THE PREPARATION OF DIMETHYLAMINOALKYL ESTERS OF INDOLECARBOXYLIC ACIDS

by

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EXPERIMENTAL (continued)

GENERAL INTRODUCTION

The intention of this work was to produce 2-indolecarboxylic acids according to the method of Reissert, and to synthesize 3-indolecarboxylic acid from indole by means of the Grignard reagent, magnesyl indole. These acids were to be esterified with dimethylaminoethanol and 1-dimethylaminopropanol-2.

Since it was known that dialkylaminoethyl esters of aromatic acids generally possess anaesthetic activity, it was expected that these dimethylaminoalkyl indolecarboxylates would also be anaesthetics.

HISTORICAL INTRODUCTION

Cocaine Type Anaesthetics

Cocaine, an alkaloid, was the first chemical compound which was found, on application to tissue, to produce the physiological effect known as anaesthesia. This observation of the utility of the compound naturally led to a study of its chemical structure. After the establishment of the structure, scientific curiosity led to the investigation of the chemical moiety responsible for the physiological activity and to the synthesis of similar anaesthetic compounds.

Cocaine is an alkaloid obtained from the leaves of the Erythroxylon species indigenous to the western side of South America. Two kinds of Erythroxylon leaves are available in commerce: Bolivian or Huanuco leaves from E. coca and Peruvian or Truxillo leaves from E. trucillense.

The leaves, chewed with lime, have been used as a stimulant by South American Indians since prehistory. The Spanish explorers reported that they found it in use as early as 1532.

Some unrefined alkaloid is exported from South America but the principal source of coca leaves is Java. The alkaloidal content of coca leaves varies from 0.5 to 1.5%. Truxillo and Java cocas are richer in alkaloid than Bolivia coca but the proportion of cocaine is 50% in the former whereas it may be 70 to 80% of the total alkaloid in Bolivia leaves. Cocaine is made either from the crude alkaloid as exported from South America or from ecgonine obtained by hydrolysis of the total alkaloids extracted from Java coca leaves.

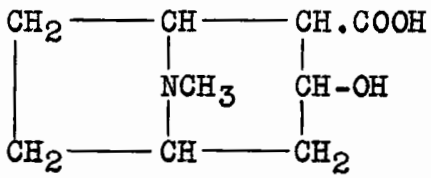
In 1860, Wöhler observed the local anaesthetic activity of cocaine. Koller, an ophthalmologist, used it clinically in 1880. Cocaine has a bitter taste, is mydriatic, produces local anaesthesia and is toxic. After absorption when taken internally it acts chiefly by stimulation of the central nervous system, succeeded by depression. Since the two phases may be present in different areas simultaneously a mixed result may ensue. With large doses the chief symptoms are those of medullary depression. Respiration becomes quicker and deeper but eventually slower and shallower, and death is due to respiratory failure. Once a valuable local anaesthetic, it has several clinical and commercial disadvantages. It is a habit

forming drug and therefore restricted under narcotic laws. It is somewhat toxic and irritant to the patient. It is also difficult to sterilize for medicinal use without hydrolysis of the methyl ester linkages.

Cocaine (II) crystallizes from alcohol in monoclinic, four- to six-sided prisms, m.p. 98°, b.p. 187-8°/0.1 mm. pressure. It is slightly soluble in cold water, readily soluble in alcohol, ether, benzene, and petroleum ether. The aqueous solution is alkaline to litmus, has a bitter taste and produces a characteristic numbness.

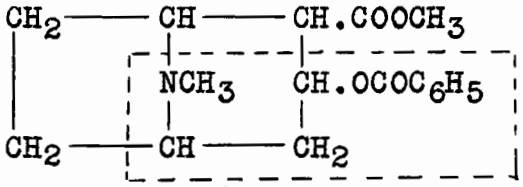
When heated with mineral acids, l-cocaine is hydrolysed to l-ecgonine, benzoic acid and methanol, and a like change takes place with baryta water. If the alkaloid is boiled with water, methanol is split off and a new base, benzoyl l-ecgonine is formed, which in turn can be hydrolysed by acids or alkalis into l-ecgonine and benzoic acid. Cocaine is therefore benzoylmethyl-l-ecgonine.

l-Ecgonine (I) cyrstallized from dry alcohol, m.p. 198° (decomposes), 205° (dry), is soluble in water and sparingly soluble in alcohol. The constitution of ecgonine was established by the work of Willstätter, Einhorn, and co-workers.



I ecgonine

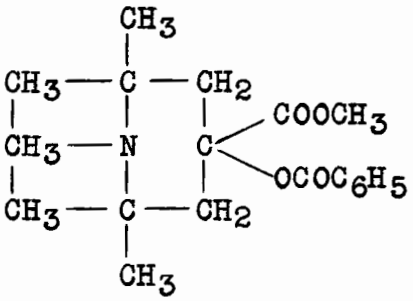
The structure of cocaine was thus established and then studied to determine exactly what portion of the molecule is responsible for the anaesthetic activity.



II

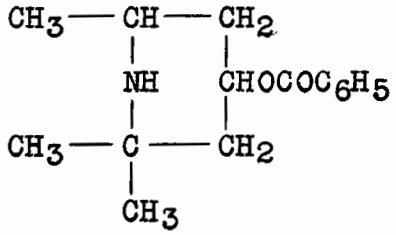
Cocaine, showing anaesthesiophoric group

α-Eucaine and β-eucaine, which approximate the cocaine structure, were among the first synthetic anaesthetics to be made. (1)



III

α-eucaine



IV

β-eucaine

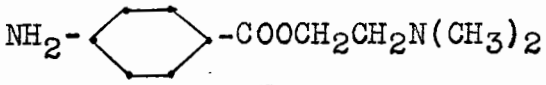
α-Eucaine (III) is somewhat painful and irritant on injection and was soon superceeded by β-eucaine (IV).

As information accumulated it was learned that certain minimal structural requirements are necessary for this type of compound. By 1890, it was known that ethyl p-amino-benzoate possesses anaesthetic activity. Einhorn made the generalization:

"All aromatic esters possess the capacity of produce anaesthesia." (2)

Einhorn prepared orthoform and new orthoform, the methyl esters of p-amino-m-hydroxybenzoic acid and m-amino-p-hydroxybenzoic acid, respectively. These possess anaesthetic activity. "This discovery led to the synthesis of a large number of analogous esters of which two alkyl p-aminobenzoates are yet finding practical use." (3) A series of alkyl p-aminobenzoates showed increasing potency as the alkanol chain increased in length. (4)

It was next discovered that the presence of a basic nitrogen atom in the esterified alcohol is desirable. It increased the activity and permitted the formation of water soluble salts. It was then recognized that the anaesthesiophoric group in cocaine is $ArCOO(C)_3NR_2$.



V

Procaine

Einhorn and Uhlfelder synthesized procaine (V) in 1909 (5). This has since become the most widely used local anaesthetic. After 1909, very many compounds related to cocaine and procaine by homology and analogy were synthesized.

The influence of the acyl group in production of local anaesthetics has been discussed by Jowett and Pyman who point out that anaesthetic activity is shown by alkamine esters of widely different structure but possessing the following characteristics:-

1) the acyl group may be benzoyl or a substituted aromatic residue,
2) the amino group may be secondary or tertiary, or be associated with single or bridged ring complexes,
3) the alcohol group may be primary, secondary or tertiary and may separate the acyl and amino groups by two or three carbon atoms.

The anaesthesiophoric grouping may be divided into three parts:

1) the basic amino nitrogen,

2) the alkanol carbon chain,

3) the aromatic acid group.

$$R_2N - (C)_n - OCOAr$$
$$1 \quad 2 \quad 3$$

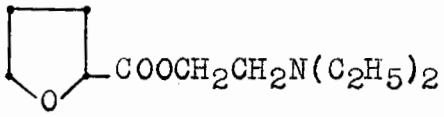
1) Though in most anaesthetics this nitrogen is found to be tertiary, derivatives of primary and secondary amines have been found to be active. In the case of the tertiary amines the anaesthetic activity tends to increase with the weight of the alkyl groups. However, when the alkyl groups are greater than ethyl the compounds are quite irritating. (6) Most useful anaesthetics have diethyl- or dimethylamino or piperdino groups as the basic nitrogen group.

2) In a series of similar compounds, as the alkyl chain increased from one to five carbon atoms, the anaesthetic activity was found to increase. (7) Few other generalizations can be made since most investigators have confined themselves to the methyl and ethyl alcohols. Active compounds have been synthesized with methyl and phenyl branches on the alkyl chain.

3) A great many different aromatic acids have been used in esters of this type. In a homologous series of p-

alkoxybenzoates it was found that the anaesthetic potency increased as the alkyl group became larger. Carboxylic acids of heterocyclic compounds have also been widely used.

Procaine analogs of 2-furoic acid (VI) (8), 2-pyrrole-carboxylic acid (VII) (8), 2-thiophenecarboxylic acid (VIII) (8), 4-tetrahydropyrancarboxylic acid (IX) (9) and 4-alkoxycinchoninic acid (X) (10) have been synthesized and found to have varying degrees of activity.



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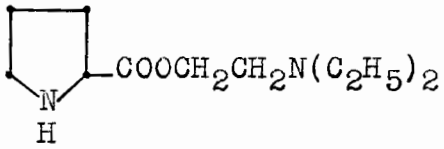

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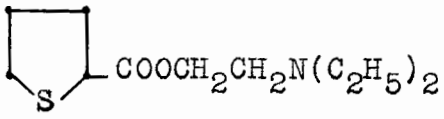
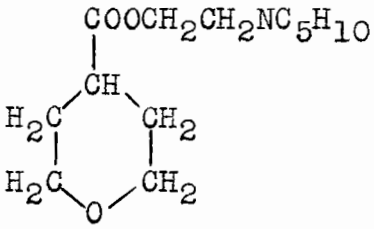
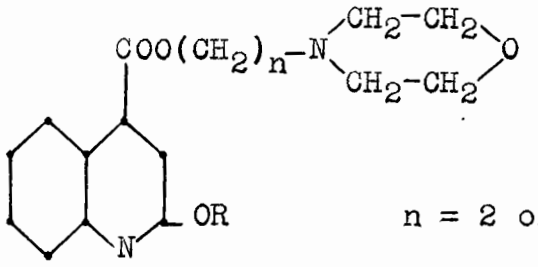


VIII



IX



n = 2 or 3

R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9

X

However, there has been little work reported on syntheses of this type of ester from carboxylic acids of fused ring heterocyclics such as indole.

