TO BETTY

STRAINED TRICYCLIC COMPOUNDS

CONTAINING NITROGEN

STRAINED TRICYCLIC COMPOUNDS CONTAINING NITROGEN

By

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PREFACE

In the original programme, we intended to prepare 2,2a,3,4-tetrahydro-1H-cyclopent[cd]indene which was unknown at the time. However, with the synthesis of such a compound by other workers, the preparation of an analogous heterocyclic compound was investigated.

The problem is a challenging one since the synthesis of these compounds had failed in the hands of many competent chemists for a great number of years. This work was undertaken with the anticipation that if such systems could be prepared, the chemical and physical properties would be expected to be different from ordinary aromatic systems due to the strain and therefore would be of interest.

ACKNOWLEDGEMENTS

The author wishes to express his sincere thanks to the University of Ottawa for providing the facilities for this work, and to Professor F. A. L. Anet for his invaluable advice and encouragement which have made this investigation possible.

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ABSTRACT

PART I

The structure of the compound obtained by treatment of β,β'-diindolyl with strong acid was investigated. The structure was established by Faseeh and Harley-Mason (14) during the course of this work as α,β'-diindolyl, with which our results are in complete agreement.

PART II

The synthesis of the isolated, strained tricyclic system, 2,2a,3,4-tetrahydro-1H-cyclopent[cd]indene and its derivatives, which were not known at the inception of this study have now been accomplished by Rapoport et al. (24, 25, 26) and in an effort to obtain a similar heterocyclic compound, we have observed an interesting rearrangement. Also, a compound believed to be cyclopent[cd]indoline was obtained but it was not completely characterized. A suitable precursor for the synthesis of cyclopent[cd]indoline has been obtained.

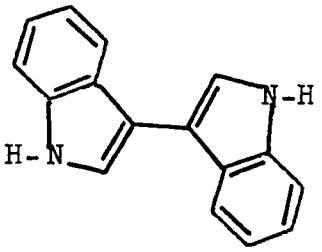
PART I

The Product from the Reaction of β,β'-Diindolyl with Strong Acids

INTRODUCTION

As the structure of compound II prepared by Gabriel, Gerhardt and Wolter (1) on treatment of β,β'-diindolyl (I) with strong acid was not elucidated, and as it was at first believed that this compound might possess the fused tricyclic system which is the general topic of this thesis, it appeared of sufficient scientific interest to define its structure.

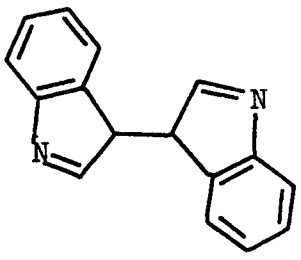
When Gabriel, Gerhardt and Wolter (1) in 1923 treated β,β'-diindolyl (I) with strong acid, they obtained a compound having an empi-



$\longrightarrow$ $C_{16}H_{12}N_2$

I II

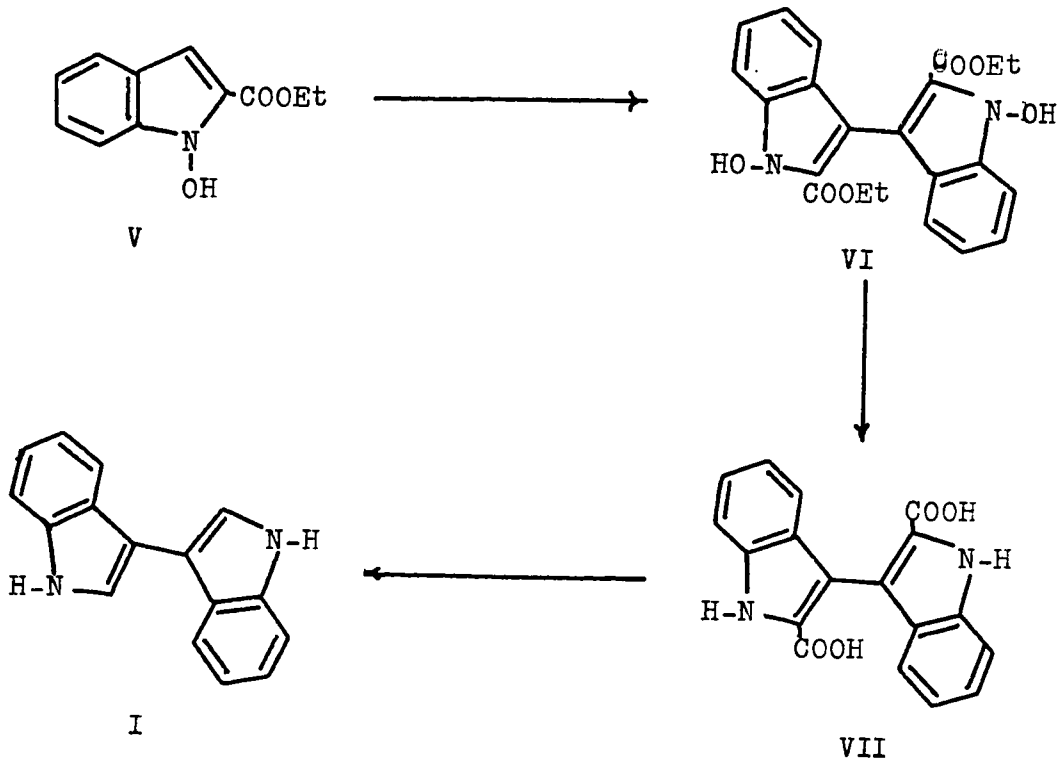
rical formula $C_{16}H_{12}N_2$ (II). It was found that this compound could be readily sublimed and upon standing became coloured, indicating that it might be unstable towards oxidation. When treated with hydrobromic or hydriodic acid in glacial acetic acid, it formed the respective mono-salts indicating that one of the nitrogens was different from the other. Gabriel and his co-workers (1) and later, Raffa and Oddo (2) suggested



