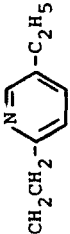
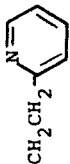
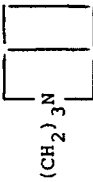
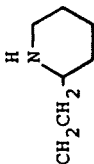
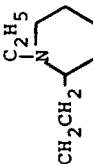
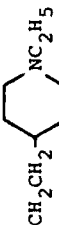
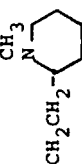
H	H		H	C ₁₇ H ₁₈ N ₂ HCl	112-13 (ip) 164-66	192 258 192, 258
CH ₃	CH ₃			C ₁₇ H ₁₈ N ₂ HCl	- 249-50 (e)	43
H	C ₆ H ₅	(CH ₂) ₃ NH ₂		C ₁₇ H ₁₈ N ₂ HCl	- 130-32 (e)	287
H	H			C ₁₇ H ₂₂ N ₂ HCl	- 182-83 (ip)	504
CH ₃	CH ₃			C ₁₇ H ₂₄ N ₂ HCl	- 236 (e)	43
H	H			C ₁₇ H ₂₄ N ₂ HCl HI	132 (b) 170-73 (et) 66-67	83 83 83
H	H			C ₁₇ H ₂₄ N ₂	125-26 (e)	258
CH ₃	H			C ₁₇ H ₂₄ N ₂ HCl	b.p. 165-67 (0.5 mm.) 187-88	192 258 192, 258

Table 12 (cont.)

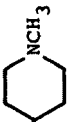
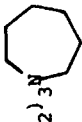
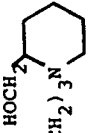
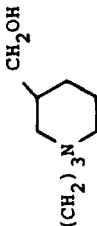
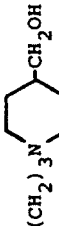
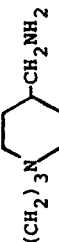
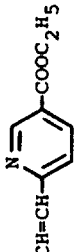
CH ₃	H		H	C ₁₇ H ₂₄ N ₂ HCl	158-60 b.p. 155-62 (0.5 mm.) 143-45	192 258 192
H	H		H	C ₁₇ H ₂₄ N ₂ HCl	- 194-96	504
H	H		H	C ₁₇ H ₂₄ N ₂ O	151-55 (ea)	505 505a
H	H		H	C ₁₇ H ₂₄ N ₂ O	161-64 (ea)	505 505a
H	H		H	C ₁₇ H ₂₄ N ₂ O	152-53 (ea)	505 505a
H	H		H	C ₁₇ H ₂₅ N ₃	116 (ea)	505, 505a
H	H		H	C ₁₈ H ₁₆ N ₂ O ₂ methiodide 4-CH ₃ C ₆ H ₄ SO ₃ H	- 260-65 294-97	437 437

Table 12 (cont.)

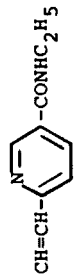
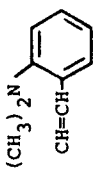
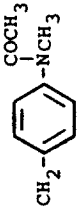
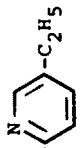
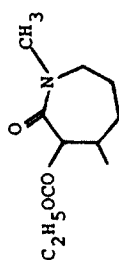
H	H		H	$C_{18}H_{17}N_3O$ methiodide ethiodide	- 308 297	83 83
H	H		H	$C_{18}H_{18}N_2$ picrate	- 145-49 (m)	234
H	H		H	$C_{18}C_{18}N_2O$	159 (e)	551
H	H		H	$C_{18}H_{19}N_3O$	146-47 (b)	162a
CH ₃	H		H	$C_{18}H_{20}N_2$ quat. salts b.p.	175-200 (0.5 mm.)	258 193
H	H		H	$C_{18}H_{22}N_2O_3$	198-200 (m)	226

Table 12 (cont.)

H	H		H	$C_{18}H_{24}N_2$ HCl	- 193-94 (ip)	504
H	H		H	$C_{18}H_{24}N_2O_2$	76-77 (ea)	505a
H	H		H	$C_{18}H_{25}N_3O$	140-41 (ea)	505
H	H		H	$C_{18}H_{26}N_2$ HCl	- 177-79 (e)	504
H	H		H	$C_{18}H_{26}N_2$ HCl	- 195-97 (e)	504
H	H		H	$C_{18}H_{26}N_2O$	129-30 (ea)	505
H	H		H	$C_{18}H_{26}N_2O$	140-41 (ea)	505
H	H		H	$C_{18}H_{26}N_2O$	198-201 (ea)	505
H	H		H	$C_{18}H_{26}N_2O$	164-65 (ea)	505 505a

Table 12 (cont.)

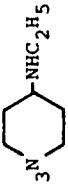
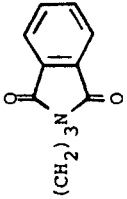
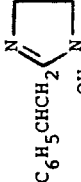
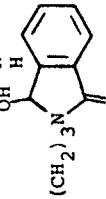
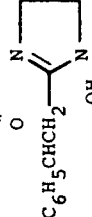
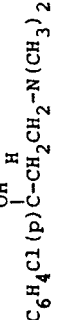
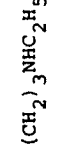
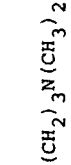
H	H		H	$C_{18}H_{27}N_3$ di-HCl	- 277-79 (m)	505 505a
H	H		H	$C_{19}H_{16}N_2O_2$	131-32 (e)	595 265a
H	H		5-Cl	$C_{19}H_{18}ClN_3$ HCl	- 258 (m)	236
H	H		H	$C_{19}H_{18}N_2O_2$	167-68	595
H	H		H	$C_{19}H_{19}N_3$ HCl	- 112 (e)	236
H	H		H	$C_{19}H_{21}ClN_2O$	142-43 (b)	575
H	C_6H_5		H	$C_{19}H_{22}N_2$ HCl	- 222-23 (e)	287
H	C_6H_5		H	$C_{19}H_{22}N_2$ HCl	- 200-01 (e)	287

Table 12 (cont.)

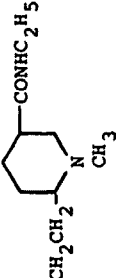
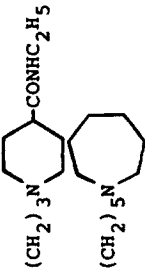
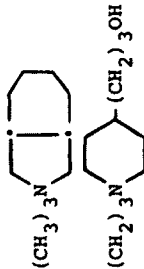
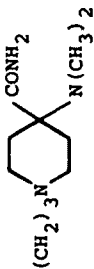
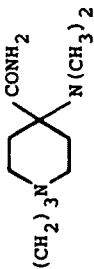
H	H	$\text{C}_6\text{H}_5\text{C}(\text{OH})\text{CH}_2\text{CH}_2\text{-N}(\text{CH}_3)_2$	H	$\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$	150-52	575
H	H		H	$\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}$ HCl	138-40 (b) 174-76	83 83
H	H		H	$\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}$	147-48 (ea)	505a
H	H		H	$\text{C}_{19}\text{H}_{28}\text{N}_2$ HCl	- 159-64 (e)	- 504
H	H		H	$\text{C}_{19}\text{H}_{28}\text{N}_2$ HCl	- 191-203 (m)	- 504
H	H		H	$\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}$	156-58 (ea)	505
H	H		H	$\text{C}_{19}\text{H}_{28}\text{N}_4\text{O}$	151	616

Table 12 (cont.)

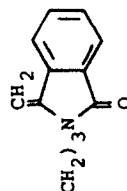
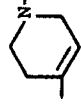
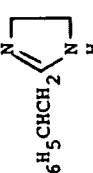
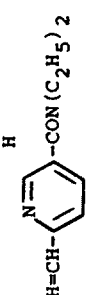
H	H		H	$C_{19}H_{29}N_3$ di-HCl	-	505 505a
H	H		H	$C_{20}H_{18}N_2O$	130-31 (c)	595
H	H		H	$C_{20}H_{19}ClN_2$	195	38
H	H		H	$C_{20}H_{20}N_2$	161-62	38
H	CH ₃		H	$C_{20}H_{21}N_3$ HCl	- 267 (e)	236
H	H		H	$C_{20}H_{21}N_3O$ HCl	- 120 (e)	236
H	H		H	$C_{20}H_{21}N_3O$ methiodide	- 250	83

Table 12 (cont.)

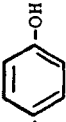
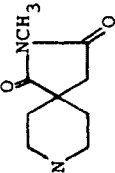
H	C ₆ H ₅	(CH ₂) ₃ NH-CH ₂ CH ₂ CH ₃	H	C ₂₀ H ₂₄ N ₂ HCl	-	228-30 (e)	287
H	C ₆ H ₅	(CH ₂) ₃ NHCH(CH ₃) ₂	H	C ₂₀ H ₂₄ N ₂ HCl	-	272-74 (e)	287
CH ₃	C ₆ H ₅	(CH ₂) ₃ N(CH ₃) ₂	H	C ₂₀ H ₂₄ N ₂	47-49 (p)	20	
H	H	CH ₂ CH ₂ CHN(CH ₃)CH ₂ - 	H	C ₂₀ H ₂₄ N ₂ O HCl	175-200 ca. 203	476, 478 476, 478	
CH ₃	H	C ₆ H ₅ CH ₂ CH ₂ N(CH ₃) ₂	H	C ₂₀ H ₂₄ N ₂ O	148-49 (b)	575	
H	H	(CH ₂) ₃ N 	H	C ₂₀ H ₂₅ N ₃ O ₂ HCl	-	233	616
H	H	(CH ₂) ₆ N 	H	C ₂₀ H ₃₀ N ₂ HCl	-	146-48	504
H	H	(CH ₂) ₃ N 	H	C ₂₀ H ₃₀ N ₂ O	130-33 (ea)	505	

Table 12 (cont.)

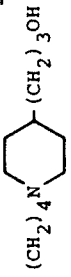
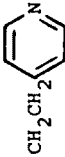
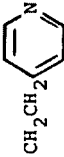
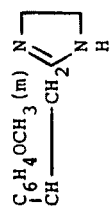
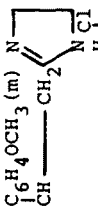
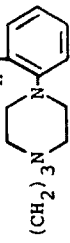
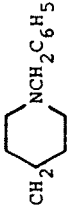
H	H		H	$C_{20}H_{30}N_2O$	140-42 (ea)	505
C_6H_5	H		H	$C_{21}H_{18}N_2$	b.p. 225-30 (0.3 mm.)	258
H	C_6H_5		H	$C_{21}H_{18}N_2$	200-01 (e)	73
H	CH_3		5-Cl	$C_{21}H_{22}ClN_3O$ HCl	- 273 (m)	236
H	H		H	$C_{21}H_{22}N_2O_2$	133-34 (b)	595
H	CH_3		H	$C_{21}H_{23}N_3O$ HCl	- 224 (e)	236
H	H		H	$C_{21}H_{24}ClN_3$	141-44	504a
H	H		H	$C_{21}H_{24}N_2$ HCl	- 248-50 (e) 242 (e)	188 533

Table 12 (cont.)

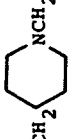
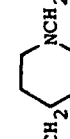
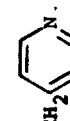
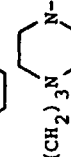
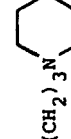
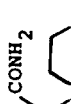
H	C ₆ H ₅	(CH ₂) ₃ N 	H	C ₂₁ H ₂₄ N ₂ HCl	121 (b) 142-44 (e)	287 287
H	C ₆ H ₅	(CH ₂) ₃ N 	H	C ₂₁ H ₂₄ N ₂ O	137 (e)	287
H	H	CH ₂  NCH ₂ CH ₂ 	H	C ₂₁ H ₂₅ N ₃	127-28 (b)	533
H	H	CH ₂  NCH ₂ CH ₂ 	H	C ₂₁ H ₂₅ N ₃	127-28 (b)	533
H	H	(CH ₂) ₃ N  N-C ₆ H ₅	H	C ₂₁ H ₂₅ N ₃	125-27 127-28 (e)	143 504a
H	C ₆ H ₅	(CH ₂) ₃ N(C ₂ H ₅) ₂	H	C ₂₁ H ₂₆ N ₂ HCl	72-73 (p) 166-67 (e)	287 287
H	C ₆ H ₅	(CH ₂) ₃ NH-C ₄ H ₉	H	C ₂₁ H ₂₆ N ₂ HCl	- 218-20 (e)	287
H	H	(CH ₂) ₃ N  C(=O)NH ₂ 	H	C ₂₁ H ₃₀ N ₄ O ₂	207	616

Table 12 (cont.)

H	H		H	$C_{21}H_{31}N_3$	145	616
H	H		H	$C_{21}H_{31}N_3O$ HI tartrate	213-14 (b) 110-12 (ea) 124-26 (ea)	83 83 83
H	H		H	$C_{21}H_{32}N_2O$	142-43 (ea)	505
H	H		H	$C_{21}H_{33}N_3$ di-HCl	- 202-08 (e)	505 505a
$CH_2C_6H_5$	H		H	$C_{22}H_{20}N_2$ HCl H_2SO_4 quat. salts	b.p. 225-30 (0.3 mm.) 199-200 180-83 -	258 192 192, 258 258 193
CH_3	C_6H_5		H	$C_{22}H_{20}N_2$	88 (p)	73
H	H		H	$C_{22}H_{22}N_2O_2$	154-56	513

Table 12 (cont.)

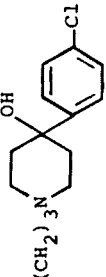
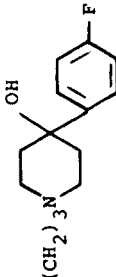
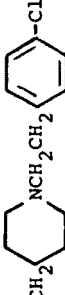
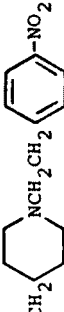
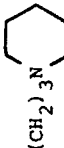
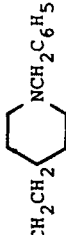
H	H		5-F	$C_{22}H_{24}ClFN_2O$ HCl	- 237(m)	614
H	H	"	5-Cl	$C_{22}H_{24}Cl_2N_2O$	146-47 (t)	614
H	H		5-F	$C_{22}H_{24}F_2N_2O$ HCl	100-05 (ea)	614
H	H		H	$C_{22}H_{25}ClN_2$	126-27 (b)	533
H	H		H	$C_{22}H_{25}N_3O_2$	156-57 (e)	533
H	H		H	$C_{22}H_{26}N_2$	130-31 (e)	533
H	C_6H_5		H	$C_{22}H_{26}N_2$	156 (e)	287
H	H		H	$C_{22}H_{26}N_2$ HCl	91-92 192-93 (e)	194, 257 194, 257

Table 12 (cont.)

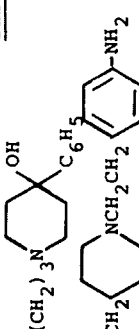
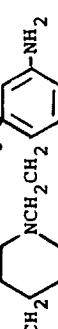
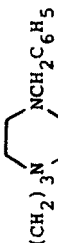
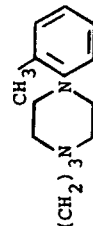
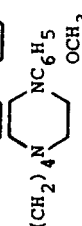
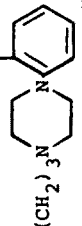
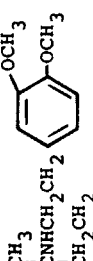
H	H		H	$C_{22}H_{26}N_2O$ HCl	-	615
H	H		H	$C_{22}H_{27}N_3$	135(e)	533
H	H		H	$C_{22}H_{27}N_3$	90-92	143
H	H		H	$C_{22}H_{27}N_3$	102-14	504a
H	H		H	$C_{22}H_{27}N_3$	96-101	504a
H	H		H	$C_{22}H_{27}N_3O$	157-59	504a
H	H		H	$C_{22}H_{28}N_2O_2$ HCl	-	476
H	H		H	$C_{22}H_{34}N_2O$ HCl	164-71(ip) 182-84(w)	505 505

Table 12 (cont.)

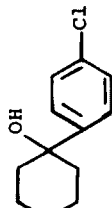
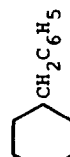
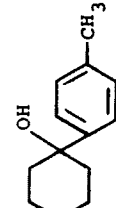
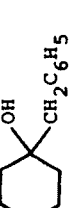
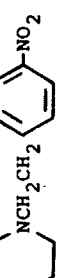
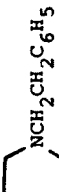
H	H		5-CH ₃ C ₂₃ H ₂₇ ClN ₂ O HCl	- 164 (e)	614
H	H		5-F C ₂₃ H ₂₇ N ₂	117 (ea)	505a
H	H		5-F C ₂₃ H ₂₇ N ₂ O HCl	- 202 (m)	614
H	H		5-F C ₂₃ H ₂₇ N ₂ O	148-50 (t)	614
H	H		H C ₂₃ H ₂₇ N ₃ O ₂ HCl	173-75 (c) 254-55 (ip)	194, 257 194, 257
CH ₃	H		H C ₂₃ H ₂₈ N ₂	99-100 (e)	533
H	H		H C ₂₃ H ₂₈ N ₂ HCl methobromide hydrogenmaleate	130-32 (e) 225-26 (ip) 233-34 103-106	194, 257 194, 257 257 257
H	H		H C ₂₃ H ₂₈ N ₂	122-24 (ea)	505a

Table 12 (cont.)

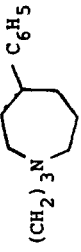
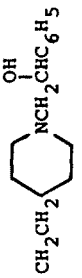
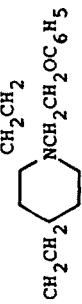
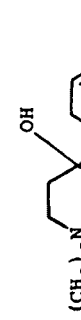
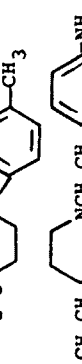
H	C ₆ H ₅		H	C ₂₃ H ₂₈ N ₂ HCl	119-20 (b) 217-18 (e)	287 287
H	H		H	C ₂₃ H ₂₈ N ₂ HCl	- 225-28 (m/w)	504
H	H		H	C ₂₃ H ₂₈ N ₂ HCl	133-35 (e) 193-94 (e)	194, 257 194, 257
H	H		H	C ₂₃ H ₂₈ N ₂ HCl	- 123-25	194
H	H		H	C ₂₃ H ₂₈ N ₂ HCl methobromide	102-03 (e) 170 (m) 206-08 (ip)	194, 257 194, 257 257
H	H		H	C ₂₃ H ₂₈ N ₂ HCl	143 (ea)	614
H	H		H	C ₂₃ H ₂₈ N ₂ di-HCl	- 293 (m)	194

Table 12 (cont.)

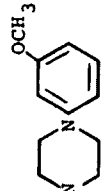
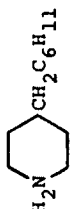
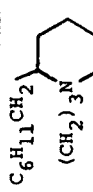
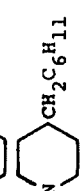
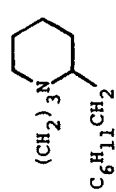
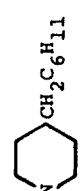
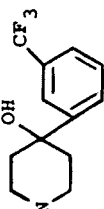
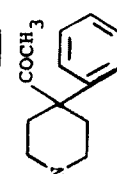
H	H		H	$C_{23}H_{29}N_3O$ HCl	-	504a
H	H		H	$C_{23}H_{32}N_2$	149-53 (ea)	505a
H	H		5-F	$C_{23}H_{33}FN_2$	120-22 (h)	505a
H	H		5-F	$C_{23}H_{33}FN_2$	104-07 (h)	505a
H	H		H	$C_{23}H_{34}N_2$	113-15 (h)	505a
H	H		H	$C_{23}H_{34}N_2$	110-12 (h)	505a
CH ₃	H		5-F	$C_{24}H_{26}F_4N_2O$ H_2SO_4	207	614
H	H		5-F	$C_{24}H_{27}FN_2O$ HCl	249 (m)	614

Table 12 (cont.)

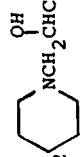
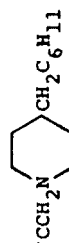
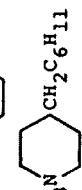
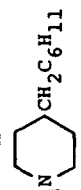
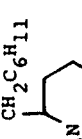
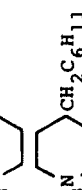
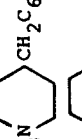
H	H		H	$C_{24}H_{30}N_2O_2$ HCl	96-97 (e)	194, 257
H	H		H	$C_{24}H_{32}N_2$	196-97 (e)	194, 257
H	H		5-CF ₃	$C_{24}H_{33}F_3N_2$	66-68 (h)	505a
H	H		5-F	$C_{24}H_{35}FN_2$	119-20 (h)	505a
H	CH ₃		H	$C_{24}H_{36}N_2$	124-27 (ea)	505a
H	CH ₃		H	$C_{24}H_{36}N_2$ 2,3,4,5,6-pentachloro- benzochloride	115-17 (h)	505a
H	H		5-CH ₃	$C_{24}H_{36}N_2$	129-47 (ip)	505a
H	H		H	$C_{24}H_{36}N_2$ $C_2H_5SO_3H$	87-105 (h)	505a
					-	
					138-39 (ac)	505a

Table 12 (cont.)

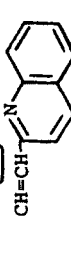
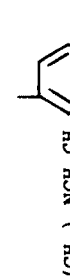
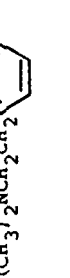
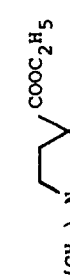
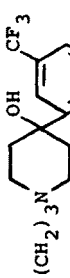
H	H		H	$C_{24}H_{36}N_2$	97-98 (h)	505a
H	H		H	$C_{25}H_{18}N_2$ CH_3I	- 252 (e)	204
H	H		H	$C_{25}H_{24}N_2O$ HCl	130-32 (b) 189-90 (m)	527 527, 575
CH ₃	C_6H_5		H	$C_{25}H_{26}N_2$ dipicrate H_2SO_4	- 130 (dec) above 120 (dec)	20 20
H	H		5-F	$C_{25}H_{29}FN_2O_2$ HCl	- 203 (ip)	614
H	H		4,7-di- CH_3	$C_{25}H_{29}F_3N_2O$ HCl	- 246-47 (e)	614
H	H		5-CF ₃	$C_{25}H_{35}F_3N_2$	143-46 (ea)	505a
H	H		H	$C_{25}H_{38}N_2$ $C_2H_5SO_3H$	126-27 (ea) 124-26 (ip)	505a 505a

Table 12 (cont.)

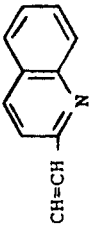
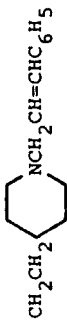
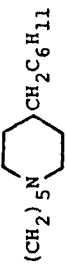
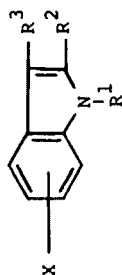
H	4-CH ₃ OC ₆ H ₄		H	C ₂₆ H ₂₀ N ₂ O HCl	- 167	76
H	C ₆ H ₅		H	C ₂₆ H ₂₈ N ₂ O HCl	- 126(ac)	262
CH ₃	CH ₃		H	C ₂₆ H ₃₂ N ₂ HCl	- 236-38(e)	43
H	CH ₃		H	C ₂₆ H ₄₀ N ₂ 4-CH ₃ C ₆ H ₄ SO ₃ H	- 178-80(ip)	505a
H	H		H	C ₂₆ H ₄₀ N ₂	82-84(h)	505a

Table 13. 4-, 5-, 6- and 7-Aminoindoles



R ¹	R ²	R ³	X	m.p., °C	Ref.
H	H	H	4-NH ₂	105-07 (subl) 108 (et)	591 407
H	H	H	5-NH ₂	127-29 (p) 129-30 (h) 130-32 (w)	208 541 273
H	H	H	6-NH ₂	66-67 64-67 68-70 241-2 (et)	72 273 407 72
H	H	H	7-NH ₂	99-101 (ip)	273
CH ₃	H	H	5-NH ₂	143-44	540
H	CH ₃	H	5-NH ₂	156-57 (h) 152-56 (subl) 157-59 (b)	541 11 9
CH ₃	H	H	6-NH ₂	b.p. 156 (3 mm.)	539

Table 13 (cont.)

H	CH ₃	H	6-NH ₂	C ₉ H ₁₀ N ₂	84-85 (CCl ₄)	541
COCH ₃	H	H	5-NH ₂	C ₁₀ H ₁₀ N ₂ O	185-86 (e/w)	255
COCH ₃	H	H	6-NH ₂	C ₁₀ H ₁₀ N ₂ O	181	255
H	H	H	4-NHCOCH ₃	C ₁₀ H ₁₀ N ₂ O	154-56 (e)	591
H	H	H	5-NHCOCH ₃	C ₁₀ H ₁₀ N ₂ O	117-18	186a
H	H	H	6-NHCOCH ₃	C ₁₀ H ₁₀ N ₂ O	170-71 (b) 169	72 407
H	CH ₃	CH ₃	4-NH ₂	C ₁₀ H ₁₂ N ₂	156-60 (dist)	483
H	CH ₃	CH ₃	5-NH ₂	C ₁₀ H ₁₂ N ₂	173-74 (e/w) 177-78	483 585
H	CH ₃	CH ₃	6-NH ₂	C ₁₀ H ₁₂ N ₂	117-18 (dist) 119-20 (b)	483 71
H	H	C ₂ H ₅	5-NH ₂	C ₁₀ H ₁₂ N ₂	116-18 (dist)	483
H	H	H	6-N(CH ₃) ₂	C ₁₀ H ₁₂ N ₂	106-07	321, 324
H	CH ₃	CH ₃	7-NH ₂	C ₁₀ H ₁₂ N ₂ HCl	131-32 (b) 360 (?)	585 159

Table 13 (cont.)

H	CH ₃	H	5-NHCOCH ₃	C ₁₁ H ₁₂ N ₂ O	159-61(e)	9
H	CH ₃	C ₂ H ₅	4-NH ₂	C ₁₁ H ₁₄ N ₂	127-28 116-18	585 159
CH ₃	CH ₃	CH ₃	5-NH ₂	C ₁₁ H ₁₄ N ₂ picrate	- 203-05(e)	483
H	CH ₃	C ₂ H ₅	5-NH ₂	C ₁₁ H ₁₄ N ₂	146-48(subl) 148-49(dist)	9 483 585
H	CH ₃	C ₂ H ₅	6-NH ₂	C ₁₁ H ₁₄ N ₂	84-85 96-97(p)	585 159
H	CH ₃	C ₂ H ₅	7-NH ₂	C ₁₁ H ₁₄ N ₂	110-12(dist) 116-117	483 585
H	CH ₃	CH ₃	6-NHCOCH ₃	C ₁₂ H ₁₄ N ₂ O	211-12(e)	71
H	H	C ₂ H ₅	5-N(CH ₃) ₂	C ₁₂ H ₁₆ N ₂ picrate	- 200-02(e)	181
H	H	H		C ₁₃ H ₁₆ N ₂	117-18	281
H	H	H		C ₁₃ H ₁₆ N ₂	154-55	281

Table 13 (cont.)

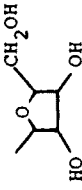
	H	H	4-NH ₂	C ₁₃ H ₁₆ N ₂ O ₄	60	591
H	CH ₃	n-C ₄ H ₉	5-NH ₂	C ₁₃ H ₁₈ N ₂	96-98 (dist)	483
H	C ₆ H ₅	H	5-NH ₂	C ₁₄ H ₁₂ N ₂	231-33 (b)	9
H	H	H	4-NHCOC ₆ H ₅	C ₁₅ H ₁₂ N ₂ O	195-96 (e)	591
H	H	H	5-NHCOC ₆ H ₅	C ₁₅ H ₁₂ N ₂ O	166-67 (b)	541
H	H	H	7-NHCOC ₆ H ₅	C ₁₅ H ₁₂ N ₂ O	217-18 (e)	273
CH ₃	H	H	5-NHCOC ₆ H ₅	C ₁₆ H ₁₄ N ₂ O	191-92 (t)	540
CH ₃	H	H	6-NHCOC ₆ H ₅	C ₁₆ H ₁₄ N ₂ O picrate	160-61 (x) 151-52	539 539
H	CH ₃	H	6-NHCOC ₆ H ₅	C ₁₆ H ₁₄ N ₂ O	210 (e)	541
H	C ₆ H ₅	H	5-NHCOCH ₃	C ₁₆ H ₁₄ N ₂ O	215-16 (e)	9
H	H	H	5-NHCOCOC ₆ H ₅	C ₁₆ H ₁₄ N ₂ O ₂	114-15	186a
CH ₃	H	H	5-N 	C ₁₇ H ₁₂ N ₂ O ₂	211-12 (b)	540

Table 13 (cont.)