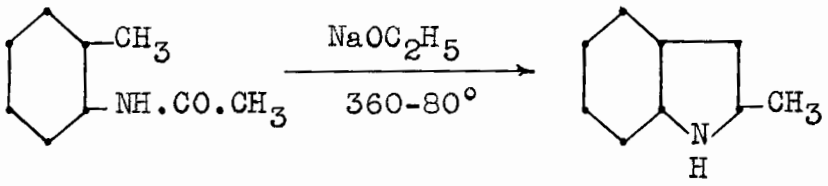
Synthesis of Indole Derivatives

There are numerous methods available for the synthesis of indole and its derivatives. The most versatile and thus most widely used method is the Fischer synthesis. Several of the others are well known and all are useful in particular cases.

All indole syntheses follow the basic pattern of starting with a benzene derivative and then closing the nitrogen ring. The point of closure of the heterocyclic ring may be at any position in it.

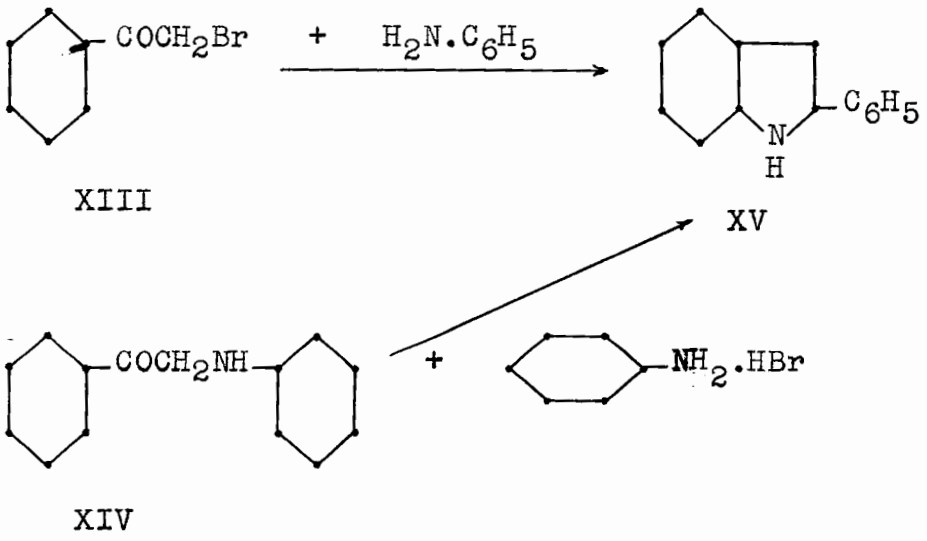
Aside from the three to be described in some detail later, the following methods of synthesis are mentioned as illustrating the variety possible.

In 1912, Madelung (11) prepared 2-methylindole by heating o-acetotoluidide (XI) with sodium ethoxide at 360-80° in the absence of air. The reaction is rather drastic and has been found to be of quite limited applicability. Indole itself cannot be made by this means.



XI XII

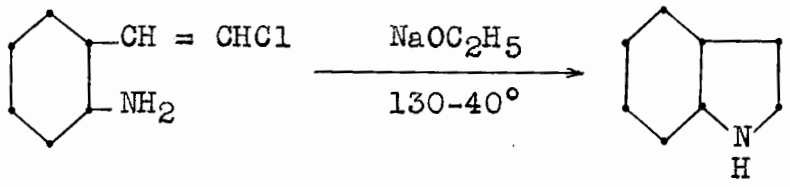
The preparation of 2-phenylindole (XV) by heating phenacyl bromide (XIII) with an excess of aniline was discovered by Mohlau (12) and extended by Bischler (13). It is the parent of a general class of reactions for the synthesis of substituted indoles from α-halo, α-arylamino, and α-hydroxyketones.



The reaction is due to the formation of phenacylaniline (XIV) and its ring closure in the presence of aniline hydrohalide. This reaction is not a simple ring closure but the actual mechanism is in doubt.

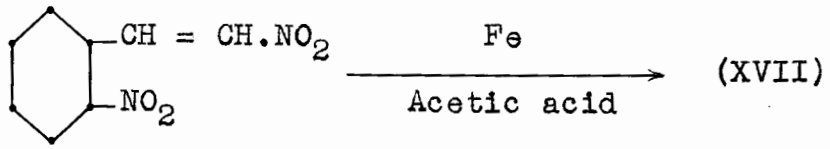
There are several syntheses in which the rings are formed by cyclization of o-aminophenyl compounds. The amino compounds are usually prepared from the corresponding o-nitro compounds.

The Lipp synthesis, the cyclization of ω -chloro α-aminostyrene (XVI) in the presence of sodium ethoxide to produce indole (XVII).



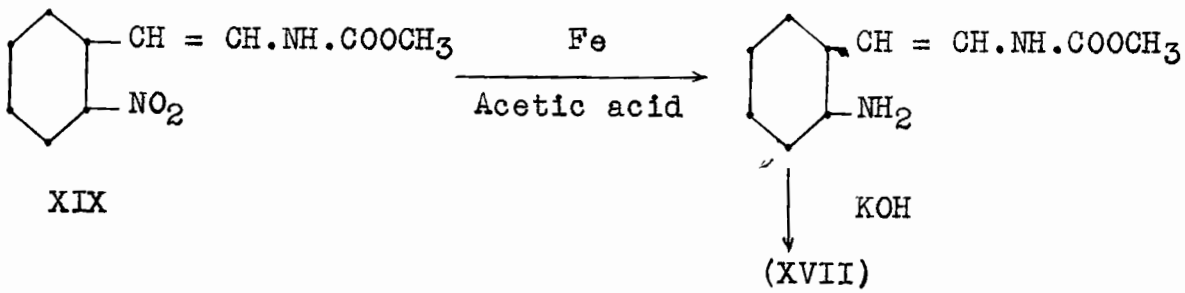
XVI XVII

Synthesis of indole (XVII) from o,ω -dinitrostyrene (XVIII) (15).



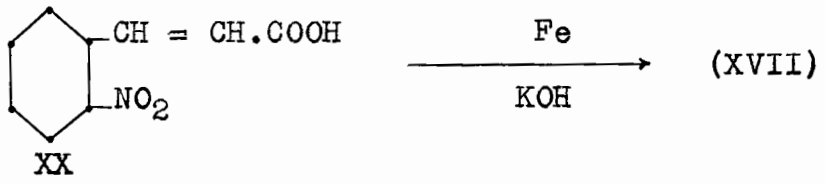
XVIII

The Weerman synthesis of indole (XVII) from ω -(N-carbmethoxyamino)-o-nitrostyrene (XIX) (16).



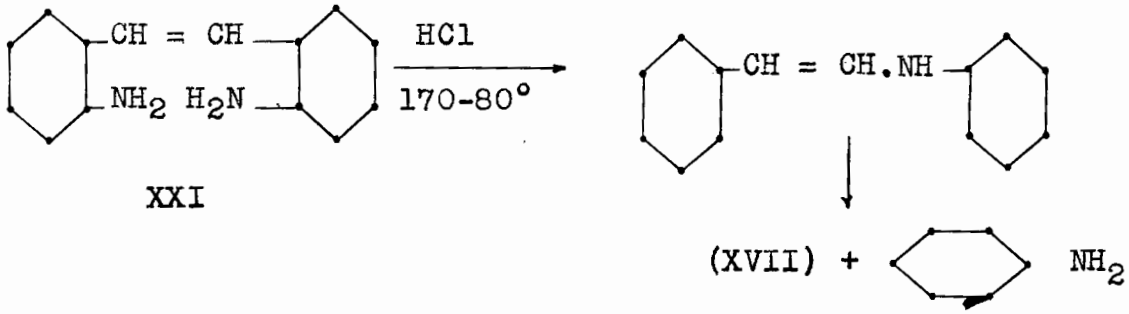
XIX

The Baeyer-Emmerling synthesis of indole (XVII) from ω-carboxy-o-nitrostyrene (XX) (17).



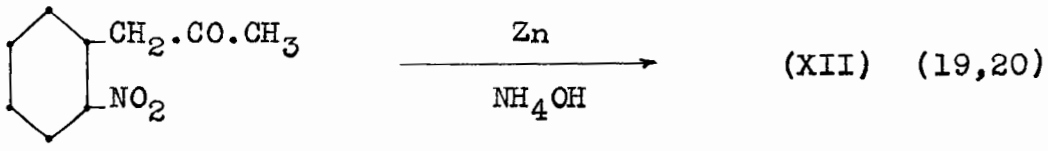
XX

The Thiele-Dimroth synthesis of indole (XVII) from di-(o-aminophenyl)-ethylene (XXI) (18).

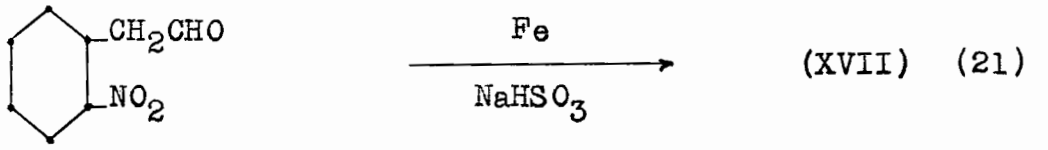


XXI

The Baeyer-Jackson synthesis of 2-methyl indole (XII) from o-nitrobenzyl methyl ketone (XXII) (19,20) and indole (XVII) from o-nitrophenylacetaldehyde (XXIII) (21).