III

that compound II had structure III. Such a structure is highly unlikely as it corresponds to the indolenine tautomer of I. No case has ever been reported where such a tautomer of an indole has been obtained (3a).

As the structure of I is important in considering the nature of II, it will be discussed first. The main evidence for the structure of compound I arises from the method of preparation. The oxidative coupling of the ethyl ester of N-hydroxyindole-2-carboxylic acid (V), accomplished by the action of ferric chloride in 50% acetic acid proceeds with ease and in almost quantitative yield to give VI. This coupling would be expected to take place on the β-carbon of the indole, in view of the reactivity of these hydrogens rather than in the benzene ring



where none of the hydrogens are as active. Furthermore, atoms 1 and 2

in the indole moiety are blocked and hence the formation of a bond on these atoms is eliminated. Reduction of the diester (VI) with tin and hydrochloric acid followed by hydrolysis gave VII. Decarboxylation of the di-acid at 240° at a pressure of 0.2 mm yielded I.

Further evidence for structure I was the faint test obtained with the Erhlich reagent in the cold which indicated that either the α- and/or β-carbon of the indole was substituted. An indole having both the α- and β-position free gives a strong test with this reagent. There seemed little doubt, therefore, that the starting material had structure I.

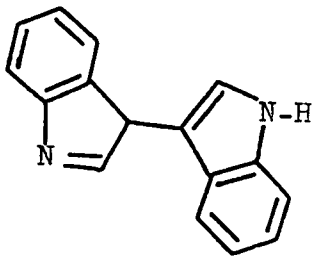
When the β,β'-diindolyl (I) was treated with a strong acid, **Gabriel et al.** (1) found that a dark red solution was obtained which gradually became yellowish giving rise to a salt. The analysis given by Gabriel et al. (1) and Dr. Anet for the free base (II) and its salts agree fairly well with the calculated values. Calc. for $C_{16}H_{12}N_2$: C, 82.79; H, 5.17%. Found [Gabriel et al (1)]: C, 82.45, 82.50; H, 5.75, 5.69%. Found (Dr. Anet): C, 82.30, 82.46; H, 5.61, 5.31%. Calc. for $C_{16}H_{12}N_2HBr$: Br, 25.57%; Found (1): Br, 25.18%. Calc. for $C_{16}H_{12}N_2I$: I, 35.28%; Found (1): I, 34.00%. The molecular weight determination (Rast) gave 222 (Dr. Anet). The required value for $C_{16}H_{12}N_2$ is 232.

Although these results, taken individually do not show the degree of polymerization, taken together, it can be safely concluded that the compound is certainly not one that contains three indole units and a compound having four indole units is also ruled out from the molecular

weight determination as well as by the relatively low sublimation temperature.

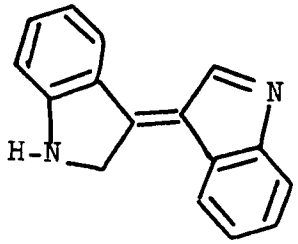
Considering the structure proposed by Gabriel et al. (1) for compound II, this structure (III) does not appear to be correct for the following reasons. First of all, III is not expected to be very stable. The indolenine form of indoles, for example, has never been isolated except where the β-carbon is fully substituted (3a), the reason being that the indole form is much more stable than the indolenine form due to its higher resonance energy. Secondly, the conjugation between the two indole systems is destroyed, hence the structure proposed by Gabriel et al. (1) which is essentially an indolenine form of the diindole would probably revert back to the diindole system.