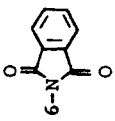
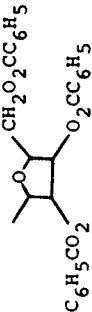
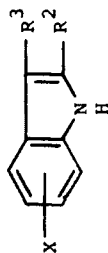
CH ₃	H	H		C ₁₇ H ₁₂ N ₂ O ₂	189-90 (b)	539
H	H	CH ₂ C ₆ H ₅	5-N(CH ₃) ₂	C ₁₇ H ₁₈ N ₂	63-64 (cyh)	181
COC ₆ H ₅	H	H	4-NHCOC ₆ H ₅	C ₂₂ H ₁₆ N ₂ O ₂	220-25	591
	H	H	4-NHCOC ₆ H ₅	C ₄₁ H ₃₂ N ₂ O ₈	163-65 (ea)	591

Table 14. 4-,5-,6-and 7-Indolyl-C-N Derivatives



R ²	R ³	X	m.p., °C	Ref.
H	H	4-CH ₂ NH ₂	132-34 (c)	455
H	H	6-CH ₂ NH ₂	134-35 (c)	455
H	H	4-CH ₂ NHCH ₃	90-92 (c)	455
H	H	6-CH ₂ NHCH ₃	120-21 (c)	455
CH ₃	H	6-CH ₂ NH ₂	107-08 (c)	455
CH ₃	H	6-CH ₂ NHCH ₃	133-35 (c)	455
CH ₃	CH ₃	5-CH ₂ NH ₂	153-55 (cyh) 156-58 (et)	68 543
CH ₃	CH ₃	6-CH ₂ NH ₂	117-18 (cyh)	68
CH ₃	CH ₃	7-CH ₂ NH ₂	131-32 (cyh)	68

Table 14 (cont.)

H	H	4-CH ₂ NHCOOC ₂ H ₅	C ₁₁ H ₁₄ N ₂ O ₂	-	455
H	H	6-CH ₂ NHCOOC ₂ H ₅	C ₁₁ H ₁₄ N ₂ O ₂	84-85 (c)	455
H	H	6-CH ₂ NHCH ₂ C≡CH	C ₁₂ H ₁₂ N ₂	96-98 (et)	455
H	H	4-CH ₂ NH- 	C ₁₂ H ₁₄ N ₂	89-91 (et)	457
H	H	5-CH ₂ NH- 	C ₁₂ H ₁₄ N ₂ oxalate	198-99 (m)	457
H	H	6-CH ₂ NH- 	C ₁₂ H ₁₄ N ₂ hydrogen- maleate	-	457
H	H	7-CH ₂ NH- 	C ₁₂ H ₁₄ N ₂	142-44 (ea)	457
				67-69 (et)	457
H	H	4-CH ₂ NHCH(CH ₃) ₂	C ₁₂ H ₁₆ N ₂ hydrogen- maleate	-	457
				139-40	457
H	H	5-NH ₂ NHCH(CH ₃) ₂	C ₁₂ H ₁₆ N ₂ hydrogen- oxalate	-	457
				168-70 (m)	457

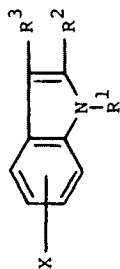
Table 14 (cont.)

H	H	6-CH ₂ NHCH(CH ₃) ₂	C ₁₂ H ₁₆ N ₂ hydrogen- oxalate	160-63 (m)	457
H	H	7-CH ₂ NHCH(CH ₃) ₂	C ₁₂ H ₁₆ N ₂ hydrogen- maleate	122-124 (ac)	457
H	H	4-CH ₂ N(CH ₃)CH ₂ C≡CH	C ₁₃ H ₁₄ N ₂	60-63 (et)	455
H	H	6-CH ₂ N(CH ₃)CH ₂ C≡CH	C ₁₃ H ₁₄ N ₂	74-76 (et)	455
H	H	6-CH ₂ -N(CH ₃)-CH=CH ₂	C ₁₃ H ₁₆ N ₂	78-80 (et)	455
CH ₃	H	6-CH ₂ NHCOOC ₂ H ₅	C ₁₃ H ₁₆ N ₂ O ₂	89-91 (c)	455
CH ₃	CH ₃	5-CH ₂ N(CH ₃) ₂	C ₁₃ H ₁₈ N ₂ picrate HCl CH ₃ I	95-96 (p) 96-98 195-96 (e) 212-14 206-08 (et)	68 543 432 543 543
CH ₃	CH ₃	6-CH ₂ N(CH ₃) ₂	C ₁₃ H ₁₈ N ₂	132-33 (et)	68

Table 14 (cont.)

CH ₃	CH ₃	7-CH ₂ N(CH ₃) ₂	C ₁₃ H ₁₈ N ₂ maleate	- 188-89(ea)	68
CH ₃	C ₃ H ₇	5-CH ₂ NH ₂	C ₁₃ H ₁₈ N ₂ picrate HCl	86-88(et) 180(e) 216-18(et)	544 544 544
CH ₃	H	$\begin{array}{c} \text{CH}_3 \\ \\ 6\text{-CH}_2\text{NCH}_2\text{C}\equiv\text{CH} \end{array}$	C ₁₄ H ₁₆ N ₂	80-82(et)	455
H	H	6-CH ₂ N(CH ₂ C≡CH) ₂	C ₁₅ H ₁₄ N ₂	87-88(et)	455
CH ₃	C ₃ H ₇	5-CH ₂ N(CH ₃) ₂	C ₁₅ H ₂₂ N ₂ picrate CH ₃ I	93-94 b.p. 197-98(4 mm.) 115-17(e) 176-78(dec)	544 544 544 544
CH ₃	CH ₃	5-CH ₂ N(C ₂ H ₅) ₂	C ₁₅ H ₂₂ N ₂ picrate HCl	b.p. 171-72 183-85 180-82	543 543 543
CH ₃	C ₃ H ₇	"	C ₁₇ H ₂₆ N ₂ picrate CH ₃ I	b.p. 208-10(6 mm.) 140-42(e) 125-27(dec)	544 544 544
CH ₃	CH ₃	5-CH ₂ NHCH ₂ C ₆ H ₅	C ₁₈ H ₂₀ N ₂	92(p)	68
CH ₃	CH ₃	6-CH ₂ NHCH ₂ C ₆ H ₅	C ₁₈ H ₂₀ N ₂ maleate	- 177	68
CH ₃	CH ₃	7-CH ₂ NHCH ₂ C ₆ H ₅	C ₁₈ H ₂₀ N ₂ HCl	- 197-98(b)	68

Table 15. 4-,5-,6- and 7-Indolyl-C-C-N Derivatives



R ¹	R ²	R ³	X		m.p., °C	Ref.
H	H	H	4-CH ₂ CH ₂ NH ₂	C ₁₀ H ₁₂ N ₂ hydrogen-oxalate	94-96 (et)	460, 461, 564
H	H	H	5-CH ₂ CH ₂ NH ₂	C ₁₀ H ₁₂ N ₂	207-08 (m)	461
H	H	H	6-CH ₂ CH ₂ NH ₂	C ₁₀ H ₁₂ N ₂ hydrogen-maleate	121-23 (ea)	564
H	H	H	7-CH ₂ CH ₂ NH ₂	C ₁₀ H ₁₂ N ₂ hydrogen-maleate	159-61 (ea)	564
H	H	H	4-CH ₂ CH ₂ NHCH ₃	C ₁₁ H ₁₄ N ₂ hydrogen-oxalate	159-61 (ea)	461
H	H	H	4-CH ₂ CHN(CH ₃) ₂	C ₁₁ H ₁₄ N ₂ hydrogen-oxalate	173-74 (m)	564
H	H	H	4-CH ₂ CHN(CH ₃) ₂	C ₁₁ H ₁₄ N ₂	193-95 (m)	461
H	H	H	4-CH ₂ CHN(CH ₃) ₂	C ₁₁ H ₁₄ N ₂	157-59 (ea)	460, 564

Table 15 (cont.)

H	H	H	CH ₃ 5-CH ₂ CHNH ₂	C ₁₁ H ₁₄ N ₂ hydrogen- oxalate	81-83 (b)	460, 564
H	H	H	CH ₃ 6-CH ₂ CHNH ₂	C ₁₁ H ₁₄ N ₂ hydrogen- maleate salts of rac., (+)- and (-)-form:	199-201 (m)	460
			OH 5-CHCH ₂ NHCH ₃		138-40 (c)	460, 564
H	H	H	5-COCH ₂ N(CH ₃) ₂	C ₁₁ H ₁₄ N ₂ O	159-61 (ea)	460
H	H	H	CH ₃ 5-COCHNHCH ₃	C ₁₂ H ₁₄ N ₂ O	144-48 (et)	564
H	H	H	4-CH ₂ CH ₂ N(CH ₃) ₂	C ₁₂ H ₁₄ N ₂ O	181-84 (b)	564
H	H	H	C ₂ H ₅ 4-CH ₂ CHNH ₂	C ₁₂ H ₁₄ N ₂ O	170-74 (m)	564
H	H	H	C ₂ H ₅ 6-CH ₂ CHNH ₂	C ₁₂ H ₁₆ N ₂ CH ₃ SO ₃ H	-	
					148-50 (m)	564
					104-06 (et)	460
H	H	H		C ₁₂ H ₁₆ N ₂ hydrogen- maleate	-	
					136-39 (ea)	460

Table 15 (cont.)

H	H	H	C_2H_5 7-CH ₂ CHNH ₂	C ₁₂ H ₁₆ N ₂ hydrogen- maleate	-	
CH ₃	H	H	CH_3 6-CH ₂ CHNH ₂	C ₁₂ H ₁₆ N ₂ hydrogen- maleate	171-73 (ea)	460
H	CH ₃	H	CH_3 6-CH ₂ CHNH ₂	C ₁₂ H ₁₆ N ₂	-	
H	H	H	CH_3 5-CH ₂ CHNH ₂	C ₁₂ H ₁₆ N ₂	145-46 (m)	564
H	H	CH ₃	CH_3 5-CH ₂ CHNH ₂	C ₁₂ H ₁₆ N ₂	124-26 (c)	462
H	H	H	CH_3 6-CH ₂ CHNH ₂ , 4-CH ₃	C ₁₂ H ₁₆ N ₂	96-98 (c)	462, 564
H	H	H	CH_3 5-CHCHNHCH ₃	C ₁₂ H ₁₆ N ₂	145-47 (ea)	462, 564
H	H	H	CH_3 5-CHCHNHCH ₃	C ₁₂ H ₁₆ N ₂ O	157-59 (e)	564
H	H	H	OH 5-CHCH ₂ N(CH ₃) ₂	C ₁₂ H ₁₆ N ₂ O	94-96 (et)	564
H	H	H	OH 5-CHCH ₂ NHCH(CH ₃) ₂	C ₁₃ H ₁₈ N ₂ O	158-59 (ea)	564
H	H	H	CH_3 6-CH ₂ CHNHCOCH ₂ H ₅	C ₁₄ H ₁₈ N ₂ O	93-95 (c)	464

Table 15 (cont.)

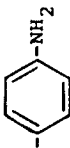
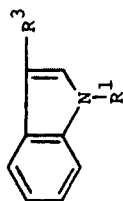
H	H	H	CH_3 5-COCHN(C ₂ H ₅) ₂	C ₁₅ H ₂₀ N ₂	88-90 (ea)	564
H	CH ₃	CH ₃	OH 6-CHCH ₂ NHCH(CH ₃) ₂	C ₁₅ H ₂₂ N ₂ O	138-40 (p) 157-58 (c)	251 251
H	H	H	CH_3 6-CH ₂ CHNHCO- 	C ₁₇ H ₁₇ N ₃ O	135-37 (c)	464
H	H	H	CH_3 5-COCH ₂ NCH ₂ C ₆ H ₅	C ₁₈ H ₁₈ N ₂ O	110-12 (et)	564
H	H	H	CH_3 6-CH ₂ CHNHCOCC ₆ H ₅	C ₁₈ H ₁₈ N ₂ O	129-30 (c)	463, 464
H	H	H	CH_3 6-CH ₂ CHNHCH ₂ C ₆ H ₅	C ₁₈ H ₂₀ N ₂ hydrogen- maleate	- 150-53 (m)	463
H	H	H	OH CH_3 5-CHCH ₂ N-CH ₂ C ₆ H ₅	C ₁₈ H ₂₀ N ₂ O	84-85 (et)	564
H	H	H	CH_3 CH_3 5-COCH- $\text{N-CH}_2\text{C}_6\text{H}_5$	C ₁₉ H ₂₀ N ₂ O	106-08 (ea)	564
H	H	H	CH_3 6-CH ₂ CHNHCOCH ₂ - 	C ₁₉ H ₂₁ N ₃ O	175-78 (m)	464

Table 15 (cont.)

H	H	H	$ \begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ 6\text{-CH}_2\text{CH}-\text{NCH}_2\text{C}_6\text{H}_6 \end{array} $	C ₁₉ H ₂₂ N ₂ hydrogen- oxalate	-	
					114 (m)	463
H	H	H	$ \begin{array}{c} \text{NC}_6\text{H}_5 \\ \\ \text{5-COCH}_2\text{N} \text{---} \text{C}_6\text{H}_5 \end{array} $	C ₂₀ H ₂₁ N ₃ O	204-06 (thf)	564
H	H	H	$ \begin{array}{c} \text{5-COCH}_2\text{N-CH(CH}_3)_2 \\ \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array} $	C ₂₀ H ₂₂ N ₂ O	181-83 (m)	564
H	H	H	$ \begin{array}{c} \text{OH} \\ \\ \text{5-CHCH}_2\text{N} \text{---} \text{C}_6\text{H}_5 \end{array} $	C ₂₀ H ₂₃ N ₃ O	193-95 (ea)	564

Table 16. 1,3-di-R-N Substituted Indoles *



R ¹	R ³		m.p., °C	Ref.
CH ₂ N(CH ₃) ₂	CH ₂ N(CH ₃) ₂	C ₁₄ H ₂₁ N ₃ dipicrate	164 (e) 159 (AcOH)	521 547
CH ₂ CH ₂ NH ₂	γ-pyridyl	C ₁₅ H ₁₅ N ₃ dimaleate	- 167 (m)	88b
CH ₂ N(CH ₃) ₂	CH ₂ CH ₂ NHCOCH ₃	C ₁₅ H ₂₁ N ₂ O CH ₃ I	93 (l) 151-53	122 122
CH ₂ N(CH ₃) ₂	γ-pyridyl	C ₁₆ H ₁₇ N ₃	37	429a
(CH ₂) ₃ NH ₂	"	C ₁₆ H ₁₇ N ₃	209-12	88b
CH ₂ N(CH ₃) ₂	COCH ₂ CH ₂ N(CH ₃) ₂	C ₁₆ H ₂₃ N ₃ O	128-29 (b)	527
CH ₂ CH ₂ N(CH ₃) ₂	γ-pyridyl	C ₁₇ H ₁₉ N ₃ di-HCl bisquat. salt	- 258-60 (m)	88b, 429 429a

*For further compounds see Ref. 623.

Table 16 (cont.)

$\text{CH}_2\text{N}(\text{CH}_3)_2$	CH_3 $\text{COCH-CH}_2\text{N}(\text{CH}_3)_2$	$\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}$ di-HCl	-	575
	γ -pyridyl	$\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}$	187-90	527
$\text{CH}_3\text{CHCH}_2\text{N}(\text{CH}_3)_2$	"	$\text{C}_{18}\text{H}_{21}\text{N}_2$ dimaleate	120	429a
$(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	"	$\text{C}_{18}\text{H}_{21}\text{N}_3$ di-HCl	-	88b
	$\text{CH}_2\text{CH}_2\text{NHCOCH}_3$	$\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}$ CH_3I	265(ac)	88b
		$\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_2$ dipicrate	115(l)	122
		$\text{C}_{18}\text{H}_{25}\text{N}_2$ dipicrate(?)	146-47	122
$\text{CH}_2\text{N}(\text{CH}_3)_2$	$\text{COCHCH}_2\text{N}(\text{CH}_3)_2$	$\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}$	b.p. 190-93 (0.5 mm.)	521
$\text{CH}_2\text{N}(\text{CH}_3)_2$	$\text{CH}_2\text{CH}_2\text{NHCOCH}_2\text{CH}_3$	$\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}$ CH_3I	176-78	521
	γ -pyridyl	$\text{C}_{19}\text{H}_{21}\text{N}_3$	b.p. 132-34 (0.09 mm.)	521
			168-69	521
			78-80	575
			98(l)	122
			dec. >195	122
			105	429a

Table 16 (cont.)

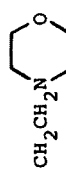
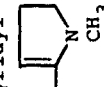
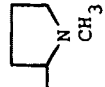
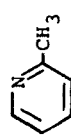
	γ -pyridyl	$C_{19}H_{21}N_3O$ di-HCl	- 172 245 (e)	429a 88b
$CH_2NHCOC_6H_5$	$CH_2N(CH_3)_2$	$C_{19}H_{21}N_3O$	107 (b)	219
$CH_2CH_2N(C_2H_5)_2$	γ -pyridyl	$C_{19}H_{23}N_3$ di-HCl	- 225 (m)	88b
$CH_2CH_2N(C_2H_5)_2$		$C_{19}H_{27}N_3$	-	577
$CH_2CH_2N(C_2H_5)_2$		$C_{19}H_{29}N_3$ di-HCl	- 210-12 (e)	577, 620
CH_2CH_2NH- 	γ -pyridyl	$C_{20}H_{23}N_3$ dimaleate	- 161 (dec)	88b 88b
CH_2CH_2N- 	γ -pyridyl	$C_{20}H_{23}N_3$ di-HCl	- 161	429a 429a
$CH_2N(CH_3)_2$	$CH_2CH_2NHCOC_6H_5$	$C_{20}H_{23}N_3O$	102 (m)	122
CH_2CH_2- 	$CH_2N(CH_3)_2$, 2- CH_3	$C_{20}H_{25}N_3$ HCl CH_3I	- 185-87 121-23 (b)	311 311

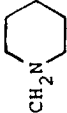
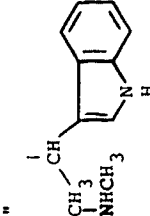
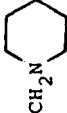
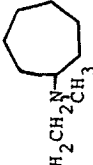
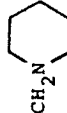
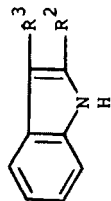
Table 16 (cont.)			
$(\text{CH}_2)_3\text{N}(\text{C}_2\text{H}_5)_2$	γ -pyridyl	$\text{C}_{20}\text{H}_{25}\text{N}_3$ bishydrogen- maleate	-
	CH_2N		88b
"	$\text{CH}_2\text{CH}_2\text{NHCOC}(\text{CH}_3)_3$	$\text{C}_{20}\text{H}_{29}\text{N}_2$ dipicrate(?)	114-17 (m)
	$\text{CH}_2\text{CH}_2\text{NHCH}_3$	$\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}$ CH_3I	b.p. 168-70 (0.3 mm.) 174-75
			127-28 (l) 160
		$\text{C}_{22}\text{H}_{26}\text{N}_4$	142-43 (c)
$(\text{CH}_2)_3\text{N}(\text{C}_3\text{H}_7)_2$	γ -pyridyl	$\text{C}_{22}\text{H}_{29}\text{N}_3$ di-HCl	-
	$\text{CH}_2\text{CH}_2\text{NHCOC}_6\text{H}_5$	$\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}$ HCl	206-08
	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$		-
			182 (m)
	γ -pyridyl	$\text{C}_{23}\text{H}_{29}\text{N}_3$ dimaleate	-
			149 (m)
	$\text{CH}_2\text{CH}_2\text{NHCOC}_2\text{N}$	$\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}$ di-HCl	88b
			104-07
			122

Table 16 (cont.)

$\text{CH}_2\text{NHCOC}_6\text{H}_5$	$\text{CH}_2\text{NHCOC}_6\text{H}_5$	$\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_2$	190 (m)	219
$(\text{CH}_2)_3\text{N}(\text{C}_4\text{H}_9)_2$	γ -pyridyl	$\text{C}_{24}\text{H}_{33}\text{N}_3$ di-HCl	-	88b
$\text{CH}_2\text{N}(\text{CH}_3)_2$	$\text{CH}_2\text{CH}_2\text{NHCOC}(\text{C}_6\text{H}_5)_2$	$\text{C}_{27}\text{H}_{29}\text{N}_3\text{O}$	105	122
 CH_2N	$\text{CH}_2\text{CH}_2\text{NHCOC}(\text{C}_6\text{H}_5)_2$	$\text{C}_{30}\text{H}_{33}\text{N}_3\text{O}$	190 (m)	122
$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{C}_6\text{H}_5)_2$	$\text{C}_{30}\text{H}_{37}\text{N}_3$ dioxalate	- 174-75 (e)	78

Table 17. 2,3-di-R-N Substituted Indoles



R ²	R ³	m.p., °C	Ref.
NHCOCH ₃	CH ₂ N(CH ₃) ₂	161 (ac)	429
γ-pyridyl	"	192-93 (ea)	75a
β-pyridyl	"	4-7 (ea)	75a
α-pyridyl	"	113-14 (ea)	75a
NHCOCH ₃	CH ₂ N(CH ₂) ₂ N(CH ₂) ₂ CH ₃	144-46 (e)	429
γ-pyridyl	γ-pyridyl 4-Br	350	429a
"	"	307	429a
α-pyridyl	CH ₂ N(C ₂ H ₅) ₂	88-90	511
	picate	182 (dec)	511
	methylmetho-	166 (w)	511
	sulfate	214 (e/w)	511
	CH ₃ I		

Table 17 (cont.)

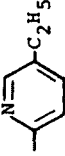
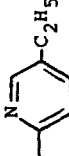
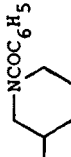
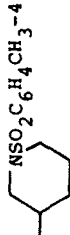
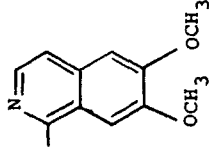
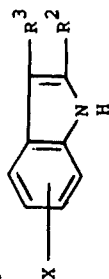
	$\text{CH}_2\text{N}(\text{CH}_3)_2$	$\text{C}_{18}\text{H}_{21}\text{N}_3$	84-86 (ea)	75a
β -pyridyl	$\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	$\text{C}_{18}\text{H}_{21}\text{N}_3$	114 (ea)	75a
γ -pyridyl	"	$\text{C}_{18}\text{H}_{21}\text{N}_3$	148-49 (ea)	75a
	"	$\text{C}_{20}\text{H}_{25}\text{N}_3$	liquid	75a
	$\text{CH}_2\text{N}(\text{CH}_3)_2$	$\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}$ picrate	- 178-80 (ac/w)	248
	"	$\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$ picrate	- 183-84	248
	$\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	$\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_2$ monopicrate dipicrate	- 218(dec) 181(dec)	510 510

Table 18. 3-and Ar-di-Substituted Indoles



R^2	R^3	X		m.p., °C	Ref.
H	$CH_2CH_2NH_2$	4-NH ₂	$C_{10}H_{13}N_3$	116 (subl)	350
H	"	5-NH ₂	$C_{10}H_{13}N_3$ dipicrate(?)	-	483
H	"	6-NH ₂	$C_{10}H_{13}N_3$ di-HCl	106-08 (subl) > 300	350 53
H	$CH_2N(CH_3)_2$	5-NH ₂	$C_{11}H_{15}N_3$	131-33 (t)	182
H	"	6-NH ₂	$C_{11}H_{15}N_3$ oxalate picrate HCl HBr di-HCl	144-45 120-22 123-25 78-80 150-52 > 300	385a 385a 385a 385a 385a 53
CH_3	$CH_2CH_2NH_2$	5-NH ₂	$C_{11}H_{15}N_3$	112	483
H	"	4-NH SO_2CH_3	$C_{11}H_{15}N_3O_2S$ HCl	- 234-36	351a

Table 18 (cont.)

H	$\text{CH}_2\text{CH}_2\text{NH}_2$	5-NHSO ₂ CH ₃	$\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ $\text{CH}_3\text{SO}_3\text{H}$	77-95 235-37	351a 351a
H	"	6-NHSO ₂ CH ₃	$\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ HCl	- 218-20	351a
CH ₃	$\text{CH}_2\text{N}(\text{CH}_3)_2$	5-NH ₂	$\text{C}_{12}\text{H}_{17}\text{N}_3$ HCl	- 234-37(w)	94
H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	4-NH ₂	$\text{C}_{12}\text{H}_{17}\text{N}_3$	131-32(subl)	350
H	"	5-NH ₂	$\text{C}_{12}\text{H}_{17}\text{N}_3$ dipicrate	- 202-04(dec)	483
H	"	6-NH ₂	$\text{C}_{12}\text{H}_{17}\text{N}_3$	98-99(subl)	350
H	$\text{CH}_2\text{CH}_2\text{NH}_2$	6-N(CH ₃) ₂	$\text{C}_{12}\text{H}_{17}\text{N}_3$ picrate monoacetate	- 215-16 ca. 160	321, 324 321, 324
H	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	6-NH ₂	$\text{C}_{12}\text{H}_{17}\text{N}_3$ di-HCl	- 261-62(m)	227
H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CHNH}_2 \end{array}$	5-NHSO ₂ CH ₃	$\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ HCl	- 261-63	351a

Table 18 (cont.)

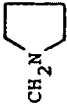
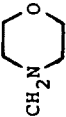
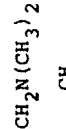
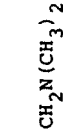
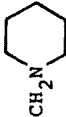
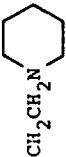
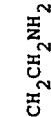
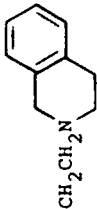
H		5-NH ₂	C ₁₃ H ₁₇ N ₃	126-28 (t)	182
H		5-NH ₂	C ₁₃ H ₁₇ N ₃ O	148-50 (t)	182
H		6-NHCOCH ₃	C ₁₃ H ₁₇ N ₃ O	169-71	385a
H		5-N(CH ₃) ₂	C ₁₃ H ₁₉ N ₃ picrate	- 216-17 (ac)	181
H		6-N(CH ₃) ₂	C ₁₃ H ₁₉ N ₃	126 (t)	321
H		5-NH ₂	C ₁₄ H ₁₉ N ₃	90-93 (t)	182
H		5-NH ₂	C ₁₅ H ₂₁ N ₃ dipicrate	- 211-12 (e/w)	483
H		5-CO- 	C ₁₆ H ₁₅ N ₃ O di-HCl	- 251-56 (e)	507
H		5-NH ₂	C ₁₉ H ₂₁ N ₃ dipicrate	- 215-17 (dec)	482

Table 18 (cont.)