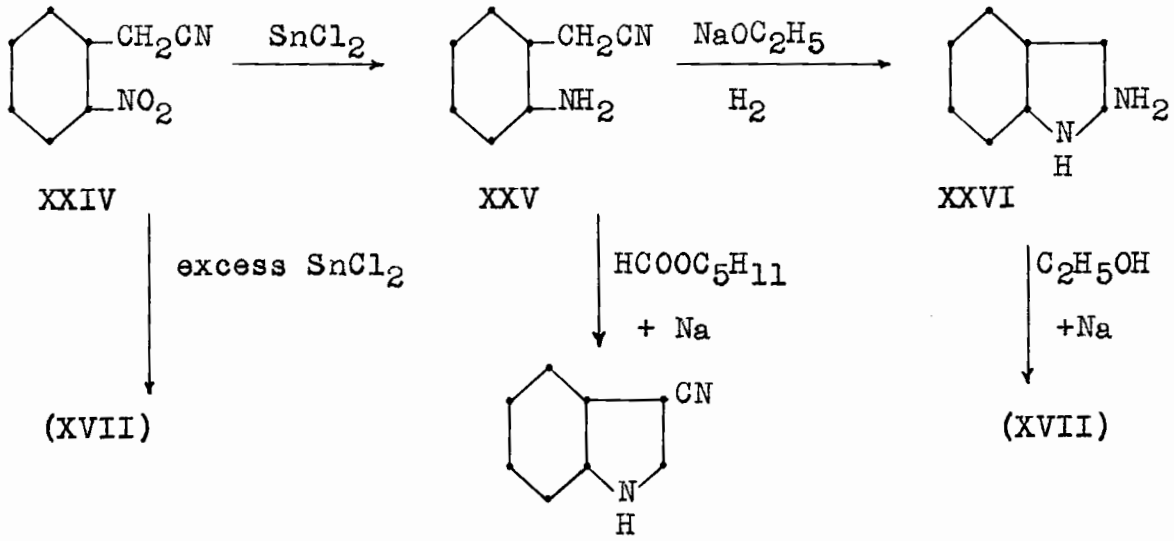


XXII



XXIII

The Pschorr-Hoppe synthesis of indole derivatives (XVII), (XXVI), (XXVII) by reduction of o-nitrophenylacetonitrile (XXIV) (22,23).



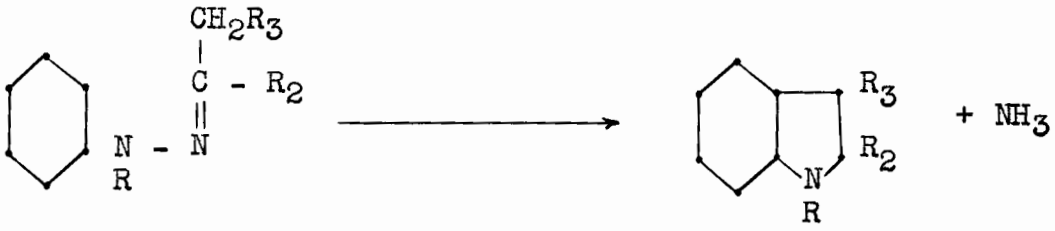
XXVII

Though it is not used in the experimental part of this work, the Fischer indole synthesis is the most versatile and most important type of reaction for the synthesis of indole derivatives in general.

In 1883, Fischer and Jourdan, (24) boiled the methylphenylhydrazone of pyruvic acid in alcoholic hydrogen chloride and obtained about 5% of 1-methyl-2-indole carboxylic acid. The work was continued by Fischer who found that anhydrous zinc chloride was a better catalyst. He developed the method of heating a hydrazone with five times

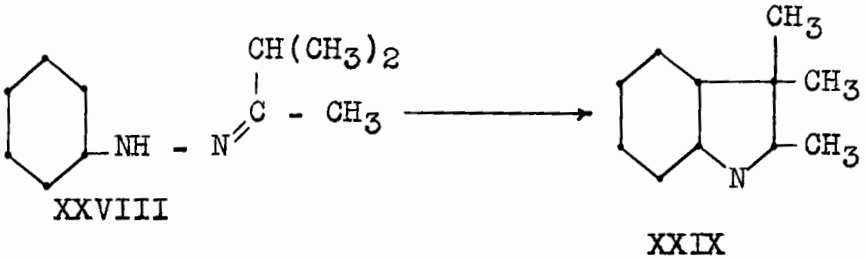
its weight of anhydrous zinc chloride at 180-200°. Since then the method has been extended and revised. The use of solvents and less zinc chloride was introduced. A large variety of acidic catalysts are now used. (25)

The general reaction may be illustrated as follows:



The scope of the reaction is very wide but the conversion of acetaldehyde phenylhydrazone to indole has not been achieved. (26) The ease of indole formation varies irregularly and greatly.

The phenylhydrazone of isopropyl methyl ketone (XXVIII), which has no methylene group, leads to an idolenine derivative, 2, 3,3-trimethyl indolenine (XXIX). (27)



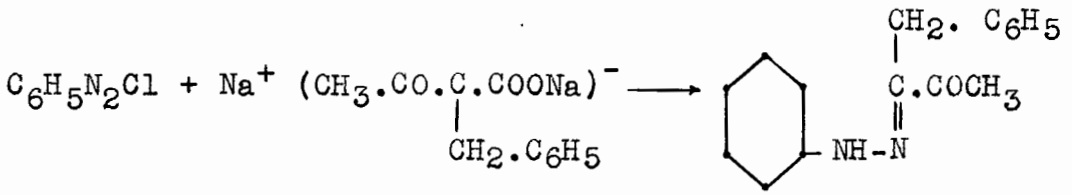
XXVIII

XXIX

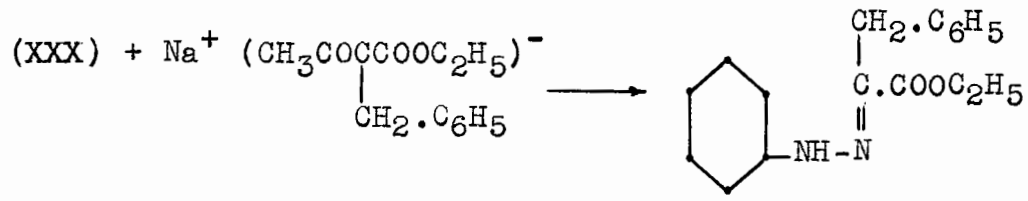
An unsymmetrical ketone would be expected to yield a mixture of two products and a meta-substituted phenylhydra-

zone should yield a mixture with substituents in the 4- and 6- positions. However, the isolation of two products from either case has not been reported.

"The Japp-Klingeman synthesis (28) has proved a valuable adjunct to the Fischer indole synthesis, for it provides a method for the preparation of the necessary phenylhydrazones from phenyl diazonium chlorides and the sodio derivatives of either β-keto acids or esters.



XXX XXXII



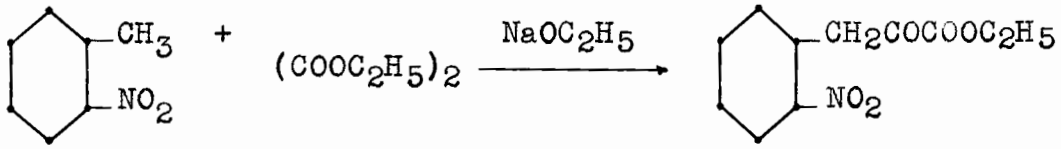
XXXIII XXXIV

In the first instance, (XXX) - (XXXII), the reaction proceeds with the loss of the carboxyl group, whereas in (XXX) - (XXXIV) the acyl group is eliminated. (29)" (30)

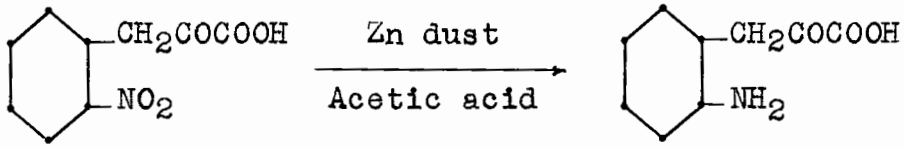
In 1897 Reissert (31) found a method for the preparation of 2-indole carboxylic acid and indole which has

since been improved upon by a number of workers. (32, 33, 34, 35, 36)

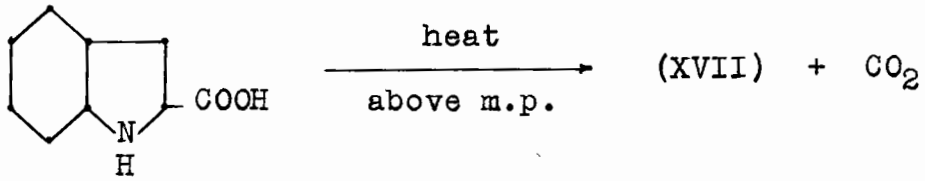
The type of reaction is well illustrated by Reissert's original preparation.



XXXV XXXVI XXXVII



XXXVIII



XXXIX

The condensation of o-nitrotoluene (XXXV) with diethyl oxalate (XXXVI) yields ethyl o-nitrophenylpyruvate (XXXVII). After hydrolysis of the ester, the free o-nitrophenylpyruvic acid (XXXVIII) was reduced with zinc dust and acetic acid to 2-indolecarboxylic acid (XXXIX).

On heating 2-indolecarboxylic acid above its melting point, carbon dioxide is evolved with the formation of indole (XVII).