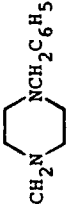
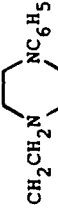
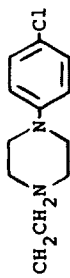
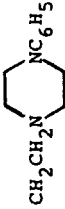
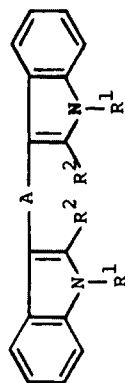
H		5-NH ₂	C ₂₀ H ₂₄ N ₄	147-48 (t)	182
CH ₃		5-NH ₂	C ₂₁ H ₂₆ N ₄	152-54 (et)	505b
CH ₃		5-NHCOCH ₃	C ₂₃ H ₂₇ ClN ₄ O	101-03 (e)	505b
CH ₃		5-NHCOCH ₃	C ₂₃ H ₂₈ N ₄ O	207-10 (m)	505b
H		6-NHCOC ₆ H ₅	C ₂₄ H ₂₁ N ₃ O ₂	220-21 (ac)	53
CH ₃		5-NHCOOC ₂ H ₅	C ₂₄ H ₃₀ N ₄ O ₂ 4-CH ₃ C ₆ H ₄ SO ₃ H	- 199-01	505b

Table 19. 3,3'-di-Indolyl Derivatives



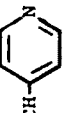
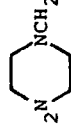
R^1	$R^{1'}$	R^2	A		m.p., °C	Ref.
H	H	H	CH-CH ₂ NH ₂	C ₁₈ H ₁₇ N ₃ HCl	162 (e) 210-15 (e)	288 288
H	CH ₂ N(CH ₃) ₂	H	CH ₂	C ₂₀ H ₂₁ N ₃	112 (e)	547
H	H	CH ₃	CH-CH ₂ NH ₂	C ₂₀ H ₂₁ N ₃	213-15 (e)	288
H	H	H	CH-CH ₂ N(CH ₃) ₂	C ₂₀ H ₂₁ N ₃ HCl	156 (b) 212-15 (e)	288 288
H	H	H	CH ₂ CH ₂ NHCONHCH ₂ CH ₂	C ₂₁ H ₂₂ N ₄ O	159 (e)	345
H	H	H	CH- 	C ₂₂ H ₁₇ N ₃ HCl	210-12 (e/w) 218-20	191 258
H	H	H	CH- 	C ₂₂ H ₁₇ N ₃ HCl	155-56 (e/w) 204-05	191 258

Table 19 (cont.)

H	H	H		$C_{22}H_{17}N_3$ HCl	130 (b) 214-15	258 258
H	H	H	$CHCOOCH_2CH_2N(CH_3)_2$	$C_{22}H_{23}N_3O_2$ HCl	79-80 (e) 192-97 (m)	288 288
H	H	H		$C_{22}H_{24}N_4$	222 224-25 (x) 231 (e)	290a 444 17
H	H	H	$CHCH_2N(C_2H_5)_2$	$C_{22}H_{25}N_3$ HCl	- 202-06 (e)	288
H	H	CH ₃	$CH-CH_2N(CH_3)_2$	$C_{22}H_{25}N_3$ HCl	207 (m) 174-76 (e)	288 288

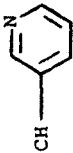
H	H	H	CHCOO(CH ₂) ₃ N(CH ₃) ₂	C ₂₃ H ₂₅ N ₃ O ₂ HCl	167-68 (e) 132-37 (m)	288 288
H	H	H	(CH ₂) ₃ NHCONH(CH ₂) ₃	C ₂₃ H ₂₆ N ₄ O	124 (ea)	265a
CH ₂ N(CH ₃) ₂	CH ₂ N(CH ₃) ₂	H	CH ₂	C ₂₃ H ₂₈ N ₄	72 (p)	547
H	H	CH ₃		C ₂₄ H ₂₁ N ₃ HBr	256 (m) 249	508a 508a
H	H	CH ₃		C ₂₄ H ₂₁ N ₃ HBr	261 (m) 190 (dec)	508a 508a

Table 19 (cont.)

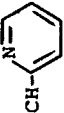
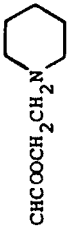
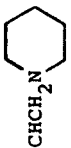
H	H	CH ₃		C ₂₄ H ₂₁ N ₃ HBr	292 (py) 227 (dec)	508a 508a
CH ₃	CH ₃	H		C ₂₄ H ₂₁ N ₃ HCl	186-88 (b) 224-25	258 258
H	H	H	CHCOOCH ₂ CH ₂ N(C ₂ H ₅) ₂	C ₂₄ H ₂₇ N ₃ O ₂ HCl	- 204-08 (m)	288 288
H	H	CH ₃	CHCH ₂ N(C ₂ H ₅) ₂	C ₂₄ H ₂₉ N ₃ HCl	176-77 (e) 181	288 288
H	H	H		C ₂₅ H ₂₇ N ₃ O ₂ HCl	179 (e) 145-50 (m)	288 288
H	H	H	CHCH ₂ NHCOC ₆ H ₅	C ₂₅ H ₂₁ N ₃ O	187-90 195 (b)	21 288
H	H	H	CHCOO(CH ₂) ₃ N(C ₂ H ₅) ₂	C ₂₅ H ₂₉ N ₃ O ₂ HCl	128 (e) 172-75 (e)	288 288
H	H	CH ₃		C ₂₅ H ₂₉ N ₃	214 (e)	288
H	H	CH ₃	CHCH ₂ CH ₂ N(C ₂ H ₅) ₂	C ₂₅ H ₃₁ N ₃	170 (e)	288

Table 19 (cont.)

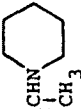
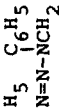
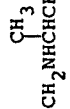
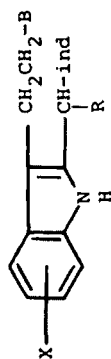
H	H	CH ₃	CHCH ₂ CH ₂ N		C ₂₆ H ₃₁ N ₃	244-45 (e)	288
H	H	CH ₃	CHCH ₂ CHN		C ₂₇ H ₃₃ N ₃	223 (e)	288
CH ₂ N	CH ₂ N	H	CH ₂		C ₂₉ H ₃₆ N ₄	132	411a
H	H	H	CH ₂ N-N=N-CH ₂		C ₃₀ H ₂₆ N ₆	178 (thf)	556
H	H	CH ₃	CHCH ₂ CH ₂ NHCHCH ₂ C ₆ H ₅		C ₃₀ H ₃₃ N ₃ lactate benzoate	139 (b) 178 (ea) 178	288 288 288

Table 20. 2-(x-Indolylmethyl)indole Derivatives



B	R	ind	X	m.p., °C	Ref.
NH ₂	3-thenyl	3-indolyl	H	192 (e)	155
NH ₂	3-pyridyl	3-indolyl	H	220 (e)	155
NH ₂	4-ClC ₆ H ₄	3-indolyl	H	259-62 (e)	155
NH ₂	C ₆ H ₅	3-indolyl	4-Cl	218 (e)	155
NH ₂	"	3-indolyl	7-Cl	188 (e)	155
NHC ₂ H ₅	"	1-CH ₃ -3-indolyl	H	179 (e)	155
NH ₂	4-(CH ₃) ₂ NC ₆ H ₄	2-CH ₃ -3-indolyl	H	185-88 (m)	155
NHC ₂ H ₅	C ₆ H ₅	2,3-(CH ₃) ₂ -6-indolyl	H		
NH ₂	"	9-CH ₃ -1,2,3,4-tetrahydro-7-carbazolyl	H	176 (e)	155
				204 (e)	155

Table 20 (cont.)

NHC_2H_5	C_6H_5	2,3,7-(CH_3) $_3$ - 6-indolyl	H	$\text{C}_{30}\text{H}_{33}\text{N}_3$	193(e)	155
NHC_2H_5	"	2,3,5-(CH_3) $_3$ - 6-indolyl	H	$\text{C}_{30}\text{H}_{33}\text{N}_3$	174(e)	155
NHC_2H_5	"	1,2,3-(CH_3) $_3$ - 6-indolyl	H	$\text{C}_{30}\text{H}_{33}\text{N}_3$ HCl	— 169(e)	155
NHC_2H_5	"	1,2,3,5-(CH_3) $_4$ - 6-indolyl	H	$\text{C}_{31}\text{H}_{35}\text{N}_3$	156(e)	155
NHC_2H_5	"	1,2,3,7-(CH_3) $_4$ - 6-indolyl	H	$\text{C}_{31}\text{H}_{35}\text{N}_3$	132(e)	155
NHC_2H_5	"	1,2,3,6,7-(CH_3) $_5$ - 5-indolyl	H	$\text{C}_{32}\text{H}_{37}\text{N}_3$	200(e)	155
NHC_2H_5	"	1,2,3,4,7-(CH_3) $_5$ - 6-indolyl	H	$\text{C}_{32}\text{H}_{37}\text{N}_3$	208(e)	155

Table 21. Miscellaneous di-Indolyl Derivatives

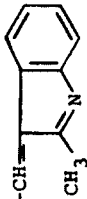
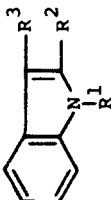
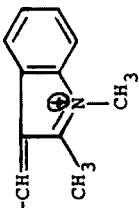
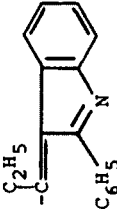
R ¹	R ²	R ³	m.p., °C	Ref.
H			- 238	108b
CH ₃	"	CH ₃	- 204	108b
CH ₃		CH ₃	- 209	108b
H			- 125 (e)	76

Table 21 (cont.)

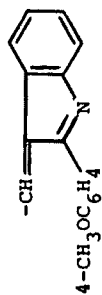
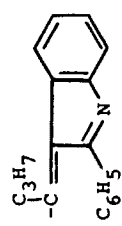
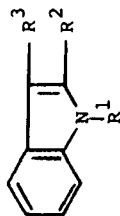
H	4-CH ₃ OC ₆ H ₄		C ₃₁ H ₂₄ N ₂ O ₂ HCl	- 267-70 (e)	76
H	C ₆ H ₅		C ₃₂ H ₂₆ N ₂	103-05 (e)	76

Table 22. 3-Indolyl-C-C-N[⊕] Derivatives



R ¹	R ²	R ³	X [⊖]	m.p., °C	Ref.
H	H		Br	235-37 (e)	125
			I	214	553
			pic	184-85	553
H	H		I	266-67 (w)	338
			ClO ₄	249-50 (w)	338
H	H		Br	201-03 (dec)	413
H	H		Br	181 (m)	605
H	H		I	218-19 (w)	553
			pic	166-67 (w)	553

Table 22 (cont.)

H	H		Br	$C_{17}H_{17}BrN_2O$	214-16 (w)	599
			Cl	$C_{17}H_{17}ClN_2O$	193-98 (w)	599
H	H		Br	$C_{17}H_{17}BrN_2O$	268-71	412
			I	$C_{17}H_{17}IN_2O$	260-62	412
H	H		I	$C_{17}H_{17}IN_2O_2$	199-200 (w)	413
			Br	$C_{17}H_{17}BrN_2O_2$	215-17	413
			ClO ₄	$C_{17}H_{17}ClN_2O_6$	212-14 (w)	413
H	H		I	$C_{17}H_{19}IN_2$	164	548
H	CH ₃		Br	$C_{17}H_{19}BrN_2O$	195 (m)	605
H	H		Br	$C_{17}H_{19}BrN_2O$	188-89 (e)	413
			ClO ₄	$C_{17}H_{19}ClN_2O_5$	156-57 (e)	413
H	H		pic	$C_{23}H_{21}N_5O_8$	143-44 (e)	553
H	H		I	$C_{18}H_{19}IN_2O$	260-62 (w)	338
			ClO ₄	$C_{18}H_{19}ClN_2O_5$	264-65 (ac)	338

Table 22 (cont.)

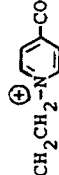
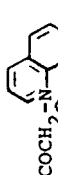
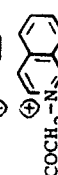
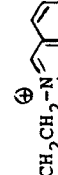
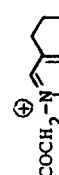
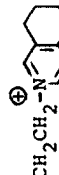
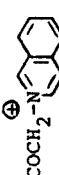
H	H		Br	$C_{18}H_{19}BrN_2O_2$	202-03(e)	125
H	H		I	$C_{19}H_{15}IN_2O$	247-49(dec) (w)	338
H	H		I	$C_{19}H_{15}IN_2O$	270-72(w)	338
H	H		Br	$C_{19}H_{17}BrN_2$	211-12(m)	247
			Cl	$C_{19}H_{17}ClN_2$	128(ac)	414
			I	$C_{19}H_{17}IN_2$	244-45(m)	414, 553
			ClO_4	$C_{19}H_{17}ClN_2O_4$	223(m)	414
			pic	$C_{25}H_{19}N_5O_7$	208(m)	414
H	H		Cl	$C_{19}H_{19}ClN_2O$	269-70	412
			I	$C_{19}H_{19}IN_2O$	251-52	412
H	H		Br	$C_{19}H_{21}BrN_2$	218-19(m)	553
			I	$C_{19}H_{21}IN_2$	222-23(m)	553
H	CH_3		I	$C_{20}H_{17}IN_2O$	225-56(w)	338
			ClO_4	$C_{20}H_{17}ClN_2O_5$	243-44(ac)	338

Table 22 (cont.)

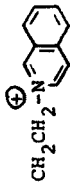
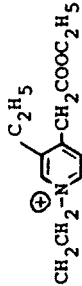
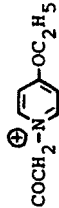
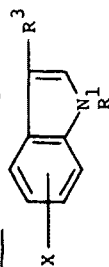
CH ₃	H		Cl	C ₂₀ H ₁₉ ClN ₂	192 (m)	414
			I	C ₂₀ H ₁₉ IN ₂	229 (m)	414
			ClO ₄	C ₂₀ H ₁₉ ClN ₂ O ₄	191 (m)	414
			pic	C ₂₆ H ₂₁ N ₅ O ₇	234 (m)	414
H	H		ClO ₄	C ₂₀ H ₂₃ ClN ₂ O ₆	156-58	597
H	H		Br	C ₂₁ H ₂₁ BrN ₂ O ₂	219 (m)	414
			I	C ₂₁ H ₂₁ IN ₂ O ₂	246-47 (w)	414
H	H		Br	C ₂₂ H ₁₉ BrN ₂ O	199-200 (w)	553
			I	C ₂₂ H ₁₉ IN ₂ O	182-83	553
H	H		pic	C ₂₃ H ₁₉ N ₅ O ₉	203-05 (e)	413

Table 23. 3-Indolyl-C=N-Derivatives



R ¹	R ³	X	m.p., °C	Ref.
H	CH=NCH ₃	H	117-18 (cyh)	369
H	CH=N-NHCOCH ₃	H	253-55 (e)	520
H	CH=NCH ₂ CH ₂ OH	H	136 (ea)	589
H	CH=N-N(CH ₃) ₂	H	105 (cyh)	589
H	CH=N- 	7-Cl	120-22 (et)	453
H	"	H	128-29 (et)	453
H		H	183-84 (ea)	620, 577
H	CH=N-CH ₂ CHOHCH ₃	H	104 (ea)	589
CH ₃	CH=N- 	H	95-97 (p)	453

Table 23 (cont.)

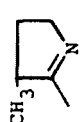
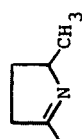
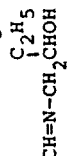
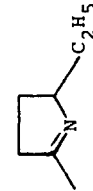
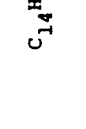
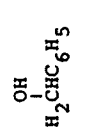
H		4-CH ₃	C ₁₃ H ₁₄ N ₂ hydrogen-oxalate	-	
H	"	7-CH ₃	C ₁₃ H ₁₄ N ₂	221-23(m) 165-67(b)	453 453
CH ₃		H	C ₁₃ H ₁₄ N ₂	119-20(et)	620
H		H	C ₁₃ H ₁₄ N ₂	144-46	620
H		H	C ₁₃ H ₁₄ N ₂	196-97(ip)	620
H		H	C ₁₃ H ₁₆ N ₂ O	169(ea)	589
COCH ₃		H	C ₁₄ H ₁₄ N ₂ O CH ₃ I	185-86(b) 217-19	620 620
H		H	C ₁₄ H ₁₆ N ₂ HCl	- 218-19(m)	620

Table 23 (cont.) *

H		H	C ₁₄ H ₁₆ N ₂	197-98 (et)	620
H		H	C ₁₄ H ₁₈ N ₄	69 (m)	589
H		H	C ₁₅ H ₁₂ N ₂	126-27	343
H		H	C ₁₅ H ₁₂ N ₂ O HCl	191-92 209 (e)	545 545
H		H	C ₁₇ H ₁₆ N ₂ O	165 (ea)	589
H		H	C ₁₈ H ₁₈ N ₂ O ₂	159 (ea)	589

*For further compounds see also Ref. 654a and F. D. Popp, J. Med. Chem. 13, 1017 (1970).

Table 24. 2-and 3-R-N Substituted-3H-Indoles

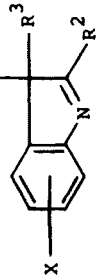
					m.p., °C	Ref.
R ²	R ³	R ^{3'}	X			
NH ₂	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂	H	C ₁₄ H ₁₆ N ₂ HCl	119-20 (w) 230-35 (w)	61 61
NH ₂	CH ₂ CH ₂ CH ₃	CH ₂ CH ₂ CH ₃	H	C ₁₄ H ₂₀ N ₂ HCl	185-86 (p) 238-39 (b)	61 61
CH ₃	CH ₃	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₁₄ H ₂₀ N ₂ HCl	- 209 (m)	557
H	C ₆ H ₅	"	H	C ₁₈ H ₂₀ N ₂ CH ₃ COOH HCl HBr	148-50 91 244-45 231	557 557 557 557
CH ₃	C ₆ H ₅	"	5-Cl	C ₁₉ H ₂₁ ClN ₂ HCl	- 158-59	557
CH ₃	C ₆ H ₅	"	7-Cl	C ₁₉ H ₂₁ ClN ₂ HCl	- 229	557

Table 24 (cont.)

CH ₃	C ₆ H ₅	CH ₃ CHCH ₂ N(CH ₃) ₂	H	C ₂₀ H ₂₄ N ₂ HCl	- 190	557
CH ₃	C ₆ H ₅	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CH}-\text{N}(\text{CH}_3)_2 \end{array}$	H	C ₂₀ H ₂₄ N ₂ HCl	98-99 234 (ea)	557 557
CH ₃	4-CH ₃ C ₆ H ₄	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₂₀ H ₂₄ N ₂ HCl	- 236-37	557
CH ₃	C ₆ H ₅	"	5-CH ₃	C ₂₀ H ₂₄ N ₂ HCl	- 220-22	557
CH ₃	C ₆ H ₅	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CH}_2\text{N}-\text{C}_2\text{H}_5 \end{array}$	H	C ₂₀ H ₂₄ N ₂ HCl	- 225 (m)	558
CH ₃	C ₆ H ₅	(CH ₂) ₃ N(CH ₃) ₂	H	C ₂₀ H ₂₄ N ₂ HCl	- 214-15 (m)	557
CH ₃	3-CH ₃ OC ₆ H ₄	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₂₀ H ₂₄ N ₂ O HCl	- 244	557
CH ₃	4-CH ₃ OC ₆ H ₄	"	H	C ₂₀ H ₂₄ N ₂ O HCl	- 228-29 (m)	557
CH ₃	C ₆ H ₅	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{CH}_2\text{N}-\text{CH}_2\text{CH}=\text{CH}_2 \end{array}$	H	C ₂₁ H ₂₄ N ₂	200 (ea)	557

Table 24 (cont.)

CH ₃	C ₆ H ₅	CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₂₁ H ₂₆ N ₂ HCl	- 208	557
CH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₂₁ H ₂₆ N ₂ O ₂ HCl	- 217-19	557
CH ₃	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂ CH=CH ₂) ₂	H	C ₂₃ H ₂₆ N ₂ HCl	b.p. 150-54 (0.05 mm.) 165-66 CH ₃ SO ₃ H 118	559 559 559
CH ₃	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂ CH=CH ₂) ₂	H	C ₂₂ H ₂₆ N ₂ HCl	- 240-44 (m)	557
CH ₃	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂ CH=CH ₂) ₂	H	C ₂₃ H ₂₈ N ₂ hydrogen- maleate	- 141 (ea)	557
C ₆ H ₅	C ₆ H ₅	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₂₄ H ₂₄ N ₂ HCl	- 206-08	557
CH ₃	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂ CH=CH ₂) ₂	H	C ₂₄ H ₃₀ N ₂ HCl	- 235-36 (ea)	557
C ₆ H ₅	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂ CH=CH ₂) ₂	H	C ₂₆ H ₂₈ N ₂ HCl	87 (p) 178	557 557

Table 24 (cont.)

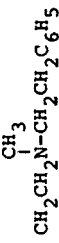
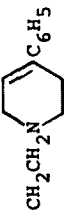
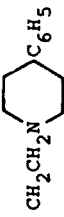
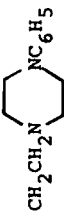
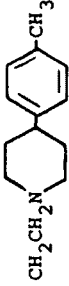
CH ₃	C ₆ H ₅		H	C ₂₆ H ₂₈ N ₂ oxalate	- 200-10	557
H	C ₆ H ₅		H	C ₂₇ H ₂₆ N ₂ HCl	b.p. 220-240 (0.04 mm.) 216-17 (ea)	468 468
H	C ₆ H ₅		H	C ₂₇ H ₂₈ N ₂ HCl CH ₃ SO ₃ H	b.p. 210-20 (0.05 mm.) 188-90 (m) 235-36 (ea)	468 468 468
				hydrogen- maleate	169-70	468
CH ₃	C ₆ H ₅		H	C ₂₇ H ₂₉ N ₃ HCl	b.p. 225-30 (0.05 mm.) 242 (ea)	468 468, 558
H	C ₆ H ₅		H	C ₂₈ H ₃₀ N ₂ HCl	- b.p. 230-32 (0.02 mm.) 218 (ea)	468 468
				hydrogen- maleate	181-82 (ea)	468
				oxalate	229-31 (m)	468
H	C ₆ H ₅		H	C ₂₈ H ₃₀ N ₂ O CH ₃ SO ₃ H	- 213 (m)	468

Table 24 (cont.)

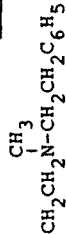
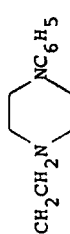
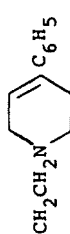
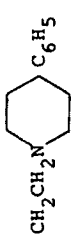
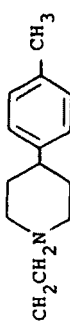
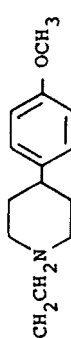
CH ₃	C ₆ H ₅		H	C ₂₆ H ₂₈ N ₂ oxalate	— 200-10	557
CH ₃	C ₆ H ₅		H	C ₂₇ H ₂₉ N ₃ HCl	b.p. 225-30 (0.05mm) 242 (ea)	559 559
CH ₃	C ₆ H ₅		H	C ₂₈ H ₂₈ N ₂ HCl	b.p. 220-240 (0.04mm) 216-17 (ea)	559 559
CH ₃	C ₆ H ₅		H	C ₂₈ H ₃₀ N ₂ HCl CH ₃ SO ₃ H	b.p. 210-20 (0.05mm) 188-90 (m) 235-36 (ea)	559 559 559
				hydrogen- maleate	169-70	559
CH ₃	C ₆ H ₅		H	C ₂₉ H ₃₂ N ₂ HCl	b.p. 230-32 (0.02mm) 218 (ea)	559 559
				hydrogen- maleate	181-82 (ea) 229-31 (m)	559 559
CH ₃	C ₆ H ₅		H	C ₂₉ H ₃₂ N ₂ O CH ₃ SO ₃ H	— 213 (m)	559

Table 25. 3-(=RN)-3H-Indoles

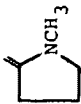
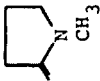
R^2	$=R^3$	X		m.p., °C	Ref.
CH_3	$=NCH(CH_3)_2$	H	$C_{12}H_{14}N_2$	b.p. 60 (0.1 mm.)	471a
H		5-Br	$C_{13}H_{13}BrN_2$	207-10 (m)	620
H	"	4-Cl	$C_{13}H_{13}ClN_2$	169-72 (m)	620
H	"	5-Cl	$C_{13}H_{13}ClN_2$	219-21 (m)	620
H	"	5-F	$C_{13}H_{13}FN_2$	211-13 (m/w)	620
H	"	H	$C_{13}H_{14}N_2$ CH_3I HI^3	229-31 (e) 252-54 302-04 (w) 293-96 (m)	620 620 620 577
C_6H_5	$=NH$	H	$C_{14}H_{10}N_2$	112-15	428
CH_3		H	$C_{14}H_{16}N_2$	123-25 (m/w)	620

Table 25 (cont.)

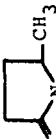
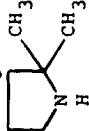
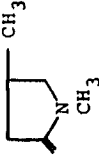
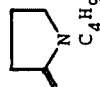
H		H	$C_{14}H_{16}N_2$ HI	- 237-39 (m)	620
H		H	$C_{14}H_{16}N_2$ HI	- 289 (e)	620
H		H	$C_{14}H_{16}N_2$	175-77 (ac)	620
H		5-CH ₃	$C_{14}H_{16}N_2$	209-12 (m)	620
H	"	7-CH ₃	$C_{14}H_{16}N_2$	210-12 (m)	620
H		H	$C_{14}H_{16}N_2$	160-62 (ac)	620
H		H	$C_{16}H_{20}N_2$	131-34 (ac)	620

Table 25 (cont.)

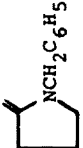
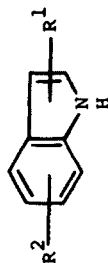
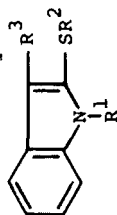
C_6H_5		$=NCH(CH_3)_2$	H	$C_{17}H_{11}N_2$	93	471a
$CH_3C=CHN$		$=CH_2$	H	$C_{17}H_{20}N_2$ CH_3I	- 245 (et)	299
H			5-Br	$C_{19}H_{17}BrN_2$	202 (m)	620
H	"	"	5-Cl	$C_{19}H_{17}ClN_2$	190 (m/w)	620
H	"	"	H	$C_{19}H_{18}N_2$	148 (b)	620
H	"	"	7- CH_3	$C_{20}H_{20}N_2$	172-74 (m/w)	620

Table 26. x-Aminoalkoxyindoles



R^1	R^2	m.p., °C	Ref.
H	$\begin{array}{c} \text{OH} \\ \\ 4\text{-OCH}_2\text{CHCH}_2\text{NHCH}(\text{CH}_3)_2 \end{array}$	$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$ 171-73 (e)	450
H	$\begin{array}{c} \text{OH} \\ \\ 5\text{-OCH}_2\text{CHCH}_2\text{NHCH}(\text{CH}_3)_2 \end{array}$	$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$ 182-85 (e)	450
H	$\begin{array}{c} \text{OH} \\ \\ 6\text{-OCH}_2\text{CHCH}_2\text{NHCH}(\text{CH}_3)_2 \end{array}$	$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$ 146-48 (e)	450
1-CH ₃	$\begin{array}{c} \text{OH} \\ \\ 4\text{-OCH}_2\text{CHCH}_2\text{NHCH}(\text{CH}_3)_2 \end{array}$	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ 79-81 (ea)	450
3-CH ₃	"	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ 95-97 (b/p)	450
1-CH ₃	$\begin{array}{c} \text{OH} \\ \\ 5\text{-OCH}_2\text{CHCH}_2\text{NHCH}(\text{CH}_3)_2 \end{array}$	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ 76-77 (ea)	450
3-CH ₃	"	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ 178-80 (e)	450
H	$\begin{array}{c} \text{OH} \\ \\ 4\text{-OCH}_2\text{CHCH}_2\text{NHCH} \begin{array}{l} \text{CH}_3 \\ \text{C}_2\text{H}_5 \end{array} \end{array}$	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ 154-56 (m)	450
H	$\begin{array}{c} \text{OH} \\ \\ 4\text{-OCH}_2\text{CHCH}_2\text{NH} \end{array}$ 	$\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2$ 118-20 (ea)	450

Table 27. 2-Aminoalkylthiaindoles*



R ¹	R ²	R ³		m.p., °C	Ref.
H	CH ₂ CH ₂ NH ₂	H	C ₁₀ H ₁₂ N ₂ S	128 (ea)	83a
H	CH ₂ CH ₂ N(CH ₃) ₂	H	C ₁₂ H ₁₆ N ₂ S	82 (cyh)	83a
H	(CH ₂) ₃ N(CH ₃) ₂	H	C ₁₃ H ₁₈ N ₂ S HCl	- 128	83a
H	CH ₂ CH ₂ NH ₂	CH(CH ₃) ₂	C ₁₃ H ₁₈ N ₂ S HCl	- 190 (w)	83a
H	CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₁₄ H ₂₀ N ₂ S HCl	- 140 (ip)	83a
H		H	C ₁₅ H ₂₀ N ₂ S HCl	- 174 (e)	83a
H		H	C ₁₅ H ₂₁ N ₃ S HCl	- 200-03 (e)	83a
CH ₃	CH ₂ CH ₂ N(C ₂ H ₅) ₂	H	C ₁₅ H ₂₂ N ₂ S HCl	- 175	83a

*For further compounds see: Ref. 641 and J. Bourdaix, Chimie Therapeutique, 5, 409 (1970)

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CHAPTER VII

Oxidized Nitrogen Derivatives of Indole and Indoline

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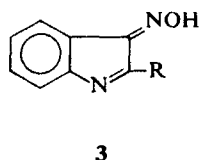
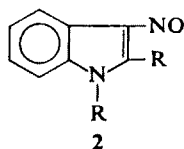
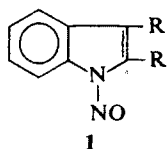
I. Nitroso Derivatives

A. Nitrosoindoles

The reactions of indoles and substituted indoles with nitrous acid and other nitrosating agents were the subject of many early investigations.¹⁻⁹ These

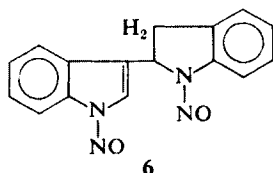
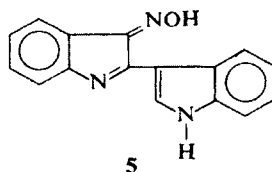
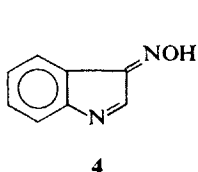
reactions are typical of other electrophilic reactions of indoles, the preferred position of attack being Position 3. If this position contains a substituent other than hydrogen, attack occurs at Position 1.