The procedure used by Reissert has been modified by several workers in order to improve the yields. Reissert conducted his condensation of o-nitrotoluene and ethyl oxalate in dilute alcohol solution at a low temperature, for a long period of time. Mayer and Balle (32) used a more concentrated solution in alcohol and heated it at reflux temperature for a short time. They suggested steam distillation to separate the unreacted o-nitrotoluene. Elks, Elliot and Hems (37) used the same reaction conditions but found that yields were improved by acidification of the reaction mixture, extraction with ether, extraction of the ether with sodium hydroxide solution and acidification of the alkaline solution, all at 0°. Finally, Dicarlo (36) obtained the best results when he refluxed the reaction mixture with water to hydrolyse the ester and then steam distilled to separate the unreacted o-nitrotoluene. He obtained the o-nitrophenylpyruvic acid quite pure immediately upon acidification of the residue solution from the distillation. No ether or sodium hydroxide solution extractions were necessary.

The Reissert method for reduction of o-nitrophenylpyruvic acid was with zinc dust and acetic acid. Kermack, Perkin, and Robinson (34) carried out the reduction successfully using ferrous sulphate and ammonium hydroxide.

Cornforth and Robinson (33) obtained good yields through the use of sodium hydrosulphite. Their method was the simplest procedure being only the addition of sodium hydrosulphite to a solution of o-nitrophenylpyruvic acid in alkali.

Thus it would seem that the best method of preparing 2-indolecarboxylic acid now is a combination of the condensation method of DiCarlo and the reduction method of Cornforth and Robinson.

The Reissert method is versatile and not at all confined to 2-indole carboxylic acid. It is applicable, for the most part to the preparation of indoles substituted in the aromatic ring. Table I illustrates the utility of the reaction.

TABLE I

Nitro compound	Indole	Reference
4-methoxy-2-nitrotoluene	6-methoxy-	34
5-methoxy-2-nitrotoluene	5-methoxy-	38
6-methoxy-2-nitrotoluene	4-methoxy-	38
3-methoxy-2-nitrotoluene	7-methoxy-	38
4-cyano-2-nitrotoluene	6-cyano-	39
nitro-p-xylene	6-methyl-	40
6-chloro-2-nitrotoluene	4-chloro-	41

The fact that indole reacts with a Grignard reagent such as methyl magnesium iodide to form the reactive magnesyl indole has been of great value in the synthesis of indole derivatives. This reaction is predictable since indole does contain an active hydrogen.

The magnesyl indole is active and may be substituted in the 1- and 3- positions. It reacts with excess alkyl halides to yield 3,3-dialkylindolenines. It has also been reacted with various aldehydes, ketones and acyl chlorides. Either the 1- or 3- position or both may be substituted depending on the reaction and conditions.

In 1922 Majima and Kotake (42) compared the effects of diethyl ether and anisole as solvents for the action of various reagents on magnesyl indole. They found that 3-indolecarboxylic acid was formed by reaction with carbon dioxide though in yields not exceeding 25% at best.

They found that a better route to 3-indolecarboxylic acid was by the reaction of ethyl chloroformate with magnesyl indole which gave ethyl 3-indolecarboxylate in yields of 53% in diethyl ether.

In 1930 the same authors (43) repeated the preparation with ethyl chloroformate and then nitrated the resulting

ethyl 3-indolecarboxylate. This time they were able to get a yield of 78% of the ethyl ester.

An alternative method used by Mingolia (44) in 1932 for the preparation of 3-indolecarboxylic acid was the action of formaldehyde on magnesyl indole and permanganate oxidation of the resulting 3-indolyl carbinol to 3-indolecarboxylic acid.

Also, in 1935, Sanna (45) reacted magnesyl indole with trichloroacetyl chloride to obtain 3-indolyl trichloromethyl ketone. This was hydrolysed to 3-indolecarboxylic acid by potassium hydroxide.

The general reaction of esterification is far too common to warrant explanation here. The following methods have been used for the esterification of dialkylaminoalkanols with carboxylic acids; generally with the intention to produce compounds possessing anaesthetic properties.

1) An acid reacted with an amino alcohol in the presence of an acidic or basic catalyst. (46)

$$R.COOH + HORNR_2 \xrightarrow{H \text{ or } OH} R.COORNR_2 + H_2O$$

2) An acid chloride reacted with an amino alcohol. (47, 48, 49, 50, 51)

$$R.COCl + HORNR_2 \longrightarrow R.COORNR_2 + HCl$$

3) An acid chloride reacted with an amino alcohol hydrochloride. (47)

$$R.COCl + HORNR_2.HCl \longrightarrow R.COORNR_2.HCl + HCl$$

4) An acid anhydride reacted with an amino alcohol. (52)

$$(RCO)_2O + HORNR_2 \longrightarrow RCOORNR_2 + RCOOH$$

5) An exchange reaction between the ethyl ester of an acid and the amino alcohol in the presence of an alkaline catalyst. (47, 53, 54, 55)

$$R.COOC_2H_5 + HORNR_2 \xrightarrow{Na \text{ or } HCl} R.COORNR_2 + C_2H_5OH$$

6) The silver salt of an acid and an amino alcohol (56) reacted to form the ester.

$$R.COOAg + HORNR_2 \longrightarrow R.COORNR_2 + AgOH$$

7) The alkali salt of an acid reacted with an alkyl chloride. (57, 58, 47)

$$RCOONa + ClR.NR_2 \longrightarrow RCOORNR_2 + NaCl$$

8) A haloalkyl ester of an acid reacted with a secondary amine. (47)

$$R.COORX + HNR_2 \longrightarrow RCOORNR_2.HX$$

9) The alkali salt of an acid reacted with an aminoalkyl chloride hydrochloride. (59)

$$R.COONa + ClRNR_2 \longrightarrow R.COORNR_2.HCl + NaCl$$

Of these methods, numbers 2, 5 and 9 were used in this work.

2) A considerable amount of work has been done regarding the reaction of acyl chlorides with amino alcohols. The amine group must be tertiary in order to prevent formation of amide linkages. A number of patents have been issued on this type of reaction. (48, 49) The acid chloride is usually prepared by the reaction of the acid with thionyl chloride (60, 61) or with acetyl chloride and phosphorous trichloride. This reaction is generally found to be successful.

5) The ester exchange reaction is widely used and there are a number of patents in this field (53, 54). The catalyst most generally used is sodium alcoholate, formed by the solution of a catalytic amount of sodium in the amino alcohol. (53, 54, 55, 47) An ester of a low boiling alcohol, such as ethanol, and the desired acid is added to the sodium in alcohol solution and the mixture distilled. The ethanol exchanges with the amino alcohol and distills first from the mixture.

9) The alkali salt of an acid will react with an alkyl halide to form an ester and an inorganic alkali halide. This reaction is valuable since the only organic product is the desired ester. For the preparation of aminoalkyl esters either the aminoalkyl chloride (57, 58, 47) or its hydrochloride (59) may be used.

Several methods are in use. They consist in the reaction of the acid with metallic sodium or potassium in inert solution, with sodium alcoholate in alcohol solution, or with potassium hydroxide in a suitable solvent such as ethyl acetate. In each case the aminoalkyl chloride is then added.

If an aminoalkyl chloride hydrochloride is used the solution must be sufficiently basic to neutralize the hydrogen chloride part of the molecule as well as to react with the acid. The advantage of the use of an aminoalkyl chloride hydrochloride is that these compounds are usually obtained and stored in this form. The hydrochloride is most easily neutralized in the main reaction solution.

DISCUSSION

Synthesis of Acids

Three acids, 2-indolecarboxylic, 5-methoxy-2-indolecarboxylic and 3-indolecarboxylic, were prepared, and subsequently, attempts were made to esterify them with N, N-dimethylaminoethanol and 1-(N,N-dimethylamino) -propanol-2.

The reaction of diethyl oxalate (XXXVI) with o-nitrotoluene (XXXV) is essentially a Claisen condensation. As carried out in alcoholic solution with sodium ethoxide catalyst, a number of factors were found to affect the yields. It is imperative that the ethanol used be completely anhydrous. The product, o-nitrophenylpyruvic acid is quite labile, especially to heat. However, Reissert's original method in which the condensation is carried out in dilute solution at 35-40° over a long period of time produced very small yields. A great improvement was effected when the conditions were forced by the use of a concentrated solution and reflux. The period of reflux had to be short due to the sensitivity of the product. The steam distillation to separate the product from the unreacted o-nitrotoluene obviated the necessity of using a series of alkaline and ether extractions for the isolation.

When the longer ether and alkaline extractions method of isolation was used the product was generally obtained as an oil which was very difficult to crystallize. If this oil was allowed to stand for several days, a substance crystallized from it which was not o-nitrophenylpyruvic acid and had a melting point of 164-5°. This compound was not further investigated.

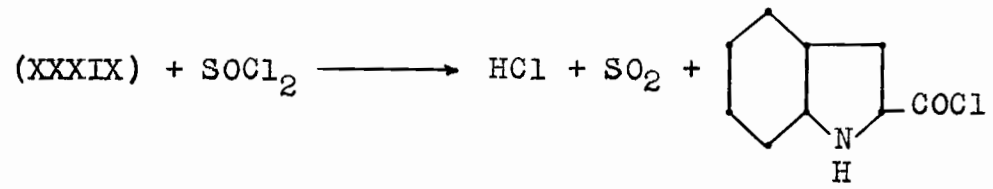
Acidification of the reaction solution after steam distillation as in the method of DiCarlo (36) always produced crystals of fairly pure o-nitrophenylpyruvic acid.

Of the three methods of reduction of o-nitrophenylpyruvic acid tried, the reduction with sodium hydrosulphite (33) was best in simplicity of technique and yields. The reduction with ferrous sulphate and ammonia (34) produced a thick black solution from which only a small yield was obtained. The reduction by zinc dust and acetic acid (31) gave a small amount of product which, though quite pure, had a slight green color.