The 1-nitrosoindoles and 3-nitrosoindoles that contain a substituent other than hydrogen in Position 1 exist in the true nitroso form (**1** and **2**, respec-



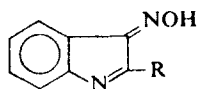
tively). However, the 3-nitroso derivatives of indole and most 2-substituted indoles that contain hydrogen in Position 1 exist in the tautomeric isonitroso or oximino form (**3**). This structure has been supported by many workers.¹⁻¹⁰ Convincing evidence for this structure was obtained by Campbell and Cooper,¹¹ who showed that large differences exist between the electronic spectra of the nitroso derivatives of 2-phenylindole and 1-methyl-2-phenylindole, the latter of which must be a true nitroso compound. It has been proposed that 2-*t*-butyl-3-nitrosoindoles are true nitroso compounds rather than oximino compounds.¹² This proposal is based upon differences between the N—O stretching frequencies in the infrared spectra of the nitroso derivatives of some 2-methylindoles and the corresponding 2-*t*-butylindoles.

The reaction of indole with nitrous acid is complex. In addition to 3-oximino-3H-indole (**4**), indole red (**5**) and **6** are obtained.¹³⁻¹⁶ Compound **4**



is obtained as the sole product by the action of amyl nitrite and sodium ethoxide on indole.^{17, 18} Compound **5** has also been obtained by the action of tetranitromethane on indole.¹⁹

The reaction of 1-methylindole with nitrous acid has not been reported. Reaction of 2-methylindole with nitrous acid in acetic acid is reported to give 2-methyl-3-oximino-3H-indole (**7**),¹⁰ but other workers²⁰⁻²² failed to isolate

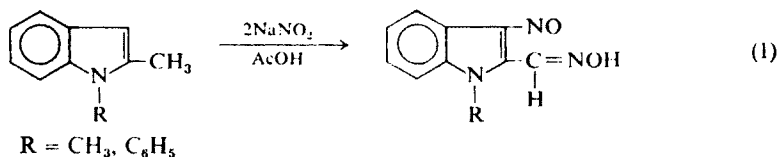


7; R = CH₃
8; R = C₆H₅

any crystalline product. Compound **7** can be prepared in high yield by the action of amyl nitrite and sodium methoxide on 2-methylindole^{4, 20} at 0°C. If this reaction is conducted in ether at room temperature, both nitrosation and oxidation occur, and the yield of **7** is reduced.²³ Reaction of nitrous acid with 3-methylindole (skatole) gives 1-nitroso-3-methylindole.^{10, 24}

3-Oximino-2-phenyl-3H-indole (**8**) is obtained in high yield by reaction of 2-phenylindole with nitrous acid in acetic acid,^{1, 21, 25} with an alkyl nitrite alone,^{23, 26} in the presence of sodium ethoxide,⁴ or by reaction of 3-oxo-2-phenyl-3H-indole with hydroxylamine.^{11, 27} The reaction of 2-phenylindole with alkyl nitrites is quantitative and has been proposed as a method for detection of small quantities of nitrites.²⁶ It is reported that reaction of 2-(4-tolyl)indole and 2-(4-phenyl)indole with nitrous acid in acetic acid gives 1-nitroso derivatives,²⁸ but these are probably 3-oximino derivatives.

Reaction of 1-ethyl-2-phenylindole and 1,2-diphenylindole with nitrous acid in acetic acid gives the expected 3-nitroso derivatives.²⁹ Under these



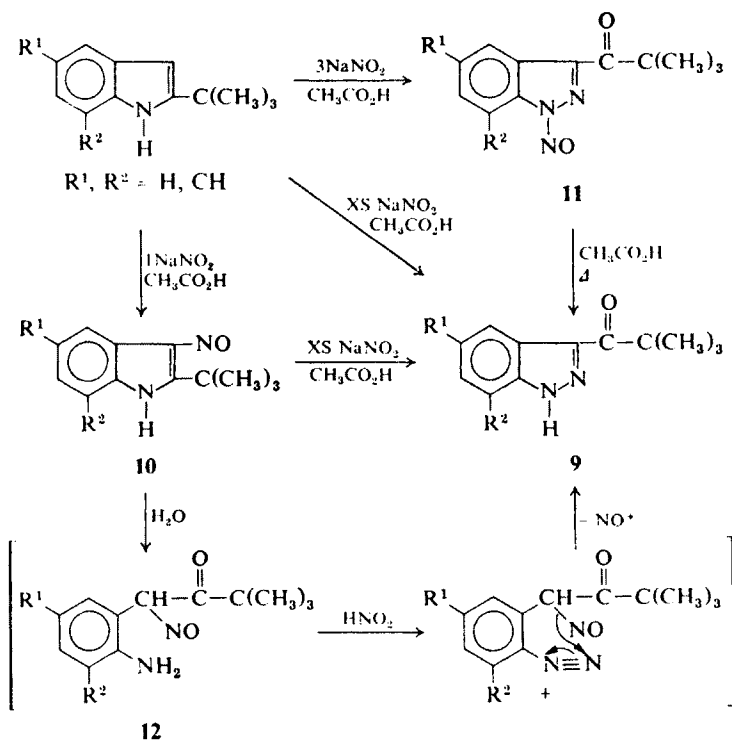
conditions, 1,2-dimethylindole and 2-methyl-1-phenylindole react with 2 moles of nitrous acid to give the corresponding 2-oximinomethyl-3-nitroso derivatives (Eq. 1).²⁹ This reaction probably proceeds by initial nitrosation of Position 3, which results in activation of the 2-methyl group toward attack by nitrosonium ions. This mechanism is supported by the fact that under these conditions, 2,3-dialkylindoles give only the 1-nitroso deriva-^{10, 28, 30}

The orientation rules given below for the reactions of alkylindoles and aralkylindoles with nitrous acid have been proposed by Verkade, Lieste, and Warner.¹⁰

1. Indoles containing 3- or 2- and 3-substituents give 1-nitrosoindoles.
2. Indoles containing 2-substituents give 3-oximino-3H-indoles.
3. Indoles containing 1- and 3-, or 1-, 2-, and 3-substituents do not react.

There are exceptions to these rules; for example, 1,2,3-trimethylindole reacts in an unknown manner. Reaction of the indole with nitrous acid in acetic acid is the preferred method for the preparation of true nitrosoindoles. The 3-oximino-3H-indoles are best prepared by reaction of the indole with amyl nitrite in ethanol containing sodium ethoxide.

Reaction of 2-*t*-butylindoles with excess nitrous acid in acetic acid gives good yields of 3-pivaloylindazoles (**9**) (Scheme 1).¹² With 1 or 3 equiv. of

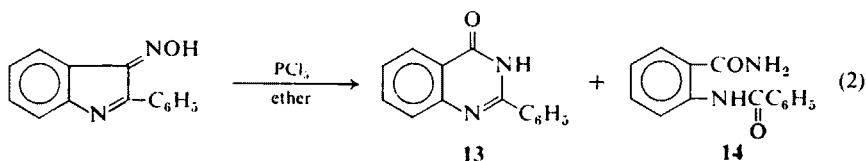


Scheme 1

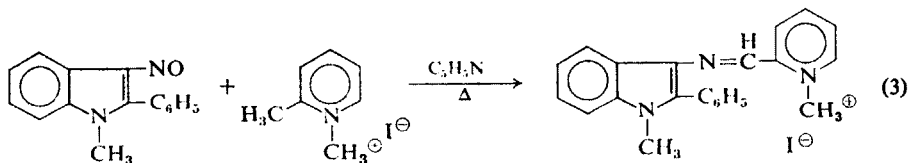
nitrous acid, **10** or **11** is obtained. No mechanism was proposed for forming **9**, but it is conceivable that the first step is hydrolysis of the oximino form of **10** to intermediate **12**. Cyclization probably does not occur by loss of water

from **12**, since this path would not explain the need for excess nitrous acid. It seems more likely that diazotization of the amino group in **12** occurs, followed by loss of a nitrosonium ion and tautomerization.

The 3-oximino-3H-indoles undergo the usual reactions of oximes, such as alkylation⁴ and acylation.^{4, 11} Reduction of 3-nitrosoindoles and 3-oximino-3H-indoles either chemically ($\text{Na}_2\text{S}_2\text{O}_4$)¹⁶ or catalytically (H_2/PtO_2)³¹ yields 3-aminoindoles. Oxidation of 3-oximino-2-phenyl-3H-indole with nitric acid gives 3-nitro-2-phenylindole.³² Treatment of 3-oximino-2-phenylindole with phosphorus pentachloride gives some 4-oxo-2-phenyl-3,4-dihydroquinazoline (**13**), but the major product is **14**, which probably results from hydrolysis of a tautomer of **13** during workup.^{33, 34}



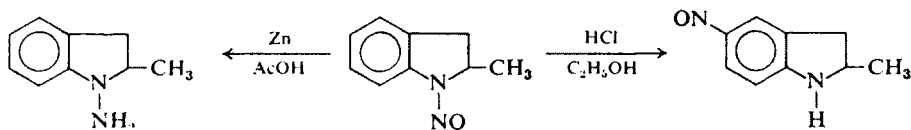
Condensation of 1-alkyl-2-aryl-3-nitrosoindoles with heterocyclic methiodides containing active methyl groups gives cyanine dyes which are useful photographic desensitizers^{29, 33} (Eq. 3).



B. Nitrosoindolines

Indoline and the 2- and 3-alkylindolines, as typical secondary amines, react with nitrous acid to give 1-nitrosoindolines.³⁴ The use of sodium nitrite in 80% sulfuric acid gives quantitative yields.³⁵ Reaction of 1-methylindoline with butyl nitrite in ether followed by dry HCl is reported to give 1-methyl-5-nitrosoindoline.³⁶

The 1-nitrosoindolines undergo reduction with zinc and acetic acid^{35, 37} to give the corresponding hydrazines. Treatment with alcoholic HCl effects rearrangement to 5-nitrosoindolines³¹ (Scheme 2).



Scheme 2

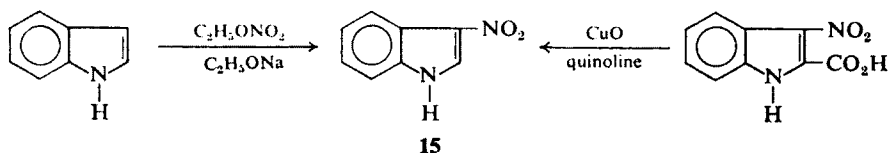
II. Nitro Derivatives

A. Indoles and Indolines with Nuclear Nitro Groups

1. Nitroindoles

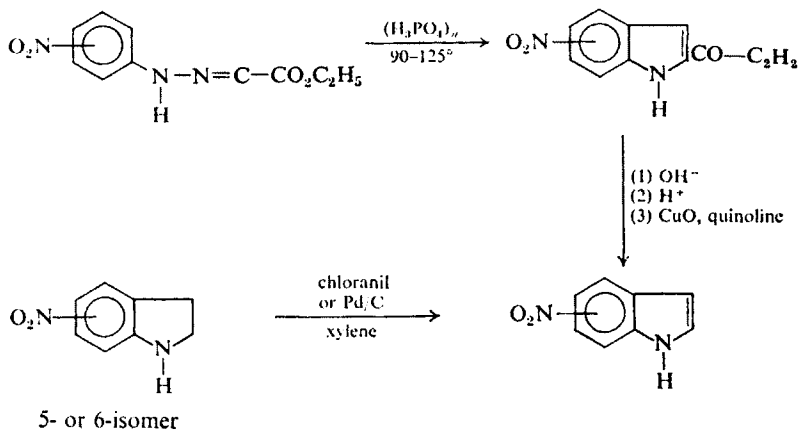
a. PREPARATION. (1). *Nitro Derivatives of Indole*. The direct nitration of indole in acidic media yields only intractable tars. This is probably due either to acid-catalyzed polymerization of indole,³⁸ decomposition initiated by oxidative attack at the 2,3-double bond, or both.

Neither 1-nitroindole nor 2-nitroindole has been prepared. Nitration of indole with ethyl nitrate in the presence of sodium ethoxide yields 3-nitroindole (**15**).³⁹ Decarboxylation of 3-nitroindole-2-carboxylic acid,⁴⁰ which is obtained by nitration of indole-2-carboxylic acid in nitric acid,⁴¹ also gives **15** (Scheme 3).



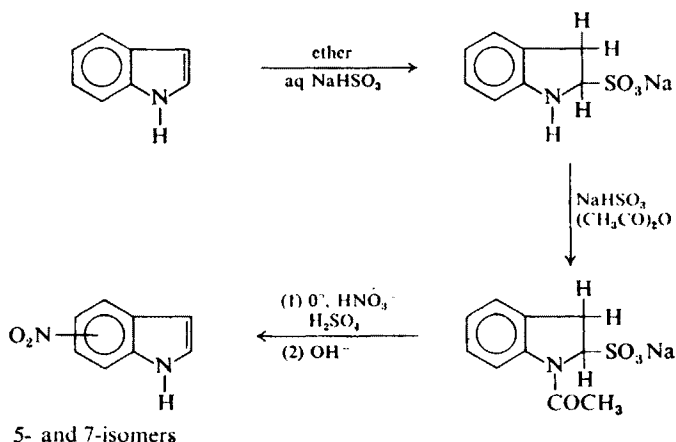
Scheme 3

The preparation of 4-, 5-, 6-, and 7-nitroindole has been achieved by cyclization of the nitrophenylhydrazones of ethyl pyruvate in polyphosphoric acid, followed by hydrolysis and decarboxylation of the resulting ethyl nitroindole-2-carboxylates⁴² (Scheme 4).



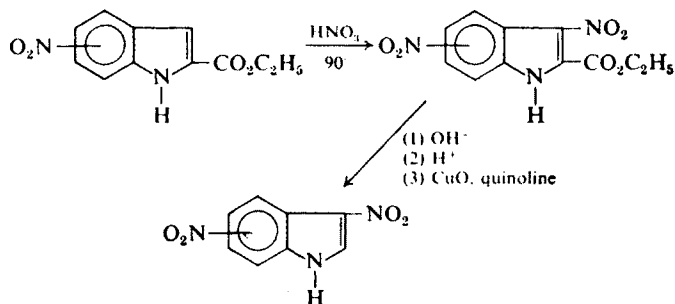
Scheme 4

The *m*-nitrophenylhydrazone of ethyl pyruvate gives upon cyclization a mixture of ethyl-4-nitroindole-2-carboxylate and ethyl 6-nitroindole-2-carboxylate, which can be separated by fractional crystallization. A better method for the preparation of 5- and 6-nitroindole is dehydrogenation of 5- and 6-nitroindoline,⁴³⁻⁴⁵ respectively (Scheme 4), which are prepared in high yield by nitration of indoline (Section II.A.2.a). Decarboxylation of 6-nitroindole-3-carboxylic acid also gives 6-nitroindole.⁴⁶ Nitration of the *N*-acetyl derivative of the indole-sodium bisulfite addition product gives, after basification, 5-nitroindole plus a small amount of 7-nitroindole⁴⁷ (Scheme 5).



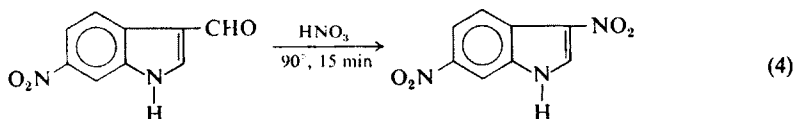
Scheme 5

The preparation of 3,4-, 3,5-, and 3,7-dinitroindole has been achieved by nitration of ethyl 4-nitroindole-2-carboxylate, ethyl 5-nitroindole-2-carboxylate, and ethyl 7-nitroindole-2-carboxylate, respectively, followed by hydrolysis of the resulting dinitroesters and decarboxylation⁴⁰ (Scheme 6).



Scheme 6

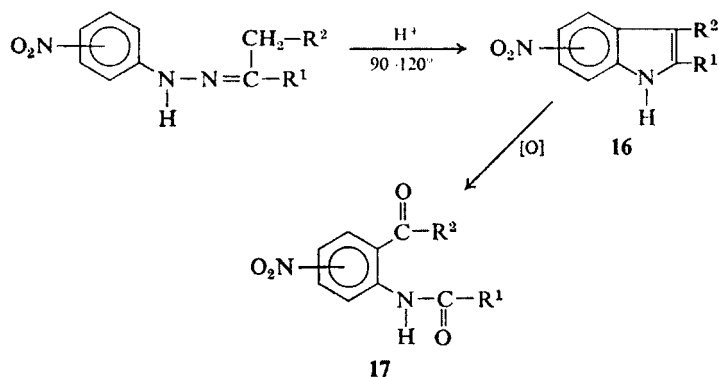
The second nitro group was shown to be in Position 3 by comparison of the ultraviolet (uv) spectra with those known to have Position 3 occupied, benzalkyldinitroindoles, and by nuclear magnetic resonance (nmr) spectroscopy. Attempts to prepare 3,6-dinitroindole by this method were unsuccessful. This compound can be prepared by nitration of 6-nitroindole-3-carboxaldehyde in nitric acid, which results in displacement of the 3-formyl group by a nitro group (Eq. 4). The attempted preparation of 5,7-dinitroindole by dehydrogenation of 5,7-dinitroindoline was unsuccessful.⁴⁸



Reaction of 1-acetyl-5-nitroindoline with fuming nitric acid gives 3,5,7-trinitroindole, which is believed to form by 7-nitration, followed by oxidation to the indole and then 3-nitration.⁴⁸

(2). *Nitro Derivatives of Alkyl- and Arylindoles.* (a). *CYCLIZATION OF NITROPHENYLHYDRAZONES.* The Fischer cyclization of dialkylketones and aralkylketones to give nitroindoles of general structure **16** has been the subject of many investigations.⁴⁹⁻⁵⁴ Cyclization of 2- and 4-nitrophenylhydrazones gives 5- and 7-nitro isomers of **16**, respectively, while 3-nitrophenylhydrazones give mixtures of the 4- and 6-nitro isomers of **16**, which can be separated chromatographically or by fractional crystallization. Although many different acidic catalysts have been used, concentrated hydrochloric acid and polyphosphoric acid appear to give the best results.⁵⁴ A noteworthy exception to this general procedure is the attempted preparation of 2-methyl-5-nitroindole from acetone 4-nitrophenylhydrazone, which has not been successful under any conditions.¹⁹ Nitrophenylhydrazones of aldehydes can be cyclized successfully only in two-phase systems such as concentrated hydrochloric acid-benzene.^{51, 112, 113} Extraction into the organic phase of the nitroindole as it forms prevents its acid-catalyzed destruction. The many alkyl- and aryl nitroindoles prepared by the Fischer indole synthesis are listed in Tables II.A.1 and II.A.2.

The structures of indoles having the general structure **16** have been proved by oxidative degradation to 2-acylamidonitroacylphenones (**17**; R¹, R² = alkyl or aryl)^{55, 56} (Scheme 7). If R² is hydrogen in **16**, the degradation product is an *N*-acylnitroanthranilic acid (**17**; R² = OH).^{19, 57, 58} The preferred reagents for oxidative degradation are chromic acid in acetic acid^{55, 56, 58} and potassium permanganate in either aqueous alkaline solution⁵⁷ or acetic acid.^{57, 59}

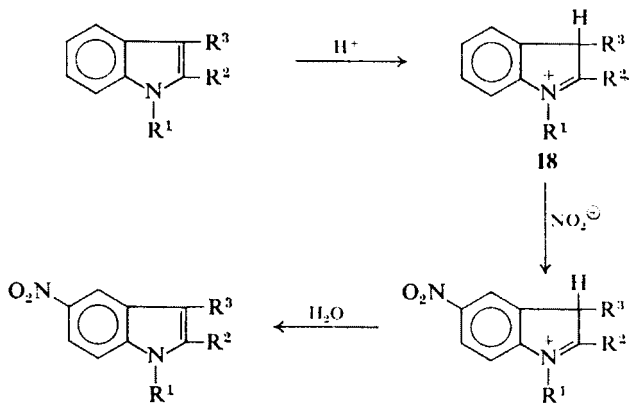


Scheme 7

The preparation of a few 2,3-dialkyl-5,7-dinitroindoles by cyclization of dialkylketone 2,4-dinitrophenylhydrazones in glacial acetic acid-sulfuric acid is reported.⁵⁴

(b). NITRATION OF ALKYL- AND ARYLINDOLES. The nitration of indoles containing vacant 2-positions does not give well-defined products in acidic media. Indole,⁵⁸ 1-methylindole,⁶⁰ 3-methylindole,^{49, 58} and 1,3-dimethylindole⁵⁸ give only high melting amorphous polymers upon treatment with concentrated nitric acid, either alone, in acetic acid, or in sulfuric acid. These polymers presumably result from the initial oxidative attack at Position 2 or at the 2,3-double bond, which are known to be susceptible to this type of attack.^{61, 62}

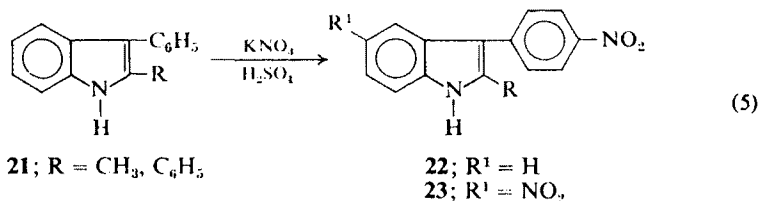
The 2-alkyl- and 2-arylindoles and their alkyl derivatives undergo smooth nitration with nitric acid in sulfuric acid at 0° . Nitration of 2-methylindole,^{58, 63}



Scheme 8

CN1C(C)(C)C2=CC=CC=C12

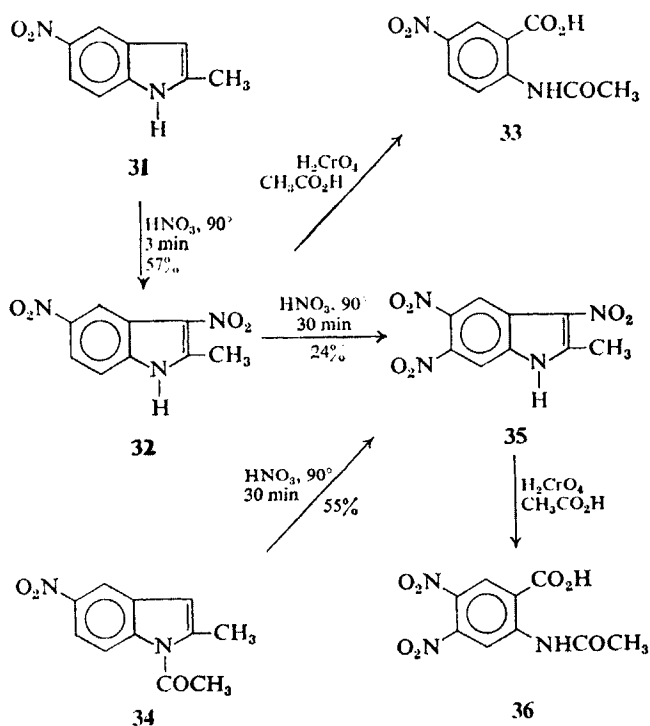
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rationalized if mixtures of the 3-phenylindole (**21**) and its conjugate acid (protonated at Position 3) exist in sulfuric acid. Nitration of the unprotonated form would give **22**; nitration of the conjugate acid would initially give a

The polynitration of 1,2-dimethylindole in nitric acid is analogous to that of 2-methylindole,¹⁹ yielding 1,2-dimethyl-3,6-dinitroindole at 50° and 1,2-dimethyl-3,4,6-trinitroindole at 90°. The yields are slightly lower due to the deactivating effect of the 1-methyl group.⁷² The products are identical with the *N*-methylation products of **24** and **29**, respectively. Nitric acid nitration of 2-phenylindole at room temperature gives 3,6-dinitro-2-phenylindole,⁵⁹ which had been erroneously reported as 3,5-dinitro-2-phenylindole.⁵⁷ A trinitro derivative of 2-phenylindole could not be obtained.

Nitration of 2-methyl-5-nitroindole (**31**) in nitric acid at 90° for 3 min yields 3,5-dinitro-2-methylindole (**32**), as shown by chromic acid oxidation to *N*-acetyl-5-nitroanthranilic acid (**33**)¹⁹ (Scheme 10). Nitration of **32** or the



Scheme 10

1-acetyl derivative of **31** (**34**) gives 2-methyl-3,5,6-trinitroindole (**35**), as shown by chromic acid oxidation to *N*-acetyl-4,5-dinitroanthranilic acid (**36**).

The polynitration of 1,2-dimethyl-5-nitroindole in nitric acid is analogous to that of 2-methyl-5-nitroindole, although yields are again lower.¹⁹ After 3 min at 90°, 1,2-dimethyl-3,5-dinitroindole is obtained, while after 30 min at 90°, 1,2-dimethyl-3,5,6-trinitroindole results. These products are identical

with the *N*-methylation products of **32** and **35**, respectively. Nitration of 5-nitro-2-phenylindole in nitric acid at room temperature gives 3,5-dinitro-2-phenylindole, but a trinitro derivative of 2-phenylindole could not be obtained.⁵⁹

In contrast to the nitration of 2-alkylindoles containing vacancies at Position 3, 2,3-dialkylindoles do not give well-defined nitration products in nitric acid. Only amorphous polymers are obtained from 2,3-dimethylindole⁵⁸ and 1,2,3-trimethylindole,¹⁹ even at 0°. Nitration of 1-acetyl-2,3-dimethylindole in acetic acid gives low yields of a mixture of the 4- and 6-nitro derivatives, in addition to products of oxidation at the 2,3-double bond.^{52, 55, 73} The 1-acetyl group apparently deactivates the molecule toward oxidation sufficiently to permit nitration.