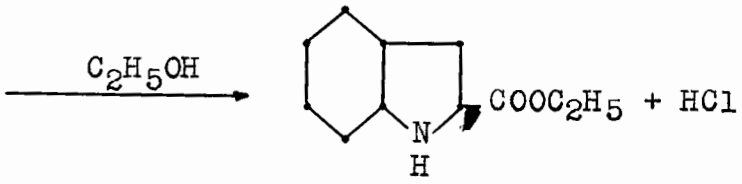
$$(XXXVII) + 3H_2 \xrightarrow[3)\ Zn - CH_3COOH]{\begin{matrix}1)\ Na_2S_2O_4 \\ 2)\ FeSO_4 - NH_4OH\end{matrix}} (XXXIX) + 3H_2O$$

The esterification of the 2-indolecarboxylic acid

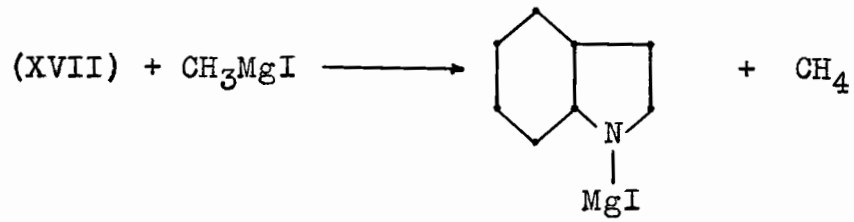
through the acid chloride (XL) and ethanol proceeded normally in each case.



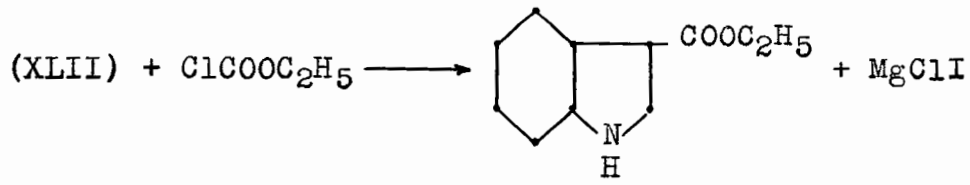
XL



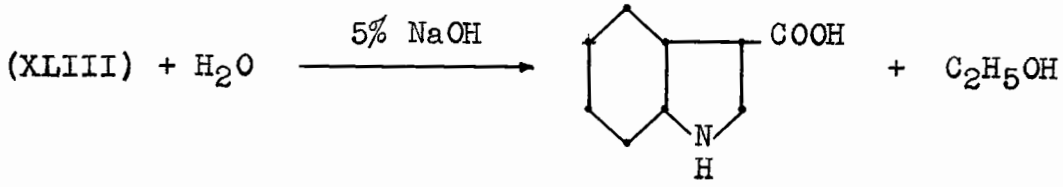
XLI



XLII



XLIII

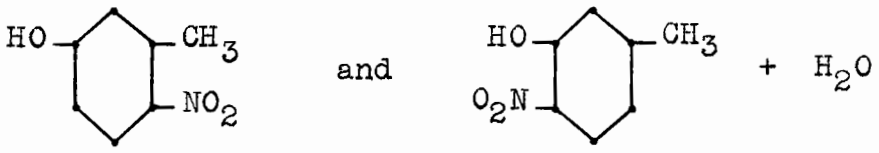


XLIV

Indole (XVII) reacts vigorously with methyl magnesium iodide to form magnesyl indole (XLII). The magnesyl indole reacts with chloroformic ester to form ethyl 3-indole-carboxylate. (XLIII) When the ether solution containing the product of this reaction was dried and evaporated, an oil was usually obtained. From this oil, a small smount of material would crystallize on standing. These crystals, m.p. 102-4°, were not further investigated. However, they correspond to the 1,3-dicarbethoxyindole described by Majima and Kotake (43). Neither methanol-water nor benzene were ideal for recrystallization of ethyl 3-indolecarboxylate. The ester was too soluble in benzene or pure methanol and a workable methanol-water mixture was hard to obtain.

In the larger scale (.5 mole) reaction, when the dry ether solution of the product was evaporated, an oil was formed which solidified on cooling. The crude product so formed was hydrolysed immediately by 5% sodium hydroxide solution. A rather large amount of unsaponifiable material was present but a good yield of pure 3-indolecarboxylic acid (XLIV) was obtained.

XLV



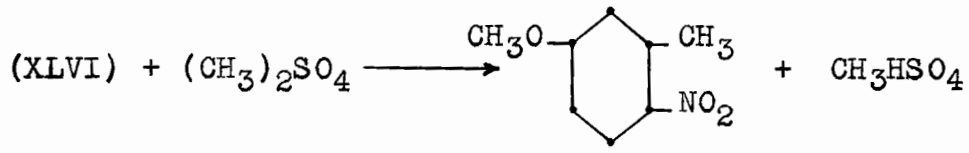
XLVI XLVII

The nitration of m-cresol (XLV) with 100% nitric acid was successful although the yields were rather small. The separation of the two isomers formed was easy since one has ortho nitro- and hydroxy- groups and is thus steam distillable. To cool this reaction a mixture of acetone and dry ice was raised about the flask in a casserole as needed. The 5-hydroxy-2-nitrotoluene (XLVI) was found to recrystallize well from hot water and also from benzene. The 5-hydroxy-4-nitrotoluene (XLVII) was recrystallized from methanol, in which it is quite soluble.

If the diluted solution was allowed to come to room temperature, after the reaction mixture was poured onto ice, the product was destroyed by the nitric acid.

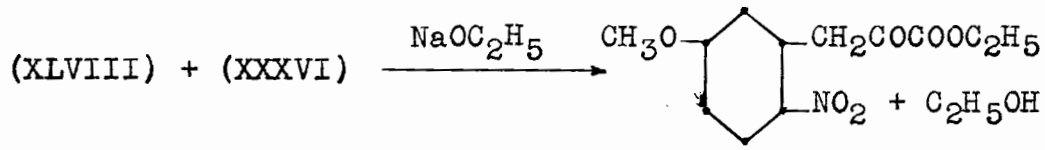
An attempt to carry out this nitration with 35% nitric acid failed when a large amount of black tar was formed. Since a considerable amount of brown nitric oxide was evolved during the reaction, oxidation of the m-cresol must have occurred. The oxidation and possible further polymerization would account for the tar formed. A small

amount of the expected nitro compounds was also formed but they were inseparable from the tar.



XLVIII

The methylation of 5-hydroxy-2-nitrotoluene (XLVI) by dimethyl sulphate proceeded normally and in reasonable yields.



XLIX

The condensation of 5-methoxy-2-nitrotoluene (XLVIII) with diethyl oxalate (XXXVI) to form ethyl 5-methoxy-2-nitrophenylpyruvic acid (XLIX) is similar to that of o-nitrotoluene with diethyl oxalate.

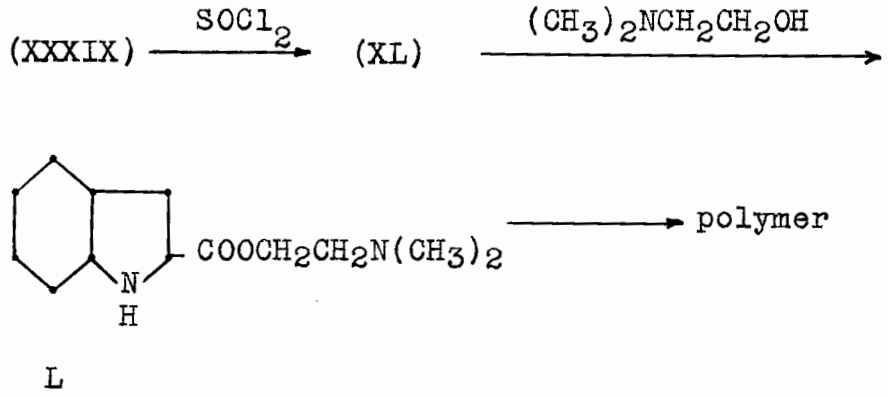
According to Blaikie and Perkin (38) it is necessary to do the reaction in ether solution rather than alcohol. This condensation also does not go to completion and some 5-methoxy-2-nitrotoluene is always recovered.

The reduction of 5-methoxy-2-nitrophenylpyruvic (XLIX) acid was carried out with sodium hydrosulphite and found to be entirely satisfactory.

Synthesis of Esters

By analogy to syntheses of similar types of compounds, the preparation of N,N-dimethylaminoethyl 2-indolecarboxylate was first attempted through the reaction of dimethylaminoethanol with 2-indolecarbonyl chloride (XL).

A reaction occurred which was rather violent as compared to the reaction of 2-indolecarbonyl chloride with ethanol. The product obtained was a polymer.



L

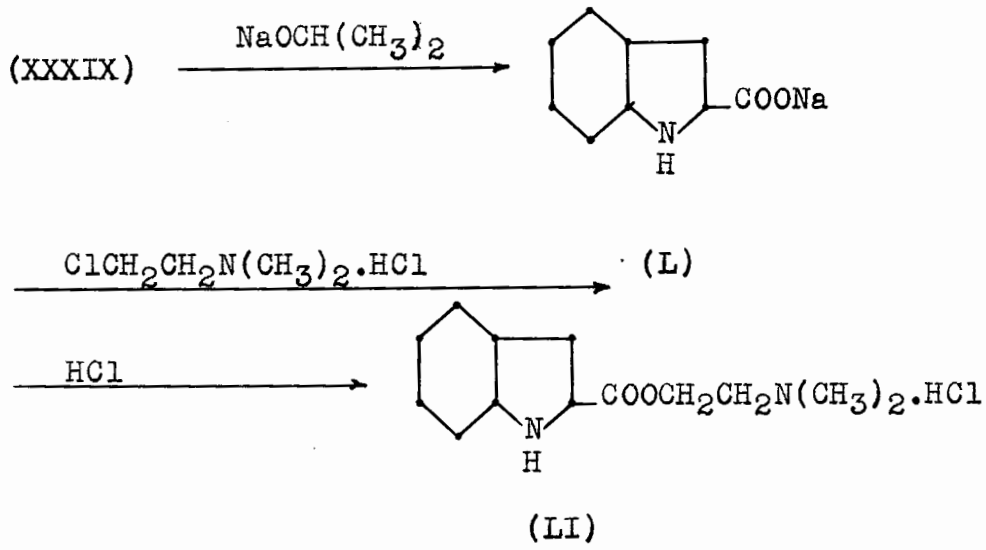
Another attempt was made by a transesterification reaction between ethyl 2-indolecarboxylate (XLI) and dimethylaminoethanol in the presence of sodium alcoholate. This reaction, even under very gentle conditions (25°) still produce a polymer. The rate of polymer formation was found to vary directly with the temperature of the reaction. At 100° the formation of a polymeric precipitate in the reaction flask took place within two minutes.