The trinitroindoles **30**, **35**, 3,5,7-trinitroindole,⁴⁸ and 2-methyl-3,5,7-trinitroindole⁷⁴ are moderately strong acids, having pK_a values of 7.3–7.4. Although the structures of many of the polynitro-2-alkylindoles were proved by oxidative degradation to known compounds, the reactions proceed with difficulty and the yields are low. This resistance to oxidation is almost certainly due to delocalization of the 2,3-double bond, the site of initial oxidative attack,^{61, 62} by resonance interaction with the nitro groups. Polynitroindoles containing a 5-nitro group (para to the indole nitrogen) undergo complete destruction within 30 sec when treated with concentrated aqueous alkali solutions. This is believed to be due to electrophilic attack at Position 7a by hydroxide ion, followed by opening of the pyrrole ring and subsequent decomposition. In contrast, polynitroindoles that do not contain 5-nitro groups, and are, therefore, not activated toward electrophilic attack, are completely inert to concentrated aqueous alkali solutions.

Evidence was previously presented which shows that in sulfuric acid, 2-alkylindoles undergo nitration in the form of their conjugate acids (protonated at Position 3) to yield 2-alkyl-5-nitroindoles. Since 2-alkylindoles give 3,6-dinitro derivatives as the first isolable products in nitric acid, this reaction must proceed by a totally different mechanism. This reaction is believed to proceed by nitration of the unprotonated 2-alkylindole.¹⁹ This hypothesis is supported by the observation that the 4- and 6-positions of 2-phenylindoles are conjugated with the indole nitrogen in neutral media.⁶⁸ While nitration in sulfuric acid occurs smoothly at 0°, thermal initiation is required to begin the violently exothermic reaction in nitric acid. This is attributed to two factors: (1) Nitric acid alone is known to be a much poorer source of nitronium ions than is nitric acid in sulfuric acid^{75, 76}; and (2) nitric acid is still sufficiently strong to protonate Position 3 of the indole, and thereby prevent attack at this position by a nitronium ion. Heating should favor dissociation of the protonated indole, creating a higher concentration of the reactive free indole. Initial nitration, which almost certainly occurs at

the highly nucleophilic Position 3, would yield a mononitro derivative of greatly reduced basicity. This intermediate should exist largely in the unprotonated form, which could undergo further nitration very rapidly and sustain the exothermic reaction.

The nitration of 2-methylindole in nitric acid can be effected at room temperature if sodium nitrite is used as a catalyst.¹⁹ Since sodium acetate does not catalyze the reaction, the catalytic effect of sodium nitrite is not that of a base diminishing the acidity of the medium to a point where a sufficiently high concentration of unprotonated indole exists to initiate the reaction. These results do suggest that the thermally initiated nitration of 2-alkylindoles might involve an initial nitrosation reaction. The thermal initiation period could be interpreted partly as an induction period during which the nitrosating agent is being formed through reduction of nitric acid by the indole. Once 3-nitrosation has occurred, the nitrosating agent would be formed by the reduction of nitric acid as it oxidizes the nitrosation product to an intermediate mononitroindole. The second nitration would then proceed on the mononitroindole as previously mentioned.

From this evidence, the nitration of 2-alkylindoles appears to involve nitration of the unprotonated indole first at Position 3, perhaps by a nitrosation-oxidation mechanism, and then at Position 6. Since nitration takes place in Position 6, and sometimes in Position 4, it appears that electronic activation of the benzene ring by the indole nitrogen occurs via the 2,3-double bond and not by direct aniline-type activation when the indole nucleus is not protonated.

Nitration of 2-alkyl- and 2-arylindoles with ethyl nitrate in the presence of sodium ethoxide yields the 3-nitro derivatives.³⁹ The preparation of 3-nitroindole by this method has been described [Section II.A.1.a.(1)]. The 3-nitro derivatives can also be prepared by oxidation of 3-oximino-3*H*-indoles with nitric^{71, 78} or nitrous acid.⁵⁷ Nitration of 3-acetyl-2-methylindole in acetic acid also gives 2-methyl-3-nitroindole.¹⁹ The displacement of the 3-acetyl group by a nitro group is discussed in detail in Section II.A.1.a.(4).

The results described above lead to the following orientation rules for the nitration of 2-alkyl- and 2-arylindoles¹⁹:

(1) Nitration of 2-alkylindoles and their alkyl derivatives under conditions of complete protonation and a high concentration of nitronium ions (nitric acid in sulfuric acid) at 0–15° yields the 5-nitroindoles. Attempted further nitration by heating leads to decomposition.

(2) Nitration of 2-alkylindoles and 1,2-dialkylindoles under conditions of incomplete protonation and a low concentration of nitronium ions (concentrated nitric acid alone or in acetic acid) yields, after thermal initiation, the 3,6-dinitroindoles. Further nitration by heating in concentrated nitric acid at 90° yields the 3,4,6-trinitroindoles.

(3) Nitration of 2-alkyl-5-nitroindoles by heating in concentrated nitric acid yields first the 3,5-dinitroindoles and then, upon further heating, the 3,5,6-trinitroindoles.

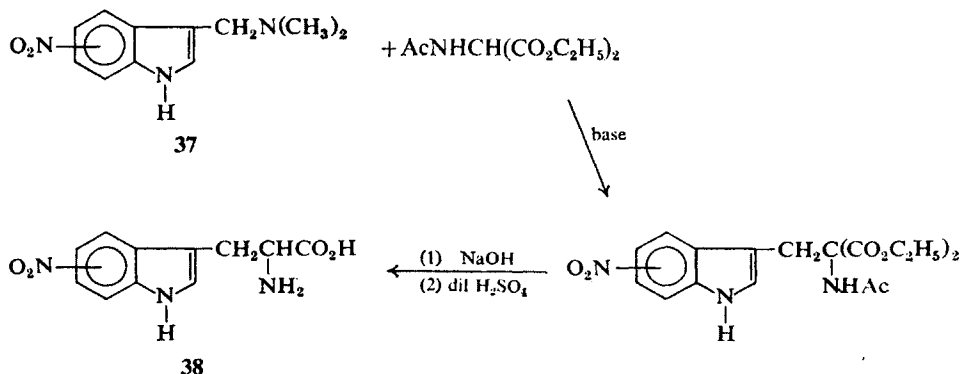
(4) The nitration of 2-arylindoles is analogous to that of 2-alkylindoles except that in concentrated nitric acid thermal initiation is not required and nitration stops at the dinitration stage.

(5) Nitration of 2-alkylindoles and 2-arylindoles with ethyl nitrate under basic conditions yields the 3-nitroindoles.

(6) Neither tetranitration nor 7-nitration of an indole nucleus has been observed.

(c) DEHYDROGENATION OF NITROINDOLINES. Alkylnitroindoles can be prepared by dehydrogenation of alkylnitroindolines with chloranil or palladium-on-charcoal in refluxing xylene.^{43, 44} This method is quite useful for the preparation of alkyl-5-nitroindoles and alkyl-6-nitroindoles because the required nitroindolines can be obtained in excellent yields by nitration of the indolines (see Section II.A.2.a).

(3) *Nitro Derivatives of Gramine and Tryptophan.* The four bz-nitro derivatives of gramine (37) have been prepared in good yield by condensation of 4-,⁷⁸ 5-,⁷⁹ 6-,⁸⁰ and 7-nitroindole^{78, 81} with formaldehyde and dimethylamine in glacial acetic acid. These derivatives of gramine have been used to prepare the corresponding nitro derivatives of tryptophan (38)⁷⁸⁻⁸¹ by the classical acetamidomalonnate synthesis of tryptophan derivatives (Scheme 11).



Scheme 11

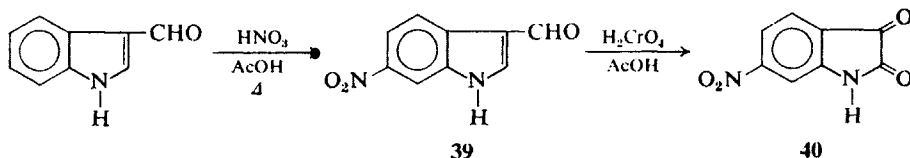
While nitration of indole and alkylindoles containing an open Position 2 under acidic conditions is unsuccessful, gramine⁸² and tryptophan^{83, 84} undergo nitration with concentrated nitric acid in acetic acid. Gramine yields mostly 6-nitrogramine, along with some 4-nitrogramine, while tryptophan yields 6-nitrotryptophan. The successful nitration of these compounds has been attributed to protonation of the side-chain amino group.⁵⁸ The resulting positive charge could, through electrostatic repulsion, prevent oxidative attack at Position 2 or the 2,3-double bond, which are vulnerable positions for electrophilic attack.

Like gramine, 1-methylgramine yields a mixture of 6-nitro and 4-nitro derivatives when treated with a nitric-acetic acid mixture. In contrast, 2-methylgramine and 1,2-dimethylgramine yield only the 6-nitro derivatives.⁸² The failure of these compounds to undergo 4-nitration is probably due to increased steric hindrance about the 4-position.

The nitrogramines^{85, 86} and nitrotryptophans⁸⁷ show little or no pharmacological activity.

(4) *Nitro Derivatives of Indoles Containing Electronegative Substituents.* Indoles containing electronegative substituents in Position 3 are stabilized sufficiently toward oxidative attack to permit successful nitration in nitric acid or a nitric-acetic acid mixture. Nitration usually occurs at the 6- or 6- and 4-positions. Displacement of the 3-substituents by a nitro group is also observed, especially if a 2-alkyl substituent is present.

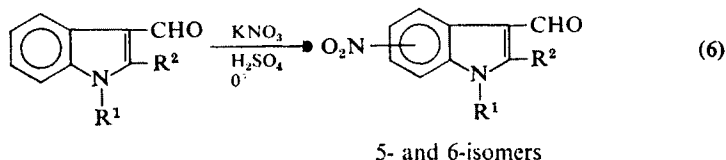
Nitration of indole-3-carboxaldehyde with nitric acid in acetic acid gives 6-nitroindole-3-carboxaldehyde (**39**).^{46, 88, 89} Oxidation of **39** with chromic acid in acetic acid provides a feasible synthetic route to 6-nitroisatin (**40**)⁸⁹ (Scheme 12). Nitration of 1-methyl-, 2-methyl-, or 1,2-dimethylindole-3-



Scheme 12

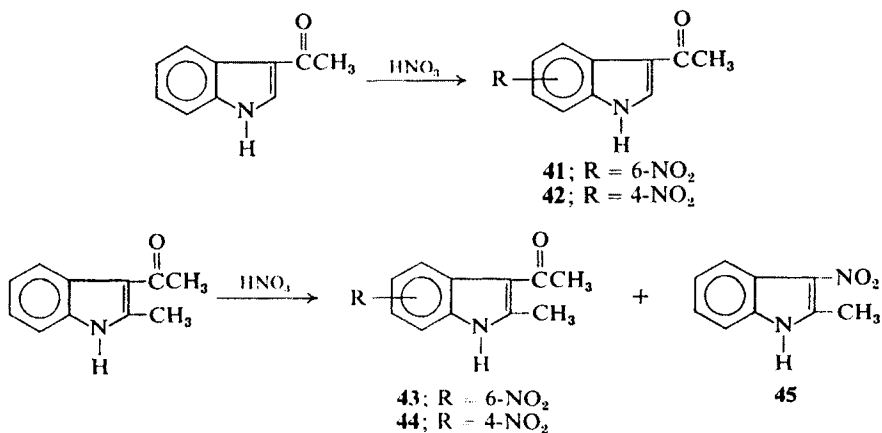
carboxaldehyde under similar conditions gives quite different results.⁹⁰ In every case, mixtures are obtained among which are found the 4-nitro derivatives, the 6-nitro derivatives, the 3-nitro- and the 3,6-dinitroindoles. The structures of the products were proved by oxidative degradation to anthranilic acid derivatives. The orientation of the nitro groups in these products indicates that only the unprotonated form of the aldehyde is undergoing nitration in nitric acid.

The nitration of indole-3-carboxaldehyde and its alkyl derivatives in sulfuric acid has also been studied.^{88, 91} In every case, inseparable mixtures of the 5- and 6-nitro derivatives are obtained (Eq. 6) in an approximate ratio of 3:2. The structures of the products were proved by degradation of the



mixtures with hydrogen peroxide in acetic acid to anthranilic acid derivatives while the composition of the mixture was determined by uv spectroscopy. The isolation of both 5- and 6-nitro derivatives suggests that both the protonated and unprotonated forms of the indole-3-carboxaldehydes are undergoing nitration. Nitrative displacement of the 3-formyl group does not occur as it did with nitric acid; this might be due to the much lower reaction temperature in sulfuric acid.

In acetic acid, 3-acetylindole does not undergo nitration.⁹² In nitric acid alone, however, a mixture containing mostly 3-acetyl-6-nitroindole (**41**) and some 3-acetyl-4-nitroindole (**42**) is obtained⁴⁰ (Scheme 13). These



Scheme 13

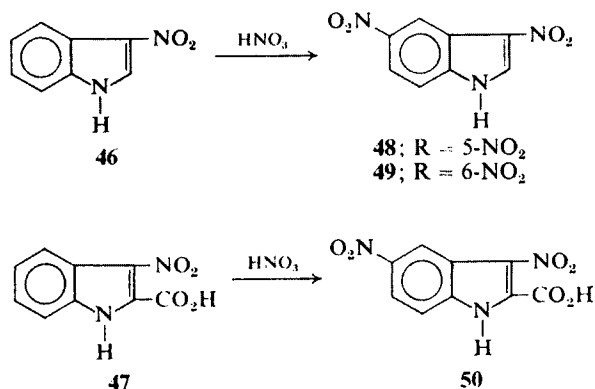
structures were established by deacetylation to 6-nitroindole and 4-nitroindole, respectively. The nitration of 3-acetyl-2-methylindole is accompanied by deacetylation, giving 3-acetyl-2-methyl-6-nitroindole (**43**), 3-acetyl-2-methyl-4-nitroindole (**44**), and 2-methyl-3-nitroindole (**45**)¹⁹ (Scheme 13). Like the indole-3-carboxaldehydes, nitration of 3-acetylindole in sulfuric acid gives an inseparable mixture of the 5- and 6-nitro derivatives.⁴⁰

The ability of the 2-methyl group to promote nitrative displacement of 3-formyl and 3-acetyl groups is attributed to its electron-releasing properties and to its steric compression of the 3-acyl group, which would reduce its conjugation with the 2,3-double bond.⁴⁰ Both factors would increase the nucleophilicity of Position 3, and thereby increase the rate of nitrative displacement.

In nitric acid, other 3-acyl derivatives of indole also undergo nitration in the 4- and 6-positions. Thus, ethyl indole-3-carboxylate,⁴⁶ indole-3-carboxylic acid,⁹³ *N,N*,2-trimethyl-indole-3-glyoxamides,⁹⁴ ethyl indole-3-glyoxylate,⁸⁸ and indole-3-carbonitrile⁴⁰ give mixtures of the 4- and 6-nitro derivatives.

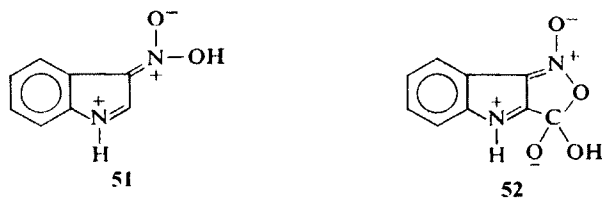
Displacement of the 3-acyl group during nitration does not occur with these compounds.

In contrast to the 3-acylindoles, which all undergo nitration in the Positions 4 and 6, 3-nitroindole (**46**) and 3-nitroindole-2-carboxylic acid (**47**) give different results. In nitric acid, **46** gives a mixture of 3,5-dinitroindole (**48**) (major) and 3,6-dinitroindole (**49**) (minor), while **47** gives only 3,5-dinitroindole-2-carboxylic acid (**50**) (Scheme 14).⁴⁰ The formation of **48** might arise



Scheme 14

by nitration of the protonated aci-nitro form (**51**) of **46**, while **50** could arise by nitration of the nitronolactol form (**52**) of **47**. Both **51** and **52** have an



immonium group adjacent to the benzene ring, a configuration that resulted in 5-nitration in the 2-alkylindole series [Section II.A.1.a.(2).(b)]. In contrast, 2-methyl-3-nitroindole gives only 4- and 6-nitration.¹⁹ The lack of 5-nitration in this case can be attributed to steric interaction of the methyl and nitro groups, which would prevent formation of an aci-nitro form analogous to **51**. This would lead to normal activation of Positions 4 and 6.

Indole-2-carboxylic acid undergoes 3-nitration⁴¹ while its ethyl ester undergoes 4-nitration.⁴⁰ This difference is attributed to increased steric hindrance of Position 3 by the ethoxycarbonyl group. It also suggests that

Position 4 might be preferred electronically to Position 6 for electrophilic attack if steric hindrance of Position 4 by a 3-substituent is not a factor.

The nitration of indoles containing electronegative 3-substituents can be summarized by the following orientation rules:

(1) If the 3-substituent is not a nitro group, nitration with concentrated nitric acid, alone or in acetic acid, yields 6-nitration, sometimes together with 4-nitration. If a 2-alkyl group is present, displacement of the 3-substituent by a nitro group frequently occurs.

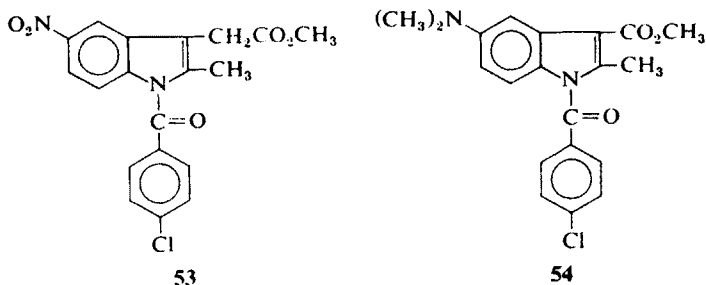
(2) If the 3-substituent is a nitro group, 5-nitration or a mixture of 5- and 6-nitration occurs in nitric acid. If a 2-alkyl substituent is present, however, only 4- and 6-nitration occur.

(3) Nitration in sulfuric acid yields inseparable mixtures of 5- and 6-nitro derivatives.

b. REACTIONS. Mononitroindoles undergo facile reduction to the corresponding amines with hydrogen in the presence of Raney nickel⁵⁸ or palladium on carbon.⁹⁵ Chemical reduction is less satisfactory; reduction of 2-methyl-5-nitroindole with tin and hydrochloric acid leads to a chlorine-containing 5-amino-2-methylindole and other products.⁵⁸ The reduction of di- and trinitroindoles has not been explored.

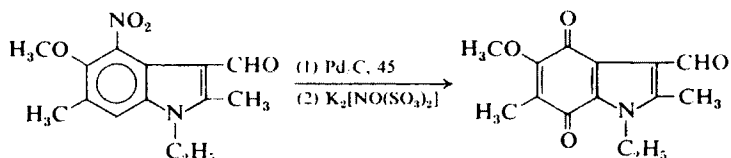
Mononitroindoles containing a vacant Position 3 undergo the usual electrophilic reactions of indoles, such as formylation with dimethylformamide and phosphorus oxychloride,⁷⁸⁻⁸¹ the Mannich reaction with formaldehyde and dimethylamine,^{58, 64} and addition to electron-deficient olefins.⁵⁸

c. USEFUL COMPOUNDS. Several patents⁹⁶⁻¹⁰⁰ assigned to Merck and Company claim that nitroindoles derived from indole-3-acetic acid, such as **53**, have antiinflammatory activity. Amines such as **54** which are prepared from the reduction product of **53**, also possess this activity.



Equation (3) (Section I.B) illustrates the condensation of 3-nitrosoindoles with 1,2,3,3-tetramethyl-3*H*-indolium salts to give dyes useful as photographic desensitizers. This reaction can also be applied to 5-nitro-1,2,3,3-tetramethyl-3*H*-indolium salts.^{29, 33} Dyes for polyacrylonitrile fabrics have been prepared from nitroindoles.¹⁰¹

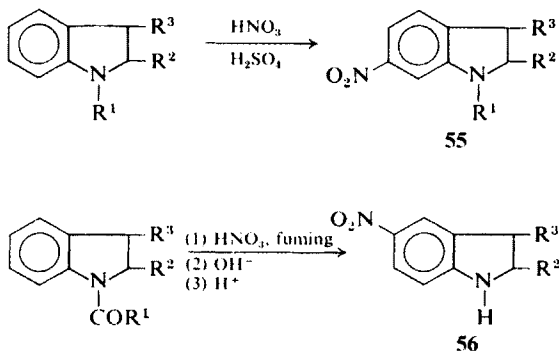
Several patents¹⁰²⁻¹⁰⁷ describe the use of nitroindoles in the preparation of 4,7-indoloquinones, which are reported to have broad spectrum antibacterial activity. The key steps are shown in Scheme 15.



Scheme 15

2. Nitroindolines

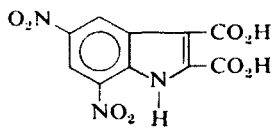
a. PREPARATION. Being typical aromatic amines, indoline, alkylindolines, and their *N*-acyl derivatives undergo nitration in a manner completely analogous to aniline and its acyl derivatives. Nitration in sulfuric acid occurs meta to the nitrogen atom to give 6-nitroindolines (**55**) in high yield.^{34, 43-45, 108} Nitration in nitric acid, followed by alkaline hydrolysis of the products, gives 5-nitroindolines (**56**)^{44, 45, 109} in high yield (Scheme 16). In the nitration of



Scheme 16

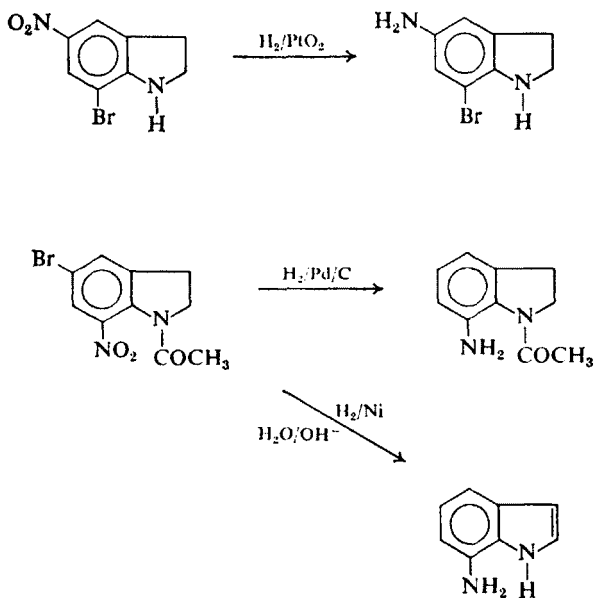
1-acetylindoline, a small amount of 5,7-dinitroindoline is obtained as a by-product.^{44, 48} If Position 5 of the 1-acylindoline is occupied, fuming nitric acid effects nitration in Position 7.^{109, 110}

The nitration of indoline has historical significance. Tafel¹¹⁰ degraded strychnine with fuming nitric acid to give "dinitrostrycholcarboxylic acid," which was shown by Menon and Robinson⁴¹ to be 5,7-dinitroindole-2,3-dicarboxylic acid (**57**). Since indoles do not undergo nitration in Position 7, **57** must arise by nitration of a 2,3-dialkylindoline intermediate, followed by subsequent degradation and oxidation to the indole.



57

b. REACTIONS. The dehydrogenation of nitroindolines to nitroindoles has been discussed [Section II.A.1.a.(1).] Catalytic reduction of nitroindolines with Raney nickel¹¹⁰ or with palladium on carbon¹⁰⁹ yields the corresponding aminoindolines. If a halogen atom is present, it is removed by reduction with Raney nickel or palladium on carbon, but not with platinum dioxide. Reduction with Raney nickel in aqueous alkaline solution causes concomitant dehydrogenation of the indoline nucleus, yielding an aminoindole as the product. These reactions are summarized in Scheme 17.



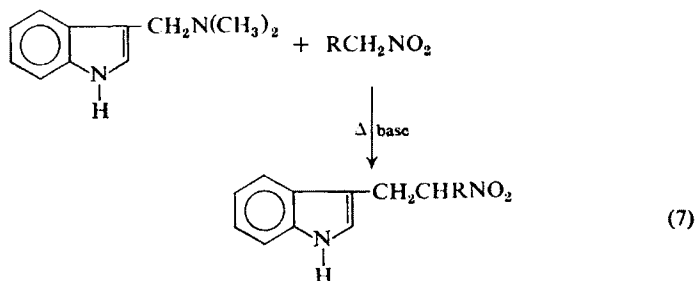
Scheme 17

B. Indoles and Indolines with Side-Chain Nitro Groups

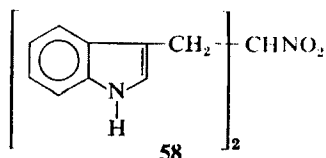
1. Preparation

a. 3-(2-NITROALKYL)INDOLES. The alkylation of nitroalkanes with gramine and its derivatives proceeds smoothly to yield 3-(2-nitroalkyl)indoles¹¹⁴⁻¹²⁰

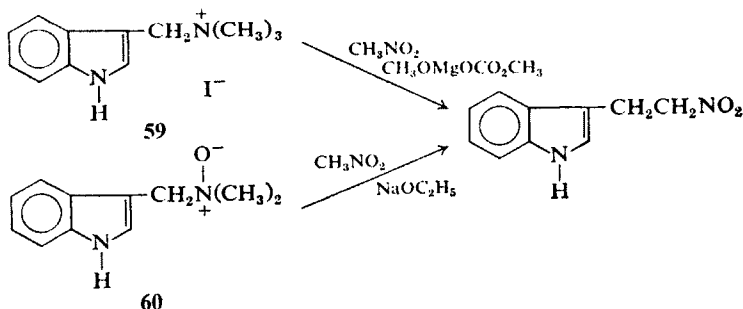
(Eq. 7). This reaction is usually carried out by heating the gramine derivative



in an excess of the nitroalkane or by heating equimolar amounts of the reactants in an inert solvent such as toluene. Basic catalysts have also been used in this reaction.^{114, 118, 119} Alkylation of the nitroalkane usually stops at the monoalkylation stage. Under these conditions, however, nitromethane is dialkylated with gramine, giving 3,3'-(2-nitromethylene)diindole (**58**).¹¹⁴



Monoalkylation of nitromethane can be accomplished by using gramine methiodide (**59**)¹²¹ or gramine-*N*-oxide (**60**)¹²² as alkylating agents, since these reactions proceed under milder conditions (Scheme 18). While gramine

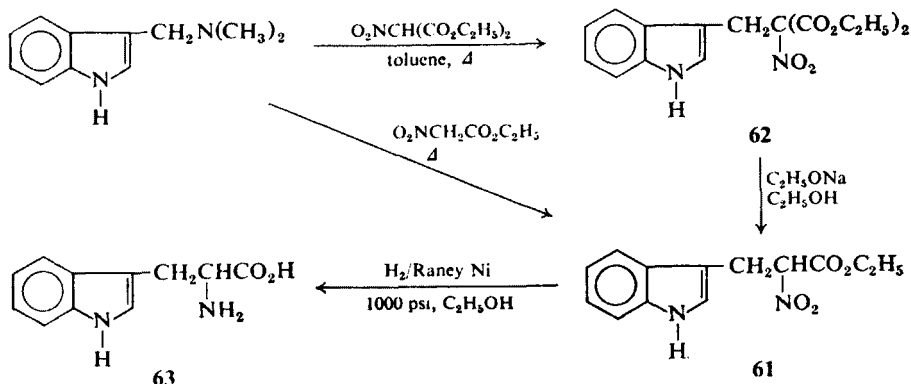


Scheme 18

alkylates nitroalkanes with ease, 3-methyl-2-dimethylaminomethylindole does not.¹¹⁵

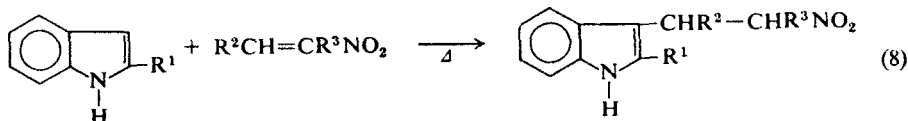
In similar fashion, gramine has been used to alkylate ethyl nitroacetate and diethyl nitromalonate, yielding ethyl α -nitroindole-3-propionate (**61**)¹²³ and ethyl α -carbethoxy- α -nitroindole-3-propionate (**62**),^{124, 125} respectively

(Scheme 19). Reduction of **61** provides a commercial synthesis of tryptophan (**63**). Similar reactions have been employed in the synthesis of serotonin and other tryptophan and tryptamine analogs.¹²⁶⁻¹²⁸

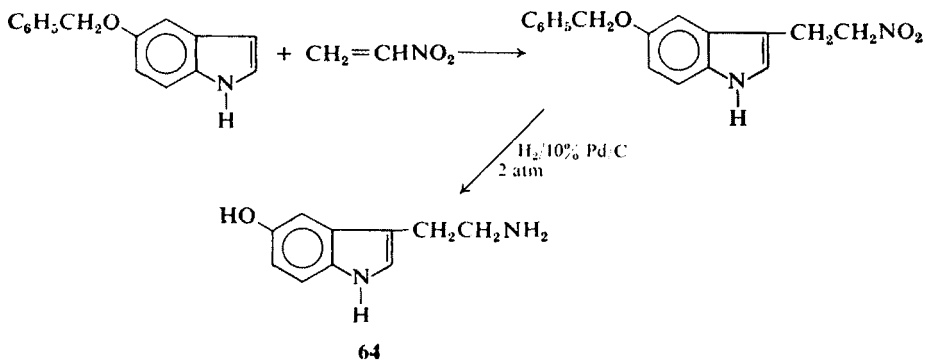


Scheme 19

The addition of indole¹²⁹ and alkylindoles¹³⁰⁻¹³² to nitroolefins also yields 3-(2-nitroalkyl)indoles (Eq. 8). Since polymerization of the nitroolefin is



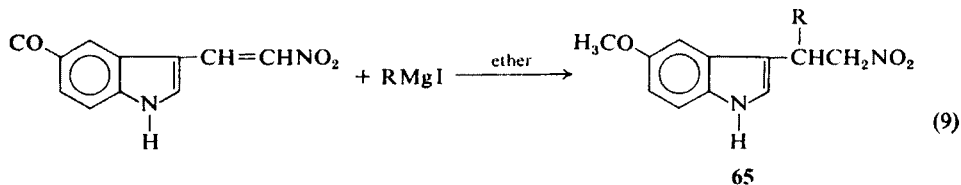
always a competing reaction, the best yields are obtained with those such as 2-nitrostyrene and 2-methyl-2-nitrostyrene, which do not polymerize readily.¹³⁰ Indoles containing 1-alkyl substituents are considerably less reactive than their unsubstituted counterparts.¹³⁰ No product is obtained with 1-methylindole and nitroethylene. The order of reactivity in this reaction appears to



Scheme 20

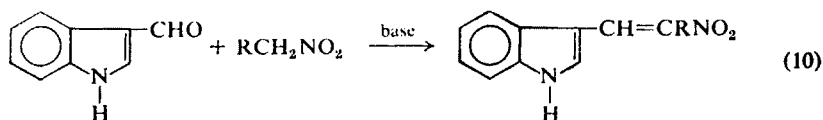
be 2-methylindole > 1,2-dimethylindole > 2-phenylindole > indole > 1-methylindole. The use of indole Grignard reagents in place of the free indoles gives slightly higher yields.^{129, 133, 134} If the 3-alkylindoles are used, addition takes place at the indole nitrogen. The addition of nitroethylene to 5-benzyl-oxyindole provides the basis for a two-step synthesis of serotonin (**64**)¹³⁵ (Scheme 20).

Grignard reagents add to 3-(2-nitrovinyl)indole derivatives (Section II.B.1.b) to give 3-(1-nitro-2-alkyl)indoles (**65**)¹³⁶⁻¹³⁹ (Eq. 9).

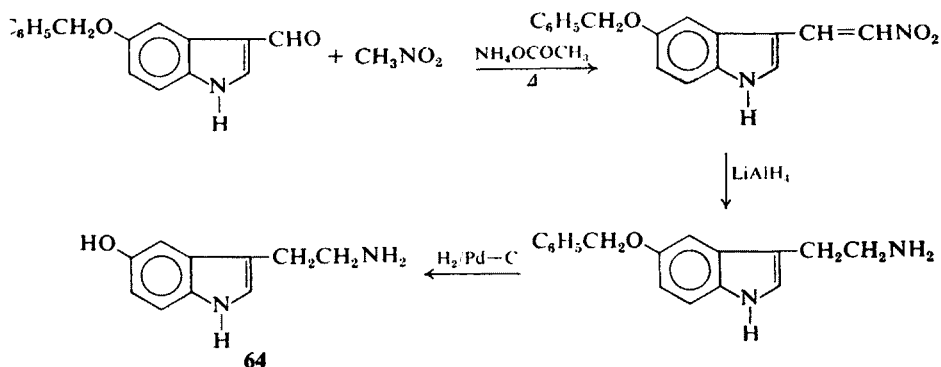


The Fischer indole synthesis has been used to prepare 5-benzyl-oxy-3-(2-nitropropyl)indole.¹⁴⁰

b. (2-NITROVINYL)INDOLES. The preparation of (2-nitrovinyl)indoles (**66**) by condensation of indole-3-carboxaldehydes with 1-nitroalkanes (Eq. 10) has been known for many years.^{141, 142} This reaction was virtually uninvesti-



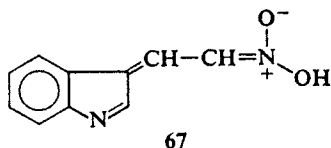
gated until 1958, when the synthesis of serotonin and some of its analogs based on this reaction was reported^{143, 145} (Scheme 21). Since that time, this



Scheme 21

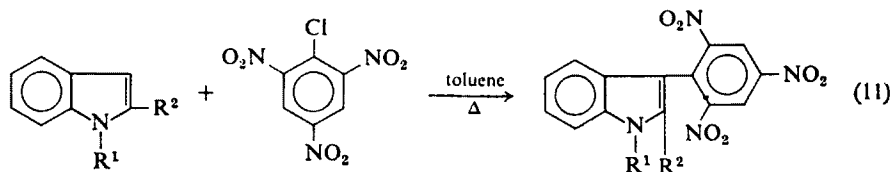
reaction has been the subject of numerous publications and patents, many of them dealing with the preparation of serotonin analogs.

The condensation of indole-3-carboxaldehydes with 1-nitroalkanes is usually carried out in the presence of weakly basic catalysts using an excess of the nitroalkane as solvent. Ammonium acetate¹⁴³ is the preferred catalyst, although alkali metal carbonates¹⁴³⁻¹⁴⁵ and alkylamines¹³⁶⁻¹³⁹ have also been used. The reactions are smooth and give good yields. On the basis of spectral evidence, it is believed that the condensation products obtained from 1-nitroalkanes and indole-3-carboxaldehydes unsubstituted in Position 1 exist in the nitronate form (67) rather than as true nitro compounds.¹⁴⁶ The many 3-(2-nitrovinyl)-indoles prepared by this method are listed in Table II.B.2.



The condensation of 1-nitroalkanes with indolecarboxaldehydes containing the formyl group in positions other than Position 3 is equally facile. Reaction conditions similar to those described above are used. Thus, indolecarboxaldehydes which contain the formyl group in Positions 2,^{147, 148} 4,¹⁴⁹ 5,¹⁴⁹ 6,¹⁴⁹ and 7,^{149, 150} have been condensed with nitroalkanes. The resulting (2-nitrovinyl)indoles are listed in Table II.B.2.

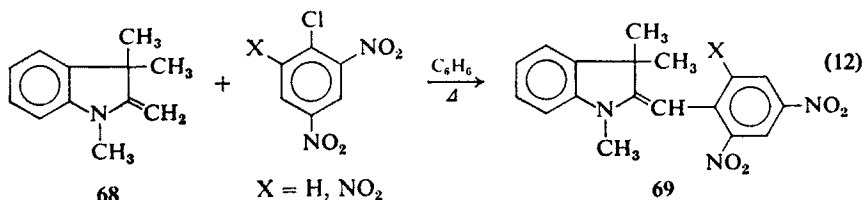
c. 2- AND 3-(NITROPHENYL)INDOLES. The cyclization of 2'-nitroacetophenone¹⁵¹ and 3'-nitroacetophenone¹⁵² phenylhydrazones with polyphosphoric acid gives 2-(2-nitrophenyl)indole and 2-(3-nitrophenyl)indole, respectively. Cyclization of 2-nitrophenylpyruvic acid phenylhydrazone and decarboxylation of the product yields 3-(2-nitrophenyl)indole¹⁵³; 2-methyl-3-(4-nitrophenyl)indole and 2-phenyl-3-(4-nitrophenyl)indole are obtained as nitration products of 2-methyl-3-phenylindole and 2,3-diphenylindole, respectively.⁷⁰ Preparation of 3-(2,4-dinitrophenyl)-2-methylindole by cyclization of 2',4'-dinitrophenylacetone phenylhydrazone is reported.¹⁵⁴



Indoles with Position 3 vacant undergo nucleophilic substitution reactions on picryl chloride to give 3-(2,4,6-trinitrophenyl)indoles¹⁵⁵ (Eq. 11). Initially, only a 1:1 molecular adduct (π -complex) of the indole and picryl chloride forms; subsequent refluxing of a toluene solution of this adduct effects the

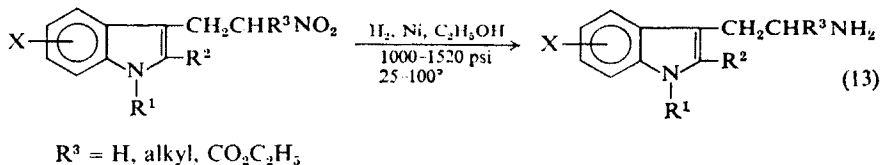
substitution reaction. Skatole (3-methylindole) does not undergo a substitution reaction with picryl chloride, but gives only the 1:1 molecular adduct.

Indolines containing a 2-methylene group also undergo nucleophilic substitution reactions with activated chlorobenzene derivatives.¹⁵⁶ In refluxing benzene, 2-methylene-1,3,3-trimethylindoline (68) reacts with 2,4-dinitrochlorobenzene and picryl chloride to give 2-(2,4-dinitrobenzylidene)-1,3,3-trimethylindoline (69, X = H) and 2-(2,4,6-trinitrobenzylidene)-1,3,3-trimethylindoline (69, X = NO₂), respectively (Eq. 12).



2. Reactions

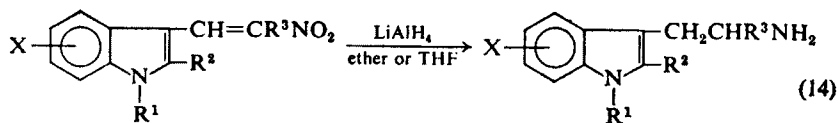
The 3-(2-nitroalkyl)indoles and ethyl β -nitroindole-3-propionates have been reduced to tryptamine and tryptophan analogs, respectively, with a variety of reducing agents. Catalytic hydrogenation over Raney nickel has been the most widely used method.^{114, 123-125, 157} The exact conditions vary with individual compounds, but most require high temperature and/or high pressure (Eq. 13). Other methods which have been employed are catalytic



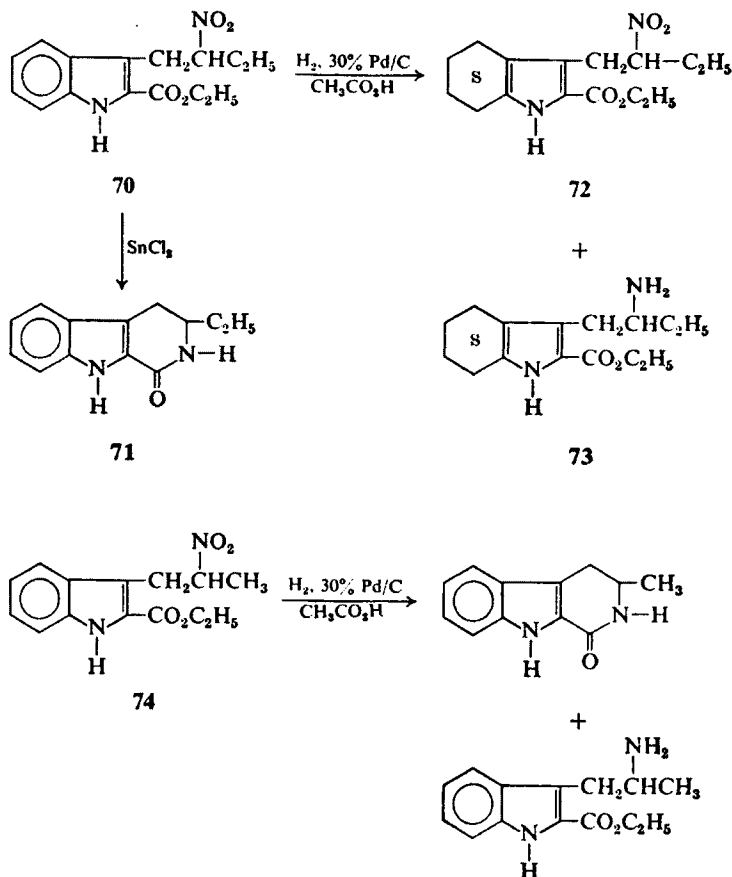
hydrogenation over platinum dioxide^{129, 133, 158} or palladium on carbon,^{135, 140} chemical reduction with lithium aluminum hydride in ether^{120, 126, 127} or tetrahydrofuran (THF),¹¹⁷ stannous chloride,¹⁵⁹ or iron and hydrochloric acid,¹⁶⁰ and electrolytic reduction.¹⁶¹ Catalytic hydrogenation over palladium on carbon is frequently used in the synthesis of serotonin analogs, since concomitant hydrogenolysis of the 5-benzyloxy protective group also occurs.^{135, 140} Derivatives of tryptamine, tryptophan, and serotonin have many interesting pharmacological properties and find use in the pharmaceutical industry.

Tryptamine derivatives can also be prepared by reduction of 3-(2-nitrovinyl)indoles (Eq. 14). This reduction is almost always carried out with

lithium aluminum hydride in ether^{143, 145} or THF.¹³⁶⁻¹³⁹ Indoles containing 2-nitrovinyl groups in positions other than Position 3 also undergo smooth reduction with lithium aluminum hydride.¹⁴⁷⁻¹⁴⁹



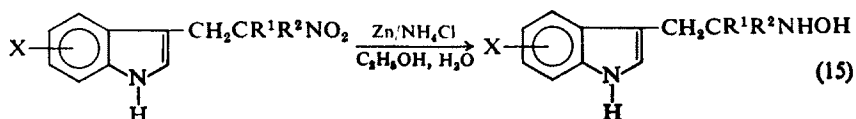
The reduction of ethyl 3-(2-nitrobutyl)indole-2-carboxylate (70) with stannous chloride is followed by spontaneous cyclization, yielding 3-ethyl-1-oxo-1,2,3,4-tetrahydro- β -carboline (71)¹⁵⁹ (Scheme 22). This reaction is quite valuable, since this type of β -carboline derivative can be used as a basis for the synthesis of yohimbine alkaloids and other heterocyclic systems.¹⁵⁹



Scheme 22

However, catalytic hydrogenation of **71** over palladium on carbon results in partial reduction of the indole nucleus, giving a mixture of ethyl 3-(2-nitrobutyl)-4,5,6,7-tetrahydroindole-2-carboxylate (**72**) and ethyl 3-(2-aminobutyl)-4,5,6,7-tetrahydroindole-2-carboxylate (**73**).¹⁶² Ethyl 3-(2-nitropropyl)indole-2-carboxylate (**74**) reduces normally (Scheme 22). It is proposed that the side chain of **70** blocks all approaches of the nitro group to the surface of the catalyst, while the shorter side chain of **74** permits contact between the catalyst and the nitro group to occur.

The reduction of 3-(2-nitroalkyl)indoles with zinc and ammonium chloride in ethanol yields 3-(2-hydroxylaminoalkyl)indoles rather than 3-(2-aminoalkyl)indoles^{163, 164} (Eq. 15). The attempted reduction of 3-(2-nitropropyl)-



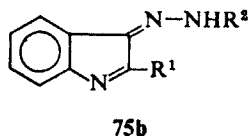
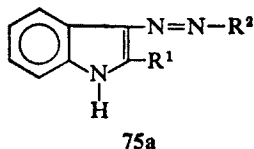
indole to 3-(2-hydroxylaminopropyl)indole by controlled catalytic hydrogenation in methanol containing hydrochloric acid over platinum resulted instead in reduction of the indole nucleus, giving a mixture of 3-(2-nitropropyl)indoline and 3-(2-nitropropyl)octahydroindole.¹⁶³

III. Azo and Azoxy Derivatives

A. Azo Derivatives

1. Azoindoles

Indole and 2-substituted indoles react with diazonium salts to give 3-arylaazoindoles (**75a**) or the tautomeric 3-arylhydrazono-3*H*-indoles (**75b**).^{1, 25, 165-173} The form in which these products exist has not been

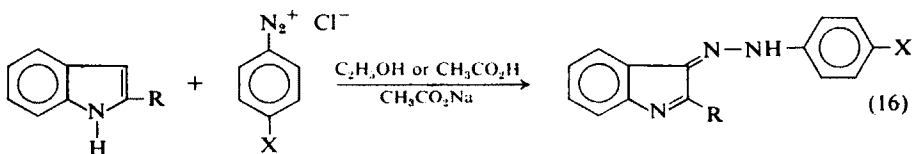


determined, but by analogy with nitroso derivatives of 2-substituted indoles, which exist as 3-oximino-3*H*-indoles, and with other arylhydrazones, it is probable that the hydrazone form, **75b**, is the correct structure.

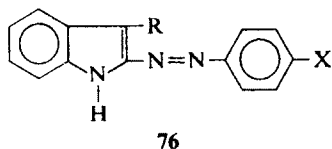
Indole reacts with benzenediazonium chloride to give a mixture of products from which 3-phenylhydrazone-3*H*-indole can be isolated in poor yield¹⁶⁵ (**75b**; $R^1 = H$, $R^2 = C_6H_5$). Other diazonium salts give similar results.^{166,167} Many of the by-products apparently arise from side reactions of the diazonium salts, since those containing strongly electronegative substituents in the para positions react smoothly with indole.^{167, 168} In fact, 4-nitrophenyldiazonium chloride gives 3-(4-nitrophenylhydrazone)-3*H*-indole (**75b**; $R^1 = H$, $R^2 = p\text{-}C_6H_4NO_2$) in nearly quantitative yield.¹⁶⁷

The reaction of indole with 4-nitrophenyldiazonium chloride has been studied in detail.¹⁶⁷ The reaction is nearly quantitative over the pH range 4–6, but lower yields result at higher pH values due to side reactions of the diazonium salt. The reaction is first order in both indole and diazonium salt. The reactive form of indole is the neutral molecule and not the conjugate base. Since no deuterium isotope effect was observed with indole-*d*₃, it is probable that the attack of diazonium ion on the indole molecule is the rate-determining step.

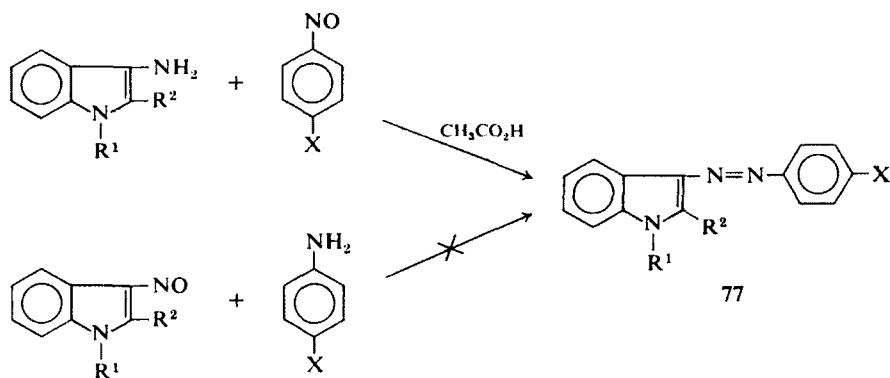
The 2-alkyl- and 2-arylindoles, which are more nucleophilic than indole itself, react smoothly with most diazonium salts to give 3-arylhydrazone-2-substituted-3*H*-indoles^{1, 25, 169–173} (Eq. 16). The reaction is usually run in cold



alcohol in the presence of a base. Under the same conditions, 3-substituted indoles react with diazonium salts to give the corresponding 2-arylazoidoles (**76**).^{172, 174}

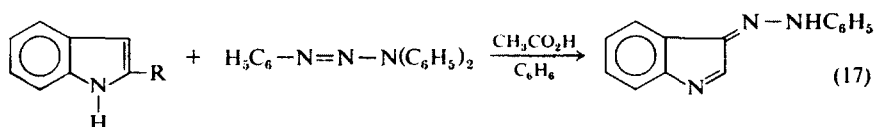


Some 1,2-disubstituted-3-arylazoidoles (**77**) have been prepared by condensation of the corresponding 3-aminoindoles with nitrosobenzene derivatives in acetic acid³¹ (Scheme 23). A possible alternative procedure, reaction of the 3-nitrosoindole with an aniline derivative, does not give **77**.³¹ It has been reported elsewhere that 3-nitrosoindoles do not react with primary amines.^{11, 29}

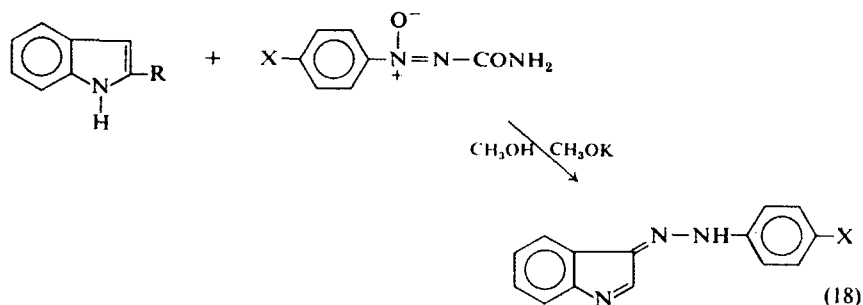


Scheme 23

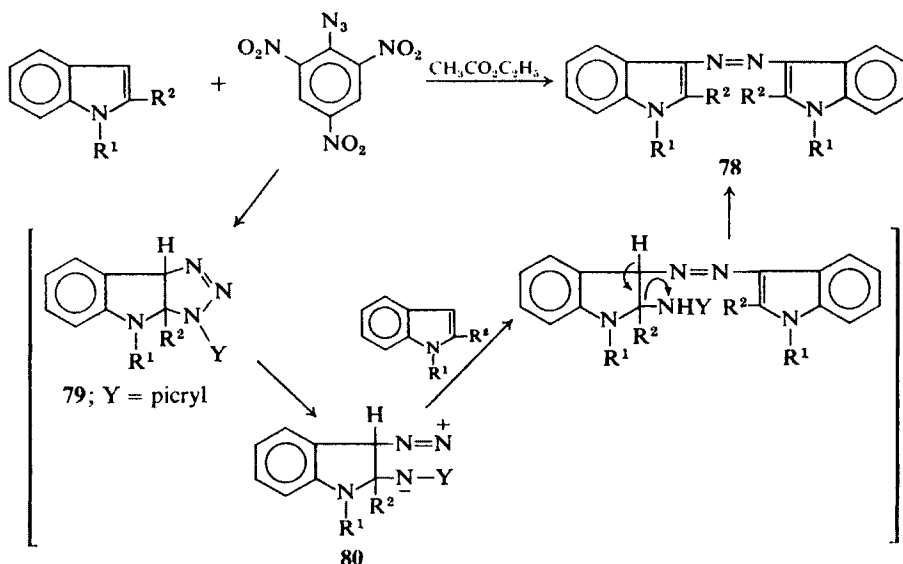
Some 3-aryldiazo-3*H*-indoles have also been prepared by reaction of indoles with phenylazodiphenylamine in the presence of acetic acid¹⁷⁵ (Eq. 17), and by reaction of indoles with arylazoxycarboxamides in the



presence of potassium methoxide (Eq. 18). The mechanism by which the latter reaction proceeds is not known.



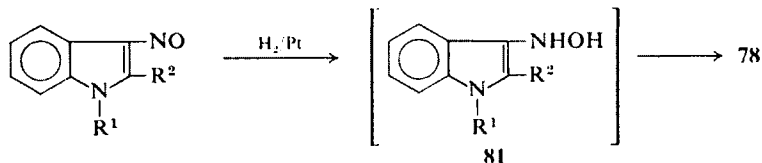
Some 3,3'-azobisindoles (78) have been prepared by reaction of the indole with picryl azide in ethyl acetate¹⁷⁷ (Scheme 24). The products separate as the charge-transfer complexes of the 3,3'-azobisindole and picramide. These can be decomposed in boiling dioxane or hot dimethyl sulfoxide. The reaction is believed to proceed by initial addition of picryl azide to the 2,3-double bond of the indole, giving the triazoline 79, which in turn gives the dipolar intermediate 80. Addition of 80 to the indole and elimination of picramide



Scheme 24

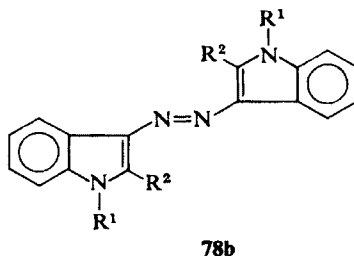
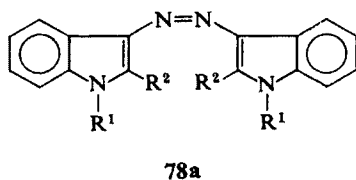
gives **78**. In place of picryl azide, *p*-toluenesulfonamide can be used, although formation of some of the 3-(4-toluenesulfonamido)indole complicates this reaction. Other 3,3'-azobisindoles have been prepared by oxidation of 3-aminoindoles with *N*-nitrosodiphenylamine,³¹ and by oxidation of 1,2-bis-(2-phenyl-3-indolyl)hydrazine with amyl nitrite.^{178, 179} The attempted coupling of diazotized 1,2-diphenyl-3-aminoindole with 1,2-diphenylindole was unsuccessful.³¹

Some 3,3'-azobisindoles have also been isolated as by-products in the platinum-catalyzed hydrogenation of 1,2-disubstituted-3-nitrosoindoles.³¹ Since it is known that 3-aminoindoles do not condense with 3-nitrosoindoles, it is believed that the products arise from self-condensation of the intermediate 3-hydroxylaminoindole (**81**) with the elimination of 2 moles of water (Scheme 25). The 3,3'-azobisindoles are extremely resistant to further reduction.



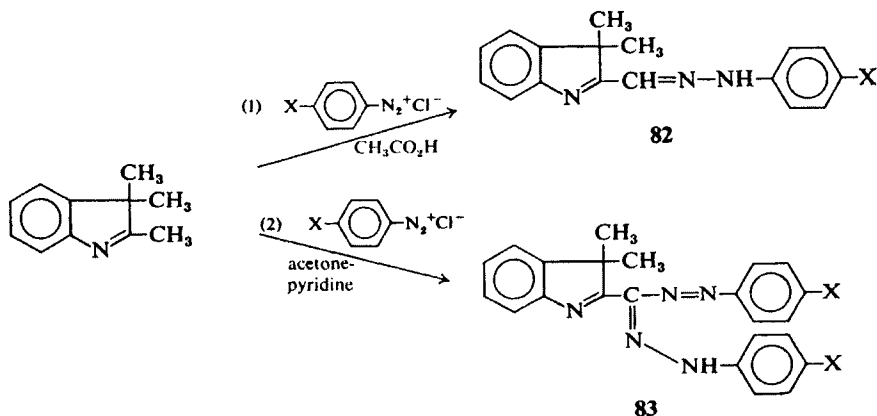
Scheme 25

If the 2 and 2' positions of **78** contain aryl groups, two isomers are frequently isolated. These are apparently the syn- (**78a**) and anti- (**78b**) isomers



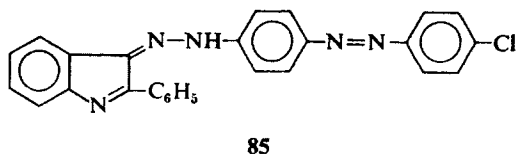
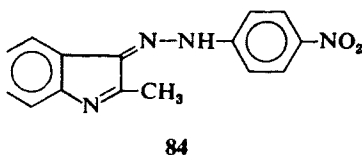
of **78**. They are unusual in that both forms are highly stable and not interconvertible. The higher melting isomer is assumed to be the more stable anti-form, and is the only isomer isolated in some reactions. Since the isomers are not interconvertible and are resistant to reduction, conclusive evidence for their structures is difficult to obtain.