An ester exchange definitely occurred as proved by the presence of ethanol in the distilled alcohols.

$$\text{(XLI)} \xrightarrow[\text{Na}]{(CH_3)_2NCH_2CH_2OH} \text{(L)} \longrightarrow \text{polymer}$$

Thus it may be assumed that the desired amino ester is unstable and easily polymerized in the free state. The type of polymerization is not known but it is promoted by traces of bases and even by acid.

The foregoing methods having failed, it was decided to carry out the reaction in such a manner that the amino group first existed as a hydrochloride and the amino ester was present only in neutral solution. To this purpose the reaction between sodium 2-indolecarboxylate and 2-chloro-N,N-dimethylethylamine hydrochloride was tried. To form the sodium salt the acid was added to a solution of sodium in isopropanol. A sufficient amount of sodium was used to neutralize both the acid and amine hydrochloride. The amino ester (L) was extracted from a neutral water solution by ether and precipitated by dry hydrogen chloride gas. At no time could the free amino ester be isolated in crystalline form. Ethyl acetate was found to be a good recrystallizing solvent for N,N-dimethylaminoethyl 2-indolecarboxylate, but absolute alcohol was also useful. The solubility in absolute alcohol is quite high.



(LI)

1-Methyl-2-dimethylaminoethyl 2-indolecarboxylate was prepared in a similar reaction. The yields from this reaction were of a low order (approximately 20-30%).

The attempted preparations of N,N-dimethylaminoethyl 5-methoxy-2-indolecarboxylate and N,N-dimethylaminoethyl 3-indolecarboxylate both failed. In each case polymerization occurred in the hydrogen chloride saturated ether solution after a short time. These compounds must be more unstable than the two prepared.

EXPERIMENTAL

Preparation of 2-Indolecarboxylic Acid

The scheme for the preparation of 2-indolecarboxylic acid was as follows:

I) Condensation of diethyl oxalate with o-nitrotoluene to yield o-nitrophenylpyruvic acid.

$$(XXXV) + (XXXVI) \xrightarrow{NaOC_2H_5} (XXXVII) + C_2H_5OH$$

II) Reduction of the o-nitrophenylpyruvic acid to 2-indolecarboxylic acid.

$$(XXXVIII) \xrightarrow{Na_2S_2O_4} (XXXIX)$$

I) Preparation of o-nitrophenylpyruvic acid

First method (32, 37) 6.9 gm. (.30 mole) of sodium was dissolved in 87.5 ml. of absolute ethanol. To this solution was added first 43.8 gm. (.30 mole) of diethyl oxalate and then 41.1 gm. (.30 mole) of o-nitrotoluene. The mixture was refluxed for fifteen minutes on a steam bath. The dark red mixture was cooled to 0° and acidified with a cold solution of 50 ml. of concentrated hydrochloric acid in 30 ml. of water. The alcohol was distilled from the resulting yellow mixture below 50° at reduced pressure.

The residue was extracted with ether. The ethereal solution was extracted with ice cold normal sodium hydroxide solution until the aqueous layer remained a deep red color with continued shaking, that is, until there was an excess of sodium hydroxide. The combined alkaline extracts were washed with a little fresh ether and acidified below 10° with dilute (1:1) hydrochloric acid. The oily precipitate was extracted with ether. The ether was evaporated and the residue was recrystallized from benzene. The combined ethereal layers from the alkaline extracts contained o-nitrotoluene which was recovered by distillation with reduced pressure. Recovery was 20.5 gm. (50%). The yield of o-nitrophenylpyruvic acid was 13.2 gm. (42% of the theoretical as calculated from the amount of o-nitrotoluene consumed). The results of other condensations are summarized in the following table.

TABLE II

Reagents			Product		Recovered	
ethyl oxalate		o-nitro-toluene		o-nitrophenyl-pyruvic acid		o-nitro-toluene
wt. gm.	mole	wt. gm.	mole	wt. gm.	% yield a	wt. gm.	% recovery
43.8	.30	41.1	.30	13.2	42	21	51
43.8	.30	41.1	.30	6.9	20.2	18.6	45.4
87.6	.60	82.2	.60	6.3	9.7	39.6	48.2
54.8	.40	41.1	.30	5.8	14.2	13.5	38.2

a) % yield is based on amount of o-nitrotoluene consumed.

Second method (36) The reagents were mixed as previously described and refluxed for fifteen minutes on a steam bath. An equal amount of water was added and the solution refluxed for one half hour more. The solution was steam distilled to remove alcohol and unreacted o-nitrotoluene. The residue was cooled and acidified with concentrated hydrochloric acid. The o-nitrophenylpyruvic acid precipitated as an oil which crystallized on shaking the cold mixture. The product was filtered and dried and used in the succeeding step without further purification. The yield obtained was 37.6 gm. (60% of total theoretical). About 25% of the original o-nitrotoluene was recovered from the steam distillate.

TABLE III

Reagents				Product		Recovered	
ethyl oxalate		o-nitro-toluene		o-nitrophenyl-pyruvic acid		o-nitro-toluene	
wt. gm.	mole	wt. gm.	mole	wt. gm.	% yield a	wt. gm.	% recovery
43.8	.30	41.1	.30	37.7	60.2	19.7	31.7
43.8	.30	41.1	.30	34	54.5		

a) % yield based on total theoretical yield.

The original method of Reissert (31) for the condensation of ethyl oxalate with o-nitrotoluene in a dilute

solution of absolute alcohol for several days at 35° to 40° was attempted. The condensation proceeded but the yields were found to be less than 10%.

II) Preparation of 2-indolecarboxylic acid (33)

10 gm. (.0478 mole) of o-nitrophenylpyruvic acid was dissolved in a solution of 2 gm. of sodium hydroxide in 70 ml. of water. Sodium hydrosulphite, about 24 gm. (.152 mole), was added to the cold stirred solution until a test portion no longer became red on the addition of excess sodium hydroxide. The solution was cooled and acidified with concentrated hydrochloric acid and heated on a steam bath to expel sulphur dioxide. The resulting mixture was extracted with ether. The ether was evaporated and the product was recrystallized from benzene. The yield of 2-indolecarboxylic acid from the crude o-nitrophenylpyruvic acid was 4.25 gm. (55%). The acid melted at 200-2°.

TABLE IV

Reagents				Product	
o-nitrophenyl-pyruvic acid		$Na_2S_2O_4$		2-indolecarboxylic acid	
wt. gm.	mole	wt. gm.	mole	wt. gm.	% yield
5	.0239	12	.076	1.2	31.2
5	.0239	12	.076	1.4	36.4
5	.0239	12	.076	1.6	41.6
10	.0478	24	.152	4.0	52
10	.0478	24	.152	3.5	45
10	.0478	24	.152	2.46	32

The Reissert (31) method for reduction of o-nitrophenylpyruvic acid with zinc dust and acetic acid was attempted as follows:

10 gm. (.0478 mole) of o-nitrophenylpyruvic acid was dissolved in 50 ml. of glacial acetic acid and the solution diluted with 100 ml. of water. The solution was brought to a boil, removed from the flame and zinc dust added in small quantities until a test portion of the solution was not colored deep red by excess sodium hydroxide. The liquid was filtered from the zinc and most of the acetic acid neutralized by dilute sodium hydroxide. The solution was extracted with ether and the ether evaporated. The residue, recrystallized from benzene, had a melting point of 203-4°. More product was obtained by dilution of the acid solution after the ether extraction, however the product was difficult to purify.

The reduction of o-nitrophenylpyruvic acid with ferrous sulphate and ammonia according to Kermack, Perkin and Robinson (34) was attempted also but in the one reaction tried the yield was very small.

III) Preparation of ethyl 2-indolecarboxylate (61)

3 ml. (4.95 gm., .0416 mole) of thionyl chloride was

added to a solution of 3 gm. (.0186 mole) of 2-indolecarboxylic acid in 100 ml. of dry ether and allowed to stand for one hour. The solution was evaporated to dryness at reduced pressure, treated twice with 60 ml. of dry ether and taken to dryness each time. The residue was dissolved in 60 ml. of dry ether, filtered, and added to 20 ml. of absolute ethanol. No reaction was noticeable. The ether and part of the alcohol were evaporated on a steam bath. The product was recrystallized from 90% ethanol. 1.4 gm. (40%) of ethyl 2-indolecarboxylate melting at 120-1° was obtained. In one reaction a small amount of 2-indolecarboxylic acid was recovered.

TABLE V

Reagents				Product	
2-indolecarboxylic acid		thionyl chloride		ethyl 2-indolecarboxylate	
wt. gm.	mole	wt. gm.	mole	wt. gm.	% yield
3	.0186	4.95	.0416	1.1	31
3	.0186	4.95	.0416	1.4	40

The esterification of 2-indolecarboxylic acid was attempted by refluxing 1 gm. (.0062 mole) of the acid in 200 ml. of 95% ethanol with 0.5 ml. of glacial acetic acid as a catalyst. However, the reaction does not go to com-

pletion and the purification of the ester, contaminated with large percentages of the acid, was very difficult and so the method was abandoned.