Diazonium salts react with 2,3,3-trimethyl-3*H*-indole to give 2-arylhydrazonomethyl-3,3-dimethyl-3*H*-indoles (**82**)¹⁸⁰ (Scheme 26). If 2 moles of the diazonium salt are used, formazans such as **83** are obtained.¹⁸¹



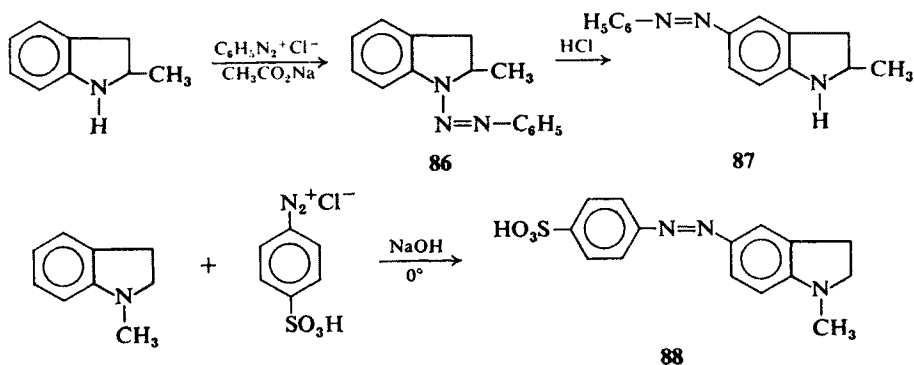
Scheme 26

The reaction of 2-methylindole and 2-phenylindole with diazonium salts forms the basis for several patents.¹⁸²⁻¹⁸⁹ The resulting highly colored 3-arylhydrazono-3*H*-indoles are useful dyes for cotton, cellulose ester, polyester, polyamide, polyurethane, and polyacrylonitrile fibers. The monoazo dyes such as **84** are usually yellow or orange; diazo dyes such as **85** are usually red.



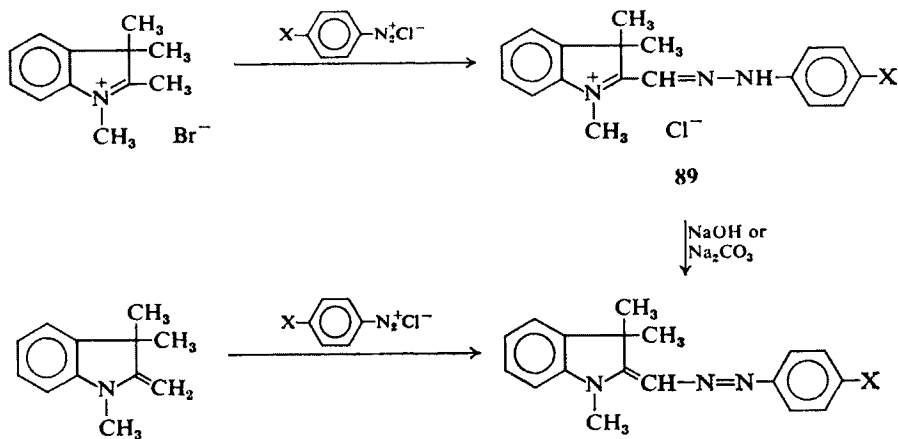
2. Azoindolines

Being a typical secondary aromatic amine, 2-methylindoline reacts with benzenediazonium chloride to give 2-methyl-1-phenylazoindoline (**86**), which rearranges to 2-methyl-5-phenylazoindoline (**87**) in the presence of mineral acids¹⁹⁰ (Scheme 27). Diazotized sulfanilic acid couples with 1-methylindoline to give 1-methyl-5-(4-sulfohenylazo)indoline (**88**)¹⁹¹ (Scheme 27).



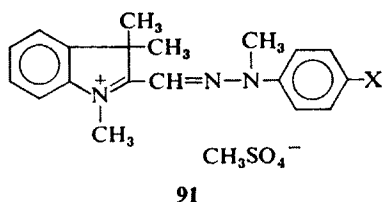
Scheme 27

Reaction of either 1,2,3,3-tetramethyl-3*H*-indolium bromide^{192, 193} or 2-methylene-1,3,3-trimethylindoline^{193, 194} with diazonium salts yields 2-arylhydrazonomethyl-1,3,3-trimethyl-3*H*-indolium salts (**89**), which upon treatment with base yield 2-arylazomethylene-1,3,3-trimethylindolines (**90**)



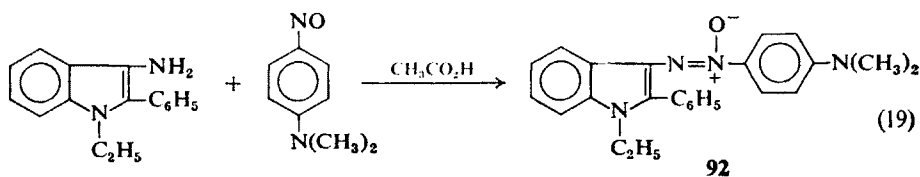
Scheme 28

(Scheme 28). Compounds such as **89** are used as dyes for polyacrylonitrile fibers.¹⁹⁵ Methylation of **90** with dimethyl sulfate gives compounds with general structure **91**, which are used as dyes for acrylic,¹⁹⁶ acetate,¹⁹⁶ and polyacrylonitrile¹⁹⁷ fibers.



B. Azoxy Derivatives

Reaction of 3-amino-1-ethyl-2-phenylindole with *N,N*-dimethyl-*p*-nitrosoaniline in acetic acid gives 3-(4-dimethylaminophenyl-*N'*-azoxy)-1-ethyl-2-phenylindole (**92**)³¹ (Eq. 19). The corresponding azoxy derivative of 1,2-diphenylindole is obtained similarly.



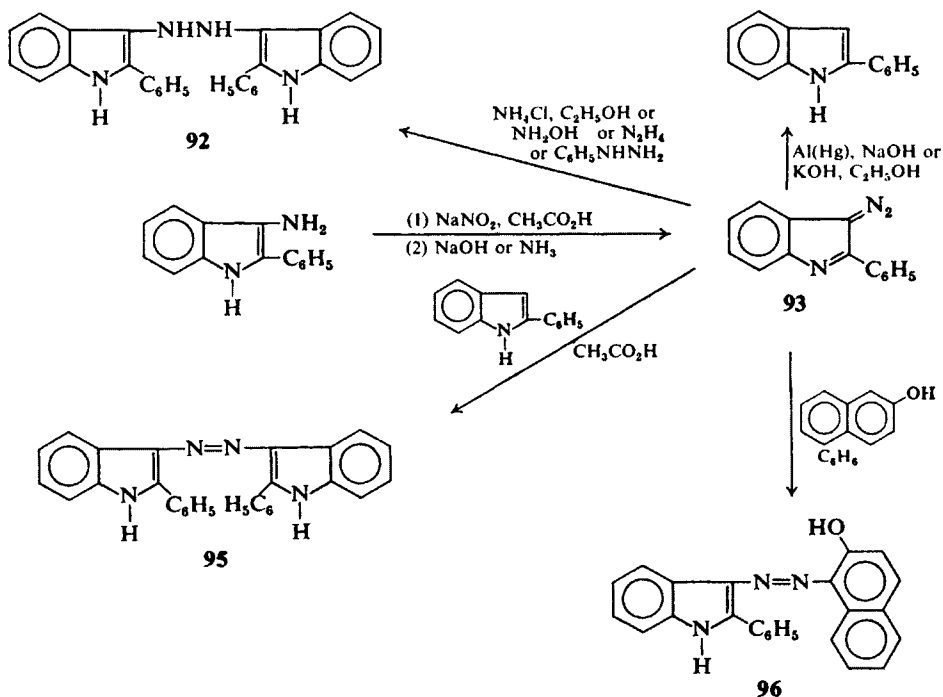
IV. Diazo Derivatives

Diazotization of 3-amino-2-phenylindole^{6, 178, 198–202} and 3-amino-2-methylindole^{198, 203} with nitrous acid in acetic acid, followed by basification of the resulting diazonium salts with alkali or ammonia, gives 3-diazo-2-phenylindole (**93**) (Scheme 29) and 3-diazo-2-methylindole, respectively. These are thermally stable, but light-sensitive compounds.

Scheme 29 illustrates some reactions of **93**. Reduction with aluminum amalgam¹⁹⁸ or ethanolic potassium hydroxide¹⁷⁹ yields 2-phenylindole. In the latter case, ethanol serves as the reducing agent. Reduction with ethanolic ammonium chloride,¹⁷⁹ hydroxylamine,¹⁷⁸ or phenylhydrazine¹⁷⁸ yields

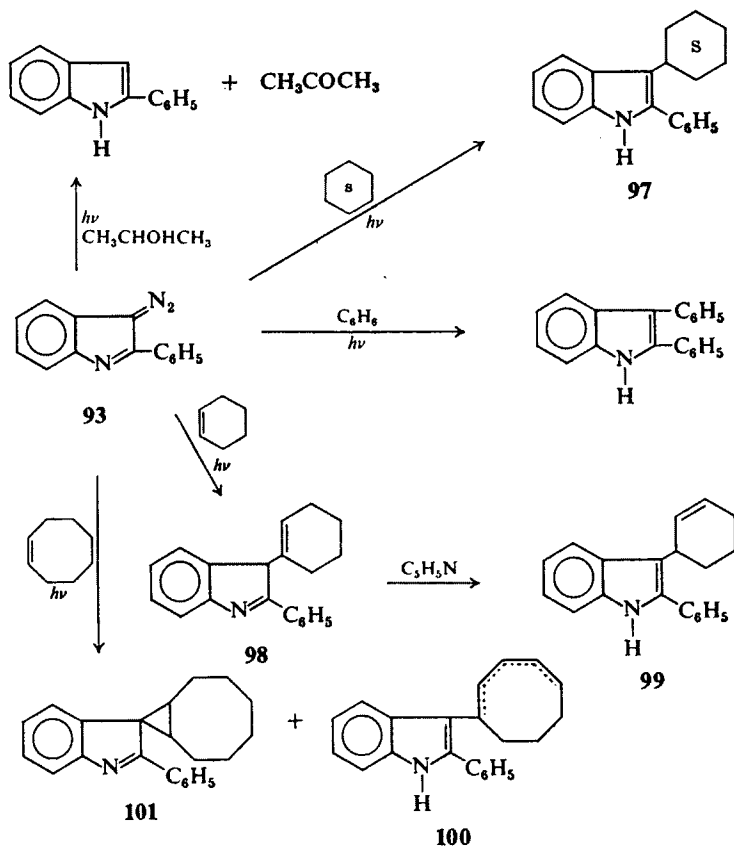
3,3'-hydrazobis-(2-phenylindole) (**94**). Coupling with 2-phenylindole in acetic acid yields 3,3'-azobis-(2-phenylindole) (**95**).²⁰² Coupling with β -naphthol in benzene yields 1-(2-phenylindol-3-ylazo)-2-naphthol (**96**).²⁰¹

The photolysis of **93** has been studied in detail²⁰² (Scheme 30). These reactions undoubtedly proceed via a carbene intermediate. In alcoholic



Scheme 29

solvents, reduction to 2-phenylindole occurs. This reaction is not sensitized by benzophenone. In hydrocarbon solvents, the products are those of insertion. In cyclohexane, 3-cyclohexyl-2-phenylindole (**97**) results; in benzene, 2,3-diphenylindole is obtained. With substituted benzenes, insertion occurs randomly to give all possible isomers (except with anisole, which undergoes insertion only in the para position). In cyclohexene, 3-(1-cyclohexen-1-yl)-2-phenyl-3H-indole (**98**) is formed. This compound rearranges rapidly in the presence of pyridine to give 3-(2-cyclohexen-1-yl)-2-phenylindole (**99**). In cyclooctene, 3-(?-cycloocten-1-yl)-2-phenylindole (**100**) is obtained in addition to a small amount of the cyclopropane **101**. This suggests that with olefinic solvents, the products arise not by insertion but by formation and subsequent rearrangement of a cyclopropane intermediate.



Scheme 30

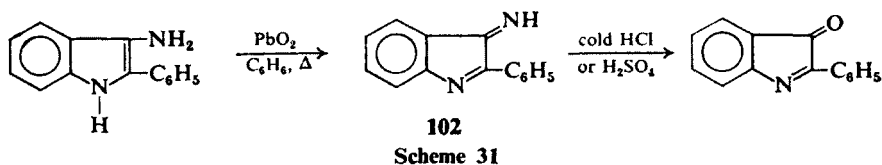
V. Azides

No azides of indole or indoline have been prepared.

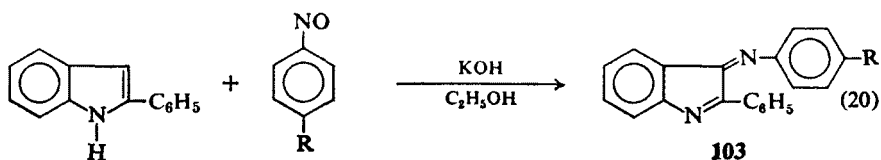
Imino Derivatives

Oxidation of 3-amino-2-phenylindole with lead dioxide in benzene gives 3-imino-2-phenylindole (**102**)²⁷ in high yield (Scheme 31). Hydrolysis of **102** with mineral acids gives 3-oxo-2-phenyl-3*H*-indole.

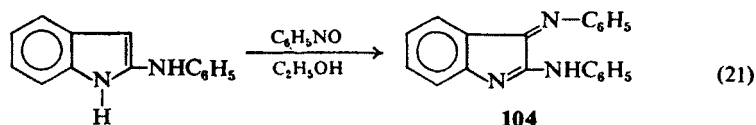
Nitrosobenzene derivatives condense readily with 2-phenylindole in the presence of alkali to give intensely colored 3-arylimino-2-phenyl-3*H*-indoles



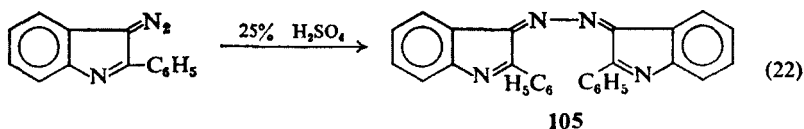
(**103**)^{7, 204} (Eq. 20). This reaction has been proposed as a test for nitroso-benzene derivatives.²⁰⁴ In a similar manner, 2-anilinoindole (oxindole anil)



condenses with nitrosobenzene to give 2-anilino-3-phenylimino-3*H*-indole (isatin dianil) (**104**)²⁰⁵ (Eq. 21). This compound can also be obtained by reaction of 2-methoxy-3-oxo-3*H*-indole (*O*-methylisatin) with aniline.²⁰⁶



Treatment of 3-diazo-2-phenylindole with 25 % sulfuric acid yields 3,3'-azinobis-(2-phenylindole) (**105**)¹⁹⁸ (Eq. 22).



VII. Isocyanates and Isothiocyanates

No isocyanates of indole or indoline have been isolated, although presumably they are intermediates in the preparation of aminoindoles from azides of indolecarboxylic acids. No isothiocyanates of indole or indoline have been reported.

VIII. Tables of Compounds

TABLE I. Nitroso- and Oximinoindoles and -indolines

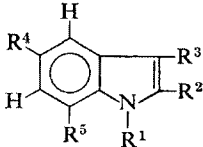
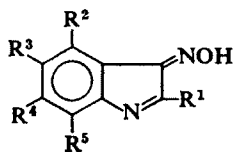
<i>A. Nitrosoindoles</i>						
						
R ¹	R ²	R ³	R ⁴	R ⁵	mp (°C)	Ref.
NO	H	CH ₃	H	H	10–12	24
NO	H	C ₆ H ₅	H	H	60–61	207
NO	C ₆ H ₅	CH ₃	H	H	84–85.5	10
NO	4-C ₆ H ₄ C ₆ H ₅	CH ₃	H	H	279–289	28
H	<i>t</i> -C ₄ H ₉	NO	H	H	235	12
H	<i>t</i> -C ₄ H ₉	NO	CH ₃	H	223–224	10
H	<i>t</i> -C ₄ H ₉	NO	CH ₃	CH ₃	179–180	12
CH ₃	C ₆ H ₅	NO	H	H	144	11
CH ₃	4-BrC ₆ H ₄	NO	H	H	161–162	10
CH ₃	4-C ₆ H ₄ C ₆ H ₅	NO	H	H	214	28
C ₂ H ₅	C ₆ H ₅	NO	H	H	130–131	29, 208
C ₂ H ₅	4-ClC ₆ H ₄	NO	H	H	137–138	29, 208
C ₂ H ₅	4-C ₆ H ₄ C ₆ H ₅	NO	H	H	164	28
C ₆ H ₅	C ₆ H ₅	NO	H	H	200–202	28

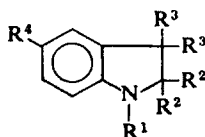
TABLE 1. (Contd.)

B. 3-Oximino-3H-indoles



R ¹	R ²	R ³	R ⁴	R ⁵	mp (°C)	Ref.
H	H	H	H	H	170	17, 18
CH ₃	H	H	H	H	198	4
					198-200	20
C ₆ H ₅	H	H	H	H	244	1
					250	4
					258 dec.	25
					276-278 dec.	59
					280	11
C ₆ H ₅	CH ₃	H	H	H	251	11
C ₆ H ₅	H	CH ₃	H	H	262	2
					273	11
C ₆ H ₅	H	H	CH ₃	H	237	11
C ₆ H ₅	H	H	H	CH ₃	232	2
					244	11
4-CH ₃ C ₆ H ₄	H	H	H	H	240	28
4-ClC ₆ H ₄	H	H	H	H	277	208
4-C ₆ H ₄ C ₆ H ₅	H	H	H	H	274-276	28
4-Pyridyl	H	H	H	H	249-250	209
2-(Indol-3-yl)	H	H	H	H	242	19
					245	16

C. Nitrosoindolines



R ¹	R ²	R ³	R ⁴	mp (°C)	Ref.
NO	H	H	H	83	35
NO	H	CH ₃	H	66	210
NO	H, CH ₃	H	H	54-55	21, 35
NO	H, CH ₃	H	NO	105-106	34
NO	H, C ₆ H ₅	H	H	99.5-100.5	35
NO	CH ₃	CH ₃	H	44.5	211
NO	CH ₃	CH ₃	CH ₃	48.5	211
H	H, CH ₃	H	NO	84.5-85.5	34
H	CH ₃	CH ₃	NO	168	211
CH ₃	H	H	NO	170 (HCl)	36

TABLE I. (Contd.)

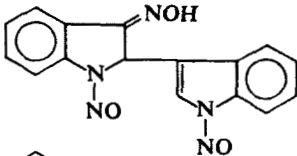
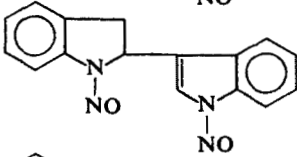
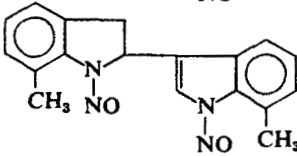
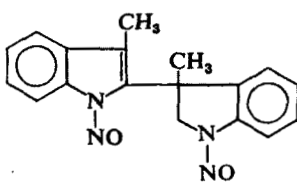
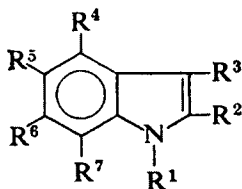
<i>D. Miscellaneous</i>		
Compound	mp (°C)	Ref.
	130-132	24
	175 160-162	14, 16 15
	127-129	15
	134	15

TABLE II. Nitroindoles and Nitroindolines

A. Indoles and Indolines with Nuclear Nitro Groups

1. Mononitroindoles and Alkyl and Aryl Derivatives



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	H	NO ₂	H	H	H	H	213–214 210	40 7
CH ₃	H	NO ₂	H	H	H	H	156–157	90
C ₂ H ₅	H	NO ₂	H	H	H	H	102	39
H	CH ₃	NO ₂	H	H	H	H	243 247 252–253	212 90 19
H	C ₆ H ₅	NO ₂	H	H	H	H	240–243	22, 32, 57, 59
CH ₃	CH ₃	NO ₂	H	H	H	H	190–191	90
C ₂ H ₅	CH ₃	NO ₂	H	H	H	H	125	39
C ₂ H ₅	C ₆ H ₅	NO ₂	H	H	H	H	175	32
H	H	H	NO ₂	H	H	H	205–206	42
H	CH ₃	H	NO ₂	H	H	H	198–199	19
H	H	C ₂ H ₅	NO ₂	H	H	H	109.5–112	113
H	H	H	NO ₂	H	H	CH ₃	182	213
CH ₃	CH ₃	H	NO ₂	H	H	H	94–97	19
H	CH ₃	CH ₃	NO ₂	H	H	H	171–173 172–173 174–176 175 176–176.5	53 55 214 52 215
H	CH ₃	C ₂ H ₅	NO ₂	H	H	H	161–163 163–164	216 56
H	CH ₃	<i>i</i> -C ₃ H ₇	NO ₂	H	H	H	153–154	214
H	CH ₃	<i>n</i> -C ₄ H ₉	NO ₂	H	H	H	123–125	214
H	CH ₃	<i>n</i> -C ₅ H ₁₁	NO ₂	H	H	H	120–121	214
H	CH ₃	C ₆ H ₅	NO ₂	H	H	H	247–248	56, 214
H	C ₆ H ₅	CH ₃	NO ₂	H	H	H	205–206	214
H	C ₆ H ₅	C ₆ H ₅	NO ₂	H	H	H	203–205 204–205 205	53 56 217, 218
H	H	H	H	NO ₂	H	H	133–136 135–137 140–141 141–142	45 44 47 42

TABLE II. (Contd.)

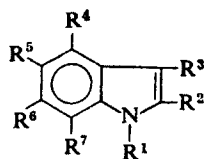
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	CH ₃	H	H	NO ₂	H	H	170 171.5–172.5 176–176.5	63 44 58
H	H	H	H	NO ₂	H	CH ₃	220	213
H	C ₂ H ₅	H	H	NO ₂	H	H	131–132.5	19
H	C ₆ H ₅	H	H	NO ₂	H	H	201–203	59
H	H	C ₂ H ₅	H	NO ₂	H	H	94–95	51
CH ₃	CH ₃	H	H	NO ₂	H	H	129–130	58
H	CH ₃	CH ₃	H	NO ₂	H	H	183–185 184 185–186 186 188 190	53, 55 54 214 49, 216 50 52
H	CH ₃	C ₂ H ₅	H	NO ₂	H	H	193–194 190–191 191–192 194	215 51 56, 216 54
H	CH ₃	<i>n</i> -C ₃ H ₇	H	NO ₂	H	H	164	219
H	CH ₃	<i>i</i> -C ₃ H ₇	H	NO ₂	H	H	166–167 166–167.5 169	214 220
H	CH ₃	<i>n</i> -C ₄ H ₉	H	NO ₂	H	H	124–125 125–126	214 51
H	CH ₃	<i>n</i> -C ₅ H ₁₁	H	NO ₂	H	H	116–117	214
H	CH ₃	C ₆ H ₅	H	NO ₂	H	H	197 197–198	52 214
H	CH ₃	4-NO ₂ C ₆ H ₄	H	NO ₂	H	H	305–307	70
H	CH ₃	C ₆ H ₅ CH ₂	H	NO ₂	H	H	160–161	221
H	C ₂ H ₅	CH ₃	H	NO ₂	H	H	182	54
H	C ₆ H ₅	CH ₃	H	NO ₂	H	H	191–192 193 194–195	214 52 70
H	C ₆ H ₅	C ₆ H ₅	H	NO ₂	H	H	200 210 211 198–200	218 218 217 56
H	C ₆ H ₅	4-NO ₂ C ₆ H ₄	H	NO ₂	H	H	300–302	70
H	C ₆ H ₅	2-Pyridyl	H	NO ₂	H	H	201–202	221
CH ₃	CH ₃	CH ₃	H	NO ₂	H	H	136–139 138.5–140.5	51 19
CH ₃	CH ₃	C ₂ H ₅	H	NO ₂	H	H	111–113	222
H	H	H	H	H	NO ₂	H	138–140 139–140.5 141–142 144–145	45 46 44 42
CH ₃	H	H	H	H	NO ₂	H	76.5–78.5 107–109.5	43 19
H	CH ₃	H	H	H	NO ₂	H	113.5–114.5	44
H	H	C ₂ H ₅	H	H	NO ₂	H	87–89	113
CH ₃	CH ₃	H	H	H	NO ₂	H	106–107.5	19

TABLE II. (Contd.)

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	CH ₃	CH ₃	H	H	NO ₂	H	126 139-141 141-142	49 53 55, 214, 215
							142	50, 52
H	CH ₃	C ₂ H ₅	H	H	NO ₂	H	170-171	56, 216
H	CH ₃	<i>i</i> -C ₃ H ₇	H	H	NO ₂	H	152-153	214
H	CH ₃	<i>n</i> -C ₄ H ₉	H	H	NO ₂	H	110-111	214
H	CH ₃	<i>n</i> -C ₅ H ₁₁	H	H	NO ₂	H	86-88	214
H	CH ₃	C ₆ H ₅	H	H	NO ₂	H	193-194	214
H	C ₆ H ₅	CH ₃	H	H	NO ₂	H	204-205	214
							56	
H	C ₆ H ₅	C ₆ H ₅	H	H	NO ₂	H	225-227	53, 56, 218
							227-228	70, 217
H	H	H	H	H	H	NO ₂	95-96 95-97	42, 223 47
H	CH ₃	H	H	H	H	NO ₂	—	224
H	CH ₃	CH ₃	H	H	H	NO ₂	158-160	55
							162	216
							162-163	214
							162.5-163.5	215
							164	52, 54
H	CH ₃	C ₂ H ₅	H	H	H	NO ₂	135-136	56, 216
							138	54
H	CH ₃	<i>i</i> -C ₃ H ₇	H	H	H	NO ₂	98-99	214
H	CH ₃	<i>n</i> -C ₄ H ₉	H	H	H	NO ₂	93-94	214
H	CH ₃	<i>n</i> -C ₅ H ₁₁	H	H	H	NO ₂	88-89	214
H	CH ₃	C ₆ H ₅	H	H	H	NO ₂	158-159	214
H	C ₂ H ₅	CH ₃	H	H	H	NO ₂	106	54
H	C ₆ H ₅	CH ₃	H	H	H	NO ₂	121-122	214
CH ₃	CH ₃	CH ₃	H	H	H	NO ₂	93	218

TABLE II. (Contd.)

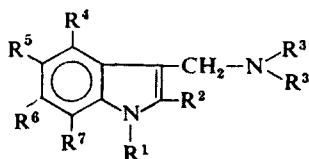
2. Mononitroindoles Containing Halogen



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
C ₂ H ₅	CH ₃	NO ₂		H ₂ Br ₂	(?)		203	39
C ₂ H ₅	CH ₃	NO ₂		HBr ₃	(?)		290	39
H	H	(CH ₂) ₂ Cl	NO ₂			H	134-135	113
H	H	(CH ₂) ₂ Cl	H	NO ₂	H	H	120-121	51
4-ClC ₆ H ₄ CH ₂	CH ₃	H	H	NO ₂	H	H	—	95
H	CH ₃	CH ₃	H	NO ₂	H	Cl	230	54
H	CH ₃	CH ₃	H	NO ₂	H	I	255	54
H	CH ₃	C ₂ H ₅	H	NO ₂	H	Cl	228	54
							175-176	222
H	CH ₃	C ₂ H ₅	H	NO ₂	H	I	253	54
H	CH ₃	(CH ₂) ₂ Cl	H	NO ₂	H	H	204-205	51
H	C ₂ H ₅	CH ₃	H	NO ₂	H	Cl	189	54
H	C ₂ H ₅	CH ₃	H	NO ₂	H	I	244	54
H	H	(CH ₂) ₂ Cl	H	H	NO ₂	H	108-110	113
CH ₃	H	H	H	Br	NO ₂	H	167-168	44
H	CH ₃	CH ₃	H	Cl	H	NO ₂	202	54
H	CH ₃	CH ₃	H	I	H	NO ₂	204	54
H	CH ₃	C ₂ H ₅	H	Cl	H	NO ₂	175	54
H	CH ₃	C ₂ H ₅	H	I	H	NO ₂	239	54
H	C ₂ H ₅	CH ₃	H	Cl	H	NO ₂	147	54
H	C ₂ H ₅	CH ₃	H	I	H	NO ₂	260	54

TABLE II. (Contd.)