Preparation of 3-Indolecarboxylic Acid

I Preparation of ethyl 3-indolecarboxylate (42, 43)

4.8 gm. (.198 mole) of magnesium and 59 ml. of dry ether were put in a 250 ml. 3-necked flask fitted with a reflux condenser, stirrer, and dropping funnel. 32 gm. (.226 mole) of methyl iodide was added dropwise. A solution of 11.8 gm. (.100 mole) of indole in 30 ml. of dry ether was added slowly. 12 gm. (10.6 ml., .110 mole) of ethyl chloroformate was added. The mixture was refluxed one hour, decomposed with ice water and acidified with acetic acid. The resulting mixture was extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate solution to remove acetic acid, then washed with water and dried over anhydrous sodium sulphate. The ether was evaporated completely and the oily residue taken up in 70% alcohol. On standing, a small amount of crystals in the form of small white needles, having a melting point of 102-4° separated. After filtration of these crystals the alcohol was evaporated from the solution

and the oil separated again. The recrystallization of the oil from methanol-water or benzene gave 11.7 gm. (62%) of ethyl 3-indolecarboxylate melting at 118-20°.

TABLE VI

Reagents								Product	
magnesium		methyl iodide		indole		ethyl chloroformate		ethyl 3-indole-carboxylate	
wt. gm.	mole	wt. gm.	mole	wt. gm.	mole	wt. gm.	mole	wt. gm.	% yield
2.4	.10	16	.113	5.9	.05	6	.05	1 apprx	10.6
2.4	.10	16	.113	5.9	.05	6	.05	6.0 crude	63.5
								3.2 recrs	33.8
4.8	.20	32	.225	11.8	.10	12	.11	11.7	62
4.8	.20	32	.225	11.8	.10	12	.11	3.2	16.9
24	1.0	156	1.1	59a	.50	55	.50	39.6 crude	44.5

a) Crude commercial indole was used in this case.

II Preparation of 3-indolecarboxylic acid

5 gm. (.0265 mole) of ethyl 3-indolecarboxylate was refluxed with 50 ml. of 5% sodium hydroxide (.0625 mole) for one hour. The solution was cooled, a small precipitate filtered out, and the solution acidified with hydrochloric acid. The precipitated acid was filtered and dried. The yield of 3-indolecarboxylic acid was 3.23 gm. (76%) melting at 216-8°.

Subsequently, this hydrolysis was carried out on the

crude ethyl 3-indolecarboxylate obtained from the previous reaction after evaporation of the dried ether solution. About twice the calculated theoretical amount of 5% sodium hydroxide solution was added, the mixture refluxed, cooled, filtered and acidified as above.

Preparation of 5-methoxy-2-indolecarboxylic acid

The scheme for the preparation of the 5-methoxy-2-indolecarboxylic acid was as follows:

I) m-Cresol (XLV) was nitrated with 100% nitric acid in glacial acetic acid to yield 5-hydroxy-4-nitrotoluene (XLVII) and 5-hydroxy-2-nitrotoluene. (XLVI)

$$\text{(XLV)} + HNO_3 \longrightarrow \text{(XLVI) and (XLVII)} + H_2O$$

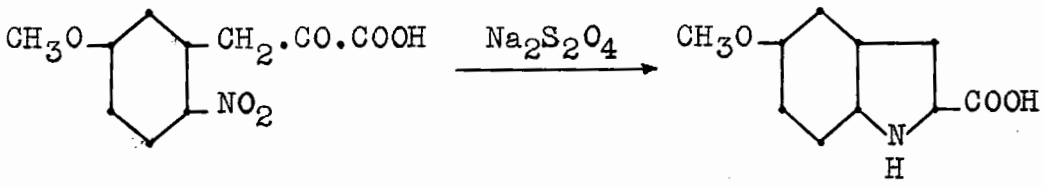
II) The 5-hydroxy-2-nitrotoluene (XLVI) was methylated with dimethyl sulphate.

$$\text{(XLVII)} + (CH_3)_2SO_4 \longrightarrow \text{(XLVIII)} + CH_3HSO_4$$

III) The 5-methoxy-2-nitrotoluene (XLVIII) was condensed with diethyl oxalate (XXXVI) to yield 5-methoxy-2-nitrophenylpyruvic acid. (XLIX)

$$\text{(XLVIII)} + \text{(XXXVI)} \xrightarrow{NaOC_2H_5} \text{(XLIX)} + C_2H_5OH$$

IV) The 5-methoxy-2-nitrophenylpyruvic acid was reduced to 5-methoxy-2-indolecarboxylic acid (LII) by sodium hydrosulphite.



I) Nitration of m-cresol (38)

200 gm. of glacial acetic acid was added slowly to 100 gm. (1.59 moles) of 100% nitric acid with vigorous stirring and the temperature was kept below 0° by intermittent dry ice cooling. A cold solution of 70 gm. (.649 mole) of m-cresol in 70 gm. of glacial acetic acid was dropped slowly into the nitric acid solution. The temperature was kept at about -10° to -5°. It was then poured onto about one kg. of cracked ice. While this mixture was still cold the solids were filtered out and washed with a little water. The solid precipitate was then steam distilled until no more yellow 5-hydroxy-4-nitrotoluene came over in the distillate. The residue was cooled and filtered and the resulting 5-hydroxy-2-nitrotoluene was recrystallized from hot water. The yield of 5-hydroxy-2-nitrotoluene was 23.8 gm. (24% of theoretical). The melting point on one recrystallization from water was 127-8°.

The 5-hydroxy-4-nitrotoluene was precipitated from the steam distillate on cooling. It was filtered and recrystallized from methanol. The yield was 12.8 gm. (13% of the theoretical). The melting point was 57-9°.

TABLE VII

Reagents				Product			
m-cresol		nitric acid 100%		5-hydroxy-2-nitrotoluene		5-hydroxy-4-nitrotoluene	
wt. gm.	mole	wt. gm.	mole	wt. gm.	% yield	wt. gm.	% yield
35	.324	50	.794	5	10	1	2
70	.649	100	1.59	23.8	24	12.6	12.7
70	.649	100	1.59	8.4	8.5	7.2	7.3
70	.649	100	1.59	5.6	5.7	2.2	2.2
70	.649	100	1.59	15.8	16	9.1	9.2
70	.649	100	1.59	22.2	22.4	9.1	9.2

Another method (62) for nitration of m-cresol with 35% nitric acid was attempted. 150 gm. (.83 mole) of cold 35% nitric acid (d. 1.20) was dropped slowly, with vigorous stirring, into a solution of 50 gm. (.463 mole) of m-cresol in 100 gm. of benzene, and the mixture was kept below 0° with an ice-salt bath. A black solution resulted and nitrogen oxides were evolved. The benzene layer was separated and the benzene was evaporated. An intractable tar resulted, from which no product could be isolated.

II) Preparation of 5-methoxy-2-nitrotoluene (38)

A solution of 25.5 gm. (.167 mole) of 5-hydroxy-2-nitrotoluene in 50 ml. of methanol was added slowly, with stirring, to a solution of 7.6 gm. (.33 mole) of sodium in 85 ml. of methanol. A deep red solution and an orange precipitate resulted. 42 gm. (.33 mole) of dimethyl sulphite was added and the mixture was refluxed until all the solid had passed into solution. Then most of the methanol was distilled off under reduced pressure. Water was added to dissolve the sulphate. The solid was collected and washed with water, 5% sodium hydroxide solution and water again. It was dried and recrystallized from petroleum ether. 16.7 gm. (60%) of 5-methoxy-2-nitrotoluene, m.p. 51-3° was obtained.

TABLE VIII

Reagents						Product	
5-hydroxy-2-nitrotoluene		sodium		dimethyl sulphate		5-methoxy-2 nitrotoluene	
wt. gm.	mole	wt. gm.	mole	wt. gm.	mole	wt. gm.	% yield
10	.065	3	.131	16.5	.132	3.8	35
25.5	.167	7.6	.33	42	.334	16.7	60
25.5	.167	7.6	.33	42	.334	15.2	54.5
14	.092	4.5	.196	25.3	.201	8.2	53.5

III) Preparation of 5-methoxy-2-nitrophenylpyruvic acid (38)

14 gm. (.205 mole) of sodium ethoxide, free from alcohol, was suspended in 120 ml. of absolute ether, and 25.2 gm. (.173 mole) of diethyl oxalate was slowly added. The solution became yellow. 20 gm. (.120 mole) of 5-methoxy-2-nitrotoluene dissolved in ether was slowly added. The solution turned red. The mixture was refluxed for eighteen hours at the end of which time a considerable orange precipitate had formed. To hydrolyse the ester formed, the total solution was shaken with 200 ml. of 5% sodium hydroxide and left to stand for one hour. This dark red solution was acidified with concentrated hydrochloric acid. The ether layer was separated and the aqueous layer was extracted twice with ether. The ether extracts were combined and washed with water and then extracted with 5% sodium hydroxide solution. The alkaline extract was acidified with concentrated hydrochloric acid. The precipitate was filtered and recrystallized from glacial acetic acid. 11.5 gm. (40%) of the acid, melting at 134-6° was obtained.

The ether solution was evaporated and the residue was recrystallized from petroleum ether. 6.82 gm. (34%) of unreacted 5-methoxy-2-nitrotoluene was recovered.

IV) Preparation of 5-methoxy-2-indolecarboxylic acid

10 gm. (.0419 mole) of 5-methoxy-2-nitrophenyl-pyruvic acid was dissolved in a solution of 2 gm. of sodium in 70 ml. of water. About 24 gm. (.152 mole) of sodium hydrosulphite was added slowly, with stirring, until a test drop of the solution was no longer colored deep red by excess sodium hydroxide. The solution was then carefully acidified with concentrated hydrochloric acid and heated on a steam bath to expell sulphur dioxide. After recrystallization from benzene the acid had a melting point of 194-6°.

Preparation of N,N-dimethylaminoethyl 2-indolecarboxylate (58,59)

0.8 gm. (.0348 mole) of sodium was dissolved in 30 ml. of isopropanol. To this solution was added 2 gm. (.0124 mole) of 2-indolecarboxylic acid and 5 gm. (.0348 mole) of 2-chloro-N,N-dimethylethylamine hydrochloride and the mixture was refluxed for twelve hours. 25 ml. of a saturated solution of sodium bicarbonate was added and the resulting mixture distilled to dryness on a steam bath at reduced pressure. The residue was extracted with benzene. A cloudy solution was obtained. On addition of ether it became more clouded. When dry hydrogen chloride gas was passed through the solution a brown oil was precipitated. On evaporation of the ether the oil turned quite black.

The benzene was poured off and the oil was found to be completely soluble in water. Activated charcoal removed the black color, leaving a light yellow solution. The water was almost completely evaporated. The oil was partly crystallized after standing for more than a week. On recrystallization from absolute alcohol a small amount of small white crystals, melting at 178-80°, was obtained.

This synthesis was repeated using the same amounts of reagents, but the mixture was refluxed for eighteen hours. After the addition of 25 ml. of saturated sodium bicarbonate solution and distillation to dryness, the residue was extracted with benzene as before. Dry hydrogen chloride gas was passed into the benzene solution to give an oil which hardened in three days. The benzene was evaporated and the residue recrystallized from absolute alcohol. The product so obtained was recrystallized from acetone-ethyl acetate (3:1) until an analytical sample of melting point 180-1° was obtained.

Analysis: Calculated for $C_{13}H_{17}O_2N_2Cl$:
C, 58.01; H, 6.32; N, 10.41 %
Found:
C, 57.99; H, 6.31; N, 10.37 %

A slightly different final method was developed. 2 gm. (.0124 mole) of 2-indolecarboxylic acid was added to a solution of 1.1 gm. (.0478 mole) of sodium in isopropanol. The mixture was refluxed for two hours. 5 gm. (.0348 mole) of 2-chloro-N,N-dimethylethylamine hydrochloride was added and refluxed for ten hours. 20 ml. of saturated sodium bicarbonate solution was added and the isopropanol distilled from the reaction mixture with reduced pressure. Water was added to dissolve the sodium chloride and the mixture was extracted with ether. The ether solution was evaporated and the oil recrystallized from acetone-ethyl acetate (3:1) mixture to obtain a product melting at 180-1°.

Two other methods for the preparation of N,N-dimethylaminoethyl 2-indolecarboxylate were tried but abandoned.

I. 1 gm. (.0062 mole) of 2-indolecarboxylic acid dissolved in 30 ml. of dry ether was treated with 1 ml. (1.65 gm., .0139 mole) of thionyl chloride and allowed to stand for one hour at room temperature. The solution was then distilled to dryness under reduced pressure. The residue was twice treated with 20 ml. of dry ether and taken to dryness in order to remove traces of hydrogen chloride, sulphur dioxide, and thionyl chloride. The residue was dissolved in 20 ml. more of dry ether, filtered,

and added to 1 ml. (0.88 gm., .010 mole) of dimethylaminoethanol in 10 ml. of dry ether. A reaction occurred as evidenced by boiling of the ether. The ether was evaporated and the residue was taken up in alcohol. No crystalline product could be isolated from this material.

II. A small piece of sodium was dissolved in 10 ml. (8.8 gm., .10 mole) of dimethylaminoethanol and 2 gm. (.0106 mole) of ethyl 2-indolecarboxylate was added to the solution. This was heated in an oil bath at 100° for ten minutes. A precipitate formed in the solution. The precipitate was amorphous in form and charred without melting. It was insoluble in benzene, ethanol, ether, petroleum ether and water. However, it was dissolved in 50% ethanol on warming. On evaporation this solution precipitated some ethyl 2-indolecarboxylate.

The reaction was repeated with the same amounts of reagents and the alcohols were distilled from the solution very slowly at 5 to 10 mm. pressure and 40-50°. The residue was evaporated dry at 80° and 5 mm. pressure for two hours. Again an amorphous insoluble residue was obtained.

This was repeated once more with the same amounts of reagents and then was evaporated at room temperature (25°)

and 3 mm. pressure for 3 days. The alcohols which were distilled out were collected in a dry ice cooled trap. It was proved by means of the iodoform test that ethanol was present in this solution. Again an amorphous solid remained in the distillation flask.

Preparation of 1-methyl-2-dimethylaminoethyl 2-indolecarboxylate

2 gm. (.0124 mole) of 2-indolecarboxylic acid was added to a solution of 1.1 gm. (.0478 mole) of sodium in 40 ml. of isopropanol and the mixture refluxed for two hours. 5 gm. (.0317 mole) of 2-chloro-N,N-dimethylpropylamine hydrochloride was added and refluxing continued for ten hours. 20 ml. of a saturated solution of sodium bicarbonate was added and the isopropanol was distilled from the mixture under reduced pressure. Water was added to dissolve the sodium chloride and the solution was extracted with ether. The ether solution was dried over anhydrous magnesium sulphate and filtered. Dry hydrogen chloride was passed into the ether solution to precipitate an oil. The ether was evaporated and the oil was persuaded to crystallize by cooling and scratching the bottom of the flask with a glass rod. The product so obtained was recrystallized from absolute ethanol. The 1-methyl-2-dimethylaminoethyl 2-indolecarboxylate melted at 175-6°.

Analysis: Calculated for $C_{14}H_{19}O_2N_2Cl$:

C, 59.36; H, 6.71; N, 9.90 %

Found:

C, 59.02; H, 6.74; N, 9.92 %

Attempted Preparation of N,N-dimethylaminoethyl 5-methoxy-2-indolecarboxylate

2 gm. (.0105 mole) of 5-methoxy-2-indolecarboxylic acid was added to a solution of 1.1 gm. (.0478 mole) of sodium on 40 ml. of isopropanol and the mixture refluxed for two hours. 5 gm. (.0348 mole) of 2-chloro-N,N-dimethylethylamine hydrochloride was added and the mixture refluxed for ten hours. 20 ml. of a saturated solution of sodium bicarbonate was added and the isopropanol distilled from the mixture under reduced pressure. The residue was extracted with ether and the ether solution dried over anhydrous magnesium sulphate. Dry hydrogen chloride gas was passed into ether solution to give a cloudy precipitate which settled as a slightly reddish oil. When the ether was evaporated the oil turned bright red and gummy. No product could be isolated.

Attempted preparation of N,N-dimethylaminoethyl 3-indolecarboxylate

2 gm. (.0124 mole) of 3-indolecarboxylic acid was added

to a solution of 1.1 gm. (.0478 mole) of sodium in 40 ml. of isopropanol and refluxed for one hour. 5 gm. (.0348 mole) of 2-chloro-N,N-dimethylethylamine hydrochloride was added and refluxed seven hours. 20 ml. of saturated sodium bicarbonate solution was added and the isopropanol distilled out under reduced pressure. Water was added and the solution was extracted with ether. The ether solution was dried over anhydrous magnesium sulphate and filtered. Dry hydrogen chloride gas was passed in and an oily precipitate formed. The solution turned reddish. On evaporation of the ether a reddish oil was formed. No product could be obtained from the oil.

This reaction was repeated using the same amounts of reagents. After the reflux period, the solution was neutralized with dilute (1:1) hydrochloric acid. This solution was distilled to dryness under reduced pressure. A red residue remained from which no product could be isolated.

THE REAGENTS USED IN THIS INVESTIGATION

1. Diethyl oxalate, Eastman Kodak Co., white label, was redistilled under reduced pressure.
2. o-Nitrotoluene, E.K.C., white label, was redistilled under reduced pressure.
3. Sodium hydrosulphite, Mallinckrodt, was used as obtained.
4. Magnesium ribbon for Grignard reactions was washed with ether.
5. Methyl iodide was redistilled.
6. Indole, Barret Chemicals, was recrystallized from water.
7. Ethyl chloroformate, U.S. Industrial Chemicals, was used as obtained.
8. 100% nitric acid, Brickman & Co., was used as obtained.
9. m-Cresol, E.K.C., yellow label, was redistilled under reduced pressure.
10. Dimethylsulphate, E.K.C., yellow label, was used as obtained.
11. 2-Chloro-N,N-dimethylethylamine hydrochloride, E.K.C., yellow label, was used as obtained.
12. Dimethylaminoethanol, E.K.C., white label, was used as obtained.
13. 2-Chloro-N,N-dimethylpropylamine hydrochloride, E.K.C. yellow label, was recrystallized from absolute alcohol.

SUMMARY AND CONTRIBUTIONS TO KNOWLEDGE

1. 2-Indolecarboxylic acid was prepared by condensation of diethyl oxalate and o-nitrotoluene and subsequently, reduction of the o-nitrophenylpyruvic acid by sodium hydrosulphite.

2. Ethyl 3-indolecarboxylate was prepared from magnesyl indole and chloroformic ester. The acid was obtained by alkaline hydrolysis of the ester.

3. m-Cresol was nitrated with 100% nitric acid to obtain 5-hydroxy-2-nitrotoluene. The latter was methylated with dimethylsulphate to produce 5-methoxy-2-nitrotoluene. Condensation of the latter with diethyl oxalate gave 5-methoxy-2-nitrophenylpyruvic acid which was reduced by sodium hydrosulphite to 5-methoxy-2-indolecarboxylic acid.

4. A new compound, dimethylaminoethyl 2-indolecarboxylate, was produced by reaction of sodium 2-indolecarboxylate with 2-chloro-N,N-dimethylethylamine hydrochloride.

5. A new compound, 1-methyl-2-(N,N-dimethylamino)-ethyl 2-indolecarboxylate was prepared by the reaction of sodium 2-indolecarboxylate with 2-chloro-N,N-dimethylpropylamine hydrochloride.

6. The attempted preparation of dimethylaminoethyl 5-methoxy-2-indolecarboxylate and dimethylaminoethyl 3-indolecarboxylate failed.

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