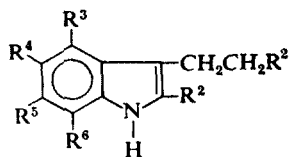
3. Mononitrogramines and Alkyl Derivatives



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	H	CH ₃	NO ₂	H	H	H	120-122	78, 82
				Hydrochloride			233-235	86
				Nitrate			203-205	82
CH ₃	H	CH ₃	NO ₂	H	H	H	Oil	82
				Hydrochloride			237-238	82
				Nitrate			198-200	82
H	H	CH ₃	H	NO ₂	H	H	169-170	79
H	CH ₃	CH ₃	H	NO ₂	H	H	173-175	58, 64
H	H	CH ₃	H	H	NO ₂	H	176-178	82, 83
							178-180	80
				Hydrochloride			229-230	80
				Hydrochloride			229-231	86
				Methiodide			203-205	80
				Nitrate			162-163	82
				Picrate			198-200	80
CH ₃	H	CH ₃		H	NO ₂	H	83-85	82
				Nitrate			173	82
H	CH ₃	CH ₃	H	H	NO ₂	H	158-160	225
							161-163	82
				Nitrate			158-160	82
				Nitrate			180-181	82
H	H	CH ₃	H	H	H	NO ₂	69-71	78
H	H	C ₂ H ₅	H	H	H	NO ₂	79-80	81
				Methiodide			173-174	81

TABLE II. (Contd.)

4. Mononitrotryptamines and Alkyl Derivatives



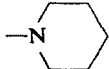
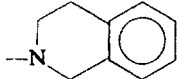
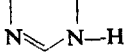
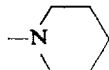
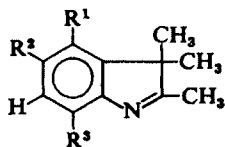
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	mp (°C)	Ref.
H	NH ₂	NO ₂	H	H	H	145–147	113
H	N(CH ₃) ₂	NO ₂	H	H	H	115–116	113
H	NH ₂	H	NO ₂	H	H	136–139	51
H	N(CH ₃) ₂	H	NO ₂	H	H		
H		H	NO ₂	H	H	268–270	51
H		H	NO ₂	H	H	272–273	51
H	NHCH ₂ CH ₂ 	H	NO ₂	H	H	247–248	112
CH ₃	NH ₂	H	NO ₂	H	H	207–208	51
CH ₃		H	NO ₂	H	H	265–266	51
H	NH ₂	H	H	NO ₂	H	275–277	51
H	N(CH ₃) ₂	H	H	NO ₂	H	185–186	113
						171.5–172.5	113

TABLE II. (Contd.)

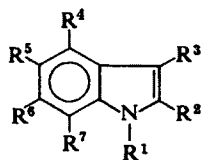
5. Nitro-2,3,3-trimethyl-3H-indoles



R ¹	R ²	R ³	mp (°C)	Ref.
NO ₂	H	H	136–137	226
	Methiodide		224	226
NO ₂	H	Cl	—	226
	Methiodide		214	226
H	NO ₂	H	124–125	51
			127	69
			128	54
			130–131.5	19
	Methobromide		—	33
	Methopicate		175–178	69
H	NO ₂	Cl	168	54
H	NO ₂	I	192	54
H	H	NO ₂	201	54
H	Cl	NO ₂	186	54
H	I	NO ₂	175	54

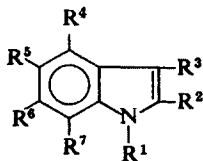
TABLE II. (Contd.)

6. Dinitroindoles



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	H	NO ₂	NO ₂	H	H	H	275.5–277	40
H	CH ₃	NO ₂	NO ₂	H	H	H	284–285	19
H	H	NO ₂	H	NO ₂	H	H	284–285	40
H	CH ₃	NO ₂	H	NO ₂	H	H	285–287	19
H	C ₂ H ₅	NO ₂	H	NO ₂	H	H	229–230	19
H	C ₆ H ₅	NO ₂	H	NO ₂	H	H	309–310	59
CH ₃	CH ₃	NO ₂	H	NO ₂	H	H	201–203	19
CH ₃	C ₂ H ₅	NO ₂	H	NO ₂	H	H	226–228.5	19
H	H	NO ₂	H	H	NO ₂	H	301–302	40
H	CH ₃	NO ₂	H	H	NO ₂	H	260	39
							265–267	227
							268	63
							300–302	90
							305	19
H	C ₆ H ₅	NO ₂	H	H	NO ₂	H	312	57
							318–320	59
CH ₃	CH ₃	NO ₂	H	H	NO ₂	H	293–295	90
							299	19
C ₂ H ₅	C ₆ H ₅	NO ₂	H	H	NO ₂	H	>280	32
H	H	NO ₂	H	H	H	NO ₂	260–261.5	40
H	NH ₂	H	H	NO ₂	H	NO ₂	265	41
H	CH ₃	CH ₃	H	NO ₂	H	NO ₂	360	54
H	CH ₃	C ₂ H ₅	H	NO ₂	H	NO ₂	>360	54
H	C ₂ H ₅	CH ₃	H	NO ₂	H	NO ₂	>360	54
H	CH ₃	CH ₃	CH ₃	NO ₂	H	NO ₂	>360	54
H	CH ₃	C ₂ H ₅	CH ₃	NO ₂	H	NO ₂	>360	54
H	C ₂ H ₅	CH ₃	CH ₃	NO ₂	H	NO ₂	>360	54

7. Trinitroindoles



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	CH ₃	NO ₂	NO ₂	H	NO ₂	H	254–256	227, 19
CH ₃	CH ₃	NO ₂	NO ₂	H	NO ₂	H	242–244	19
H	CH ₃	NO ₂	H	NO ₂	NO ₂	H	265–267	19
CH ₃	CH ₃	NO ₂	H	NO ₂	NO ₂	H	267–269	19
H	H	NO ₂	H	NO ₂	H	NO ₂	232–233	47
H	CH ₃	NO ₂	H	NO ₂	H	NO ₂	205–206	74
							213–215	19

TABLE II. (Contd.)

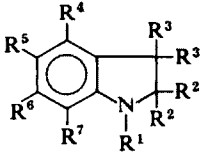
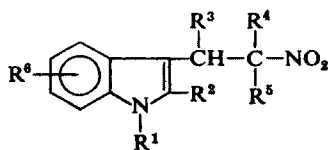
8. Nitroindolines								
								
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
CH ₃	=CH ₂	CH ₃ , CH ₃	NO ₂	H	H	H	146	226
H	H, H	H, H	H	NO ₂	H	H	91-91.5	44
							92-93	109
							92-94	45
H	H, CH ₃	H, H	H	NO ₂	H	H	82	228
							—	44
H	H, H	H, H	H	NO ₂	H	Br	149-151	109
CH ₃	H, CH ₃	H, H	H	NO ₂	H	H	48-49	34
2-BrC ₆ H ₄ CH ₂	H, CH ₃	H, H	H	NO ₂	H	H	96-98	229
NO	H, CH ₃	H, H	H	NO ₂	H	H	133.5	34
							135	228
NO	H, C ₆ H ₅	H, H	H	NO ₂	H	H	160	228
CH ₃	=CH ₂	CH ₃ , CH ₃	H	NO ₂	H	H	203-204	230
H	H, H	H, H	H	H	NO ₂	H	65.5-67	45
							66-67	231
							66.5-67.5	44
CH ₃	H, H	H, H	H	H	NO ₂	H	49.4-50.5	43
H	H, CH ₃	H, H	H	H	NO ₂	H	50	108
							—	44
							200	108
H	H, H	H, CH ₃	H	Hydrochloride				
				H	NO ₂	H	75	108
				Hydrochloride			192	108
NO	H, CH ₃	H, H	H	H	NO ₂	H	103-104	108
NO	H, H	H, CH ₃	H	H	NO ₂	H	100	108
CH ₃	H, H	H, H	H	Br	NO ₂	H	73-74	44
H	H, H	H, H	H	Br	H	NO ₂	198-199	232
NO	H, CH ₃	H, H	H	H	H	NO ₂	108	228
H	H, H	H, H	H	NO ₂	H	NO ₂	243-244	44
							244-245	47

TABLE II. (Contd.)

B. Indoles and Indolines with Side-Chain Nitro Groups

1. 3-(2-Nitroalkyl)indoles



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	bp or mp (°C)	Ref.
H	H	H	H	H	H	52–54	121
						53.5–4	122
						55.5–56.1	157
						67–68	129
H	CH ₃	H	H	H	H	89–90	130
H	H	CH ₃	H	H	H	90–91	133
						116.5 (dimorphic forms)	
H	H	C ₆ H ₅	H	H	H	99–100	133
H	H	H	CH ₃	H	H	178–180 (0.5 mm)	114
						—	
						—	164
H	H	H	C ₂ H ₅	H	H	75.5–76	119
						90–91	114
CH ₃	CH ₃	H	H	H	H	71–72	130
CH ₃	H	C ₆ H ₅	H	H	H	94–95	130
H	CH ₃	C ₆ H ₅	H	H	H	104–105	130, 233
H	C ₆ H ₅	C ₆ H ₅	H	H	H	144–147	130
H	C ₆ H ₅	4-ClC ₆ H ₄	H	H	H	147–148	131
H	H	C ₆ H ₅	CH ₃	H	H	161–162	133
H	H	H	CH ₃	CH ₃	H	66.5–68	114
						75–75.2	119
H	H	H	—(CH ₂) ₅ —		H	163–164	163
H	H	H	CH ₃	H	5-Cl	60	163
						—	164
H	H	H	CH ₃	H	6-CH ₃	125 (10 ⁻⁴ mm)	163
H	H	H	C ₂ H ₅	H	6-F	—	117
H	H	H	C ₂ H ₅	H	7-CH ₃	—	116
CH ₃	CH ₃	C ₆ H ₅	H	H	H	139–140	130
H	CH ₃	C ₆ H ₅	CH ₃	H	H	198–199	130
H	CH ₃	C ₆ H ₅	C ₂ H ₅	H	H	177.5–179.5	130
						170.5–172.5 (dimorphic forms)	
H	C ₆ H ₅	C ₆ H ₅	CH ₃	H	H	226–228	130

TABLE II. (Contd.)

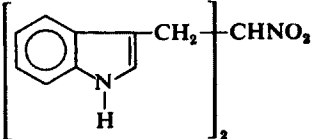
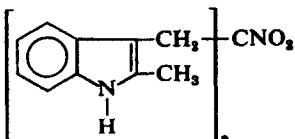
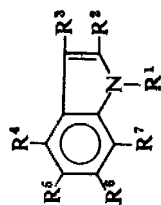
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	bp or mp (°C)	Ref.
H	CH ₃	CH ₃	H	H	6-CH ₃	—	164
H	H	CH ₃	CH ₃	CH ₃	H	120–130 (10 ⁻⁴ mm)	163
H	H	H	CH ₃	CH ₃	4-CH ₃	130–131	163
H	H	H	CH ₃	CH ₃	5-Cl	92–93	163
						—	119
H	H	H	CH ₃	CH ₃	5-Br	109–109.5	119
H	H	H	CH ₃	CH ₃	6-CH ₃	84–86	163
H	H	H	CH ₃	CH ₃	6-Cl	93–95	163
H	H	H	CH ₃	CH ₃	7-CH ₃	104–107	163
CH ₃	CH ₃	C ₆ H ₅	CH ₃	H	H	226–228	130
						206	114, 115
						222	115
							

TABLE II. (Contd.)

2. (2-Nitrovinyl)indoles



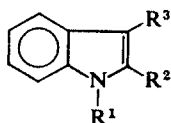
R¹	R²	R³	R⁴	R⁵	R⁶	R⁷	mp (°C)	Ref.
H	—CH=CHNO₂	H	H	H	H	H	150–151	147
H	H	—CH=CHNO₂	H	H	H	H	165–166	234
							166–167	235
							167–169	236
							169–170	237
							171–172	143, 145
							191–195	141
							195–196	145
							134–136	145
							225	238
							293	238
							160–161	143, 145
							220–221	119
							186–187	143, 145
							203–	119
							203.5	
							149–151	131
							184–187	145
							193–195	144
							195–196	143
							—	239, 240
							159–160	163
							161	238
							232	238
							165	238
							187–188	163
							—	241
							—	241
							201–202	242, 243
							—	241

TABLE II. (Contd.)

¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	H	—CH=(CH ₃)NO ₂	H	CH ₃	H	H	184–187	143
H	H	—CH=C(CH ₃)NO ₂	H	Br	H	H	219–220	244
H	H	—CH=C(CH ₃)NO ₂	H	Cl	H	H	—	242
H	H	—CH=C(CH ₃)NO ₂	H	F	H	H	179–180	245
H	H	—CH=C(CH ₃)NO ₂	H	H	CH ₃	H	172–173	163
H	H	—CH=C(CH ₃)NO ₂	H	H	Cl	H	224–226	242, 243
H	H	—CH=C(CH ₃)NO ₂	H	H	H	CH ₃	175	163
H	H	—CH=C(CH ₃)NO ₂	H	H	H	Cl	—	246
H	H	—CH=C(CH ₃)NO ₂	H	H	H	Cl	179–181	242, 243
H	H	—CH=C(CH ₃)NO ₂	CH ₃	H	H	CH ₃	181–182	246
H	H	—CH=C(CH ₃)NO ₂	Br	H	H	CH ₃	—	241
H	H	—CH=C(CH ₃)NO ₂	Cl	H	H	CH ₃	—	241
H	H	—CH=C(CH ₃)NO ₂	H	Cl	H	Cl	227–230	163
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	H	H	129–132	247
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	H	H	134–135	248
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	H	H	134–136	143
H	H	—CH=C(C ₂ H ₅)NO ₂	CH ₃	H	H	H	—	239
H	H	—CH=C(C ₂ H ₅)NO ₂	Br	H	H	H	172–173	241
H	H	—CH=C(C ₂ H ₅)NO ₂	Cl	H	H	H	—	241
H	H	—CH=C(C ₂ H ₅)NO ₂	H	Cl	H	H	195–196	242, 243
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	H	H	170–171	242, 243
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	Cl	H	183–184	242, 243
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	Cl	Cl	157–158	242, 243
H	H	—CH=C(C ₂ H ₅)NO ₂	CH ₃	H	H	CH ₃	—	241
H	H	—CH=C(C ₂ H ₅)NO ₂	Br	H	H	CH ₃	—	241
H	H	—CH=C(C ₂ H ₅)NO ₂	Cl	H	H	CH ₃	—	241
H	H	—CH=C(C ₂ H ₅)NO ₂	—CH=C(CH ₃)NO ₂	H	H	H	—	149
H	H	—CH=C(C ₂ H ₅)NO ₂	—CH=C(C ₂ H ₅)NO ₂	H	H	H	—	149
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	—CH=CHNO ₂	H	136–138	149
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	—CH=C(CH ₃)NO ₂	H	158–160	149
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	—CH=C(C ₂ H ₅)NO ₂	H	148–150	149
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	—CH=C(C ₂ H ₅)NO ₂	H	130–132	149
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	H	—CH=CHNO ₂	240–242	150
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	H	—CH=CHNO ₂	197	150
H	H	—CH=C(C ₂ H ₅)NO ₂	H	H	H	—CH=C(CH ₃)NO ₂	126–129	149

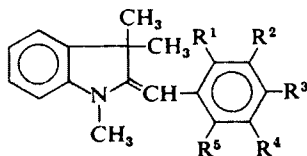
TABLE II. (Contd.)

3. 2-and 3-(Nitrophenyl)indoles



R ¹	R ²	R ³	mp (°C)	Ref.
H	2-C ₆ H ₄ NO ₂	H	140-141	151
H	3-C ₆ H ₄ NO ₂	H	172-173	152
H	H	2-C ₆ H ₄ NO ₂	119	153
H	CH ₃	4-C ₆ H ₄ NO ₂	214-216	70
H	C ₆ H ₅	4-C ₆ H ₄ NO ₂	234-235	70
H	CH ₃	2,4-C ₆ H ₃ (NO ₂) ₂	202	154
H	H	2,4,6-C ₆ H ₂ (NO ₂) ₃	212	155
CH ₃	H	2,4,6-C ₆ H ₂ (NO ₂) ₃	227	155
H	CH ₃	2,4,6-C ₆ H ₂ (NO ₂) ₃	243	155

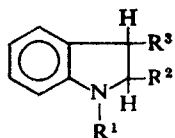
4. 2-(Nitrobenzylidene)-1,3,3-trimethylindolines



R ¹	R ²	R ³	R ⁴	R ⁵	mp (°C)	Ref.
NO ₂	H	NO ₂	H	H	137	249
					139-140	156
NO ₂	H	NO ₂	Cl	H	187-188	156
NO ₂	H	NO ₂	Cl	Cl	133-134	156
NO ₂	H	NO ₂	(CH=CH) ₂		220	156
NO ₂	H	NO ₂	H	NO ₂	175-177	156
NO ₂	Cl	NO ₂	Cl	NO ₂	168	156

TABLE II. (Contd.)

5. Other Hydrogenated Indoles with Side-Chain Nitro Groups

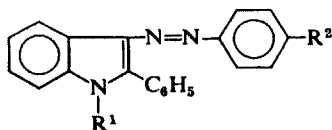


R ¹	R ²	R ³	bp or mp (°C)	Ref.
H	H	CH ₂ CH(CH ₃)NO ₂	100 (10 ⁻⁵ mm)	162
		Hydrochloride	165-166	162
H	H	CH ₂ C(CH ₃) ₂ NO ₂	106 (10 ⁻⁵ mm)	162
		Hydrochloride	164-166	162
4-CH ₂ C ₆ H ₄ NO ₂	CH ₃	H	88-89	229
2,4-CH ₂ C ₆ H ₃ BrNO ₂	CH ₃	H	95-96	229
2,5-CH ₂ C ₆ H ₃ BrNO ₂	CH ₃	H	120-122	229
3-(2-Nitropropyl)-octahydroindole			84 (10 ⁻⁵ mm)	162
			106-107 (0.15 mm)	162
3-(2-Methyl-2-nitropropyl)-octahydroindole			90-95 (10 ⁻⁵ mm)	162

TABLE III. Azo- and Azoxy indoles and -indolines

A. Azo- and Hydrazonoindoles

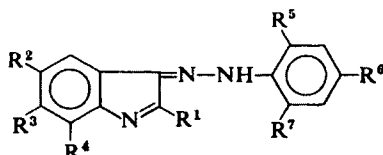
1. 3-Arylazindoles



R ¹	R ²	mp (°C)	Ref.
CH ₃	H	148	175
CH ₃	NO ₂	—	181
C ₂ H ₅	H	140	31
C ₂ H ₅	N(CH ₃) ₂	154	31
C ₆ H ₅	H	198-199	31
C ₆ H ₅	N(CH ₃) ₂	239	31

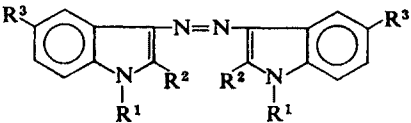
TABLE III. (Contd.)

2. 3-Arylhydrazono-3H-indoles



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	mp (°C)	Ref.
H	H	H	H	H	H	H	133-134	165
							134-135	167
							135	176
H	H	H	H	H	Br	H	170	176
H	H	H	H	H	Cl	H	179-181	167
H	H	H	H	H	NO ₂	H	195-197	167
CH ₃	H	H	H	H	H	H	113-115	175
							115	170
							115-116	169
CH ₃	H	H	H	H	Cl	H	168	176
CH ₃	H	H	H	H	NO ₂	H	219-220	171
							225-226	173
							—	183
CH ₃	H	H	H	H	—N=N—C ₆ H ₅	H	—	183, 185
CH ₃	H	H	H	NO ₂	NO ₂	H	137-141	173
CH ₃	CH ₃	H	H	H	NO ₂	H	236	173
CH ₃	CH ₃	H	H	NO ₂	NO ₂	H	171-175	173
CH ₃	H	H	CH ₃	H	NO ₂	H	228	173
CH ₃	H	H	CH ₃	NO ₂	NO ₂	H	—	173
CH ₃	CH ₃	H	CH ₃	H	NO ₂	H	244-245	173
CH ₃	CH ₃	H	CH ₃	NO ₂	NO ₂	H	—	173
C ₂ H ₅	H	H	H	H	NO ₂	H	60	171
C ₆ H ₅	H	H	H	H	H	H	166	170
							166-167	175
C ₆ H ₅	H	H	H	H	NO ₂	H	280	171
C ₆ H ₅	H	H	H	H	—N=N—C ₆ H ₅	H	—	183, 185
C ₆ H ₅	H	H	H	CH ₃	—N=N—(2-C ₆ H ₄ CH ₃)	H	—	185
C ₆ H ₅	H	H	H	CH ₃	—N=N—(4-C ₆ H ₄ Cl)	H	—	183, 185
C ₆ H ₅	H	H	H	Br	Br	Br	149-150	1, 25
C ₆ H ₅	CH ₃	H	H	H	H	H	193	11
C ₆ H ₅	H	CH ₃	H	H	H	H	177	11
C ₆ H ₅	H	H	CH ₃	H	H	H	155	11
NHC ₆ H ₅	H	H	H	H	H	H	189-190	206

TABLE III. (Contd.)

3. 3,3'-Azobisindoles				
				
R ¹	R ²	R ³	mp (°C)	Ref.
H	CH ₃	H	282–285	177
H	CH ₃	Cl	310–312	177
H	C ₆ H ₅	H	256–259 (syn)	177
			263 (syn)	178, 179
			282–283 (anti)	202
			292–293 (anti)	177
CH ₃	CH ₃	H	300–305	177
C ₂ H ₅	C ₆ H ₅	H	251–252	31
C ₆ H ₅	C ₆ H ₅	H	185 (syn)	31
			336 (anti)	31

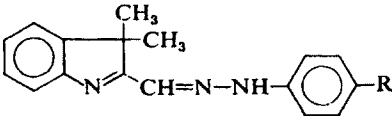
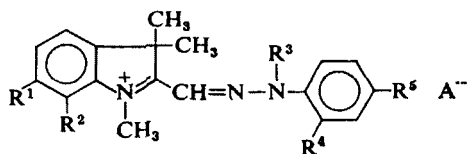
4. 3,3-Dialkyl-2-hydrazonomethyl-3H-indoles			
			
R		mp (°C)	Ref.
H		142–143	175
	Picrate	214	175
NO ₂		236	178

TABLE III. (Contd.)

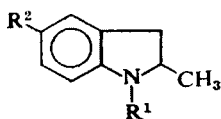
5. 2-Hydrazone-methyl-1,3,3-trimethyl-3H-indolium Salts



R ¹	R ²	R ³	R ⁴	R ⁵	A ⁻	mp (°C)	Ref.
H	H	H	H	H	Cl ⁻	—	196
CH ₃	H	H	H	H	I ⁻	250	193
H	CH ₃	H	H	H	I ⁻	232	193
H	H	H	NO ₂	H	Cl ⁻	—	195
H	H	H	NO ₂	CH ₃	Cl ⁻	—	195
H	H	H	NO ₂	Cl	Cl ⁻	—	195
H	H	H	NO ₂	N(CH ₃) ₂	Cl ⁻	—	195
H	H	CH ₃	H	H	I ⁻	241–242	196
						253–255	250
					4-CH ₃ C ₆ H ₄ SO ₃ ⁻	202–203	197
					SO ₄ ²⁻	—	196
H	H	C ₂ H ₅	H	H	I ⁻	—	196
					4-CH ₃ C ₆ H ₄ SO ₃ ⁻	—	196
					SO ₄ ²⁻	—	196
H	H	CH ₃	H	NH ₂	SO ₄ ²⁻	—	197

B. Azoindolines

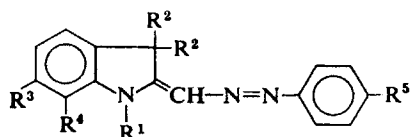
1. Arylazoindolines



R ¹	R ²	mp (°C)	Ref.
—N=N—C ₆ H ₅	H	51.5	190
H	—N=N—C ₆ H ₅	—	190

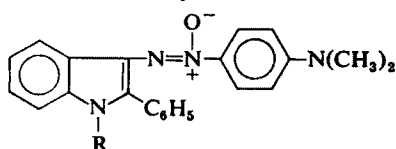
TABLE III. (Contd.)

2. 2-Arylazomethylene-1,3,3-trialkylindolines



R ¹	R ²	R ³	R ⁴	R ⁵	mp (°C)	Ref.
CH ₃	CH ₃	H	H	H	105-106	196
					106-107	175, 251
					109	180
			Hydrobromide		233	250
			Hydrochloride		186	192
			Hydrochloride		229	250
			Hydriodide		240	251
			Picrate		203-205	250
			Picrate		205	175
CH ₃	CH ₃	CH ₃	H	H		
			Picrate		200	193
CH ₃	CH ₃	H	CH ₃	H	146	193
			Picrate		208	193
CH ₃	CH ₃	H	H	CH ₃	153-154	196
CH ₃	CH ₃	H	H	Cl	141-145	180
CH ₃	CH ₃	H	H	NO ₂	168	192
					183	194
					185	180
			Hydrobromide		250	192
			Hydrochloride		286	192
			Perchlorate		270	194
C ₂ H ₅	C ₂ H ₅	H	H	H	—	193
			Picrate		168	193
C ₂ H ₅	C ₂ H ₅	H	H	NO ₂	—	192
			Hydrochloride		280	192

C. Azoxyindoles



R	mp (°C)	Ref.
C ₂ H ₅	154	31
C ₆ H ₅	239	31
Methiodide	210-211	31

TABLE IV. 3-Diazo-3*H*-indoles

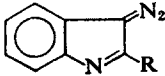
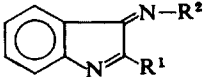
		
R	mp (°C)	Ref.
CH ₃	94	198
	—	203
Picrate	172	198
Dihydrochloride	~100	198
C ₆ H ₅	107–108	201, 202
	115	178, 198
	—	203
Hydrochloride	175	203
Nitrate	164–165	198
Picrate	155	198
4-Pyridyl	101–102	209
2-Naphthyl	—	203
2-(Indol-3-yl)	>300	16
	—	203

TABLE V. 3-Imino-3*H*-indoles

			
R ¹	R ²	mp (°C)	Ref.
CH ₃	C ₆ H ₅	183	7
CH ₃	4-C ₆ H ₄ N(CH ₃) ₂	185	7
C ₆ H ₅	H	114–115	27
C ₆ H ₅	C ₆ H ₅	154	204
		155	7
C ₆ H ₅	3-C ₆ H ₄ CH ₃	136	204
C ₆ H ₅	4-C ₆ H ₄ CH ₃	146	204
C ₆ H ₅	3-C ₆ H ₄ Br	169	204
C ₆ H ₅	4-C ₆ H ₄ Br	154	204
C ₆ H ₅	3-C ₆ H ₄ Cl	148	204
C ₆ H ₅	4-C ₆ H ₄ Cl	157	204
NHC ₆ H ₅	C ₆ H ₅	210	206
		212–213	205
Indol-3-yl	H	198	16
3,3'-Azinobis-(2-phenyl-3 <i>H</i> -indole)		~180	198
		234–235	202

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