A structure similar to that of Gabriel et al. (1) is VIII but



VIII

this can also be discounted for the reasons mentioned above. Another more likely structure from the point of view of the conjugation is the

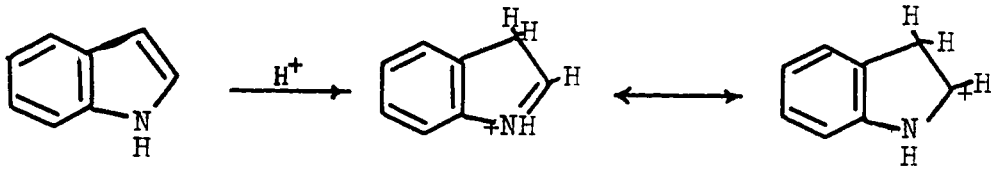


IX

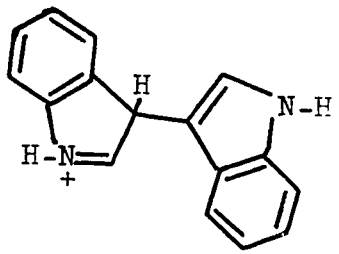
structure derived from the migration of the double bond out of the indole system to give IX. However, here some of the resonance energy is lost in disrupting the indole system and hence IX is also unfavourable. Furthermore, if this structure is more stable than structure I then the diindolyl formed from the decarboxylation at a high temperature of 240° would be expected to have the above structure (IX). This is not the case, however, since diindolyl is insoluble and unchanged in dilute acid whereas a compound having a basic nitrogen should form a salt.

DISCUSSION

Normally, when indoles are treated with an acid, polymerization takes place, but indoles substituted in the 2- or the 3- position are fairly stable to acid (3a, 4, 5). Protonation occurs on the 3-position to give an ion having a resonance hybrid structure. One of these forms has an electrophilic centre on the α-carbon;

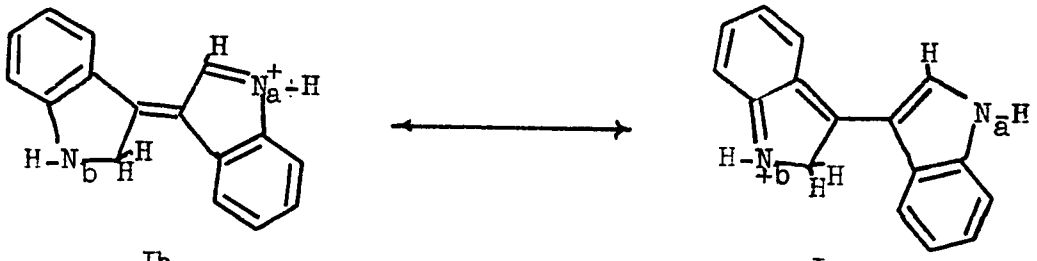


A similar structure can be written for the ion of β,β'-diindolyl, a protonation could take place on the β-carbon which would give rise to



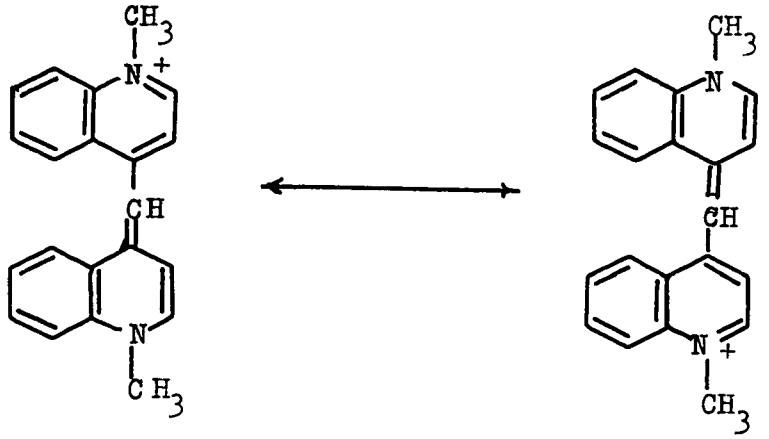
Ia

the ion Ia. This would not be expected to be too stable since the conjugation has been broken. Also, this structure does not explain the red colour which is observed when β,β'-diindolyl is treated with a strong acid. If, however, the α-carbon, vinylogous to the β-carbon is protonated, the resulting ion would have the form Ib which is more favourable due to the fully conjugated system and also because several resonance structures can be written for it. In two of the more important resonance forms, the positive charge can be placed on nitrogen N_a as in Ia or on the other

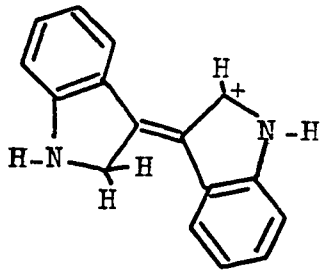


Ib Ic

nitrogen, N_b as in Ic. This distribution of charges on two nitrogens, which is similar to that of many of the nitrogen dyes explains the deep red colouration of the diindolyl in acid. An example of such a dye is the cyanine blue (6, 7) which has the following structure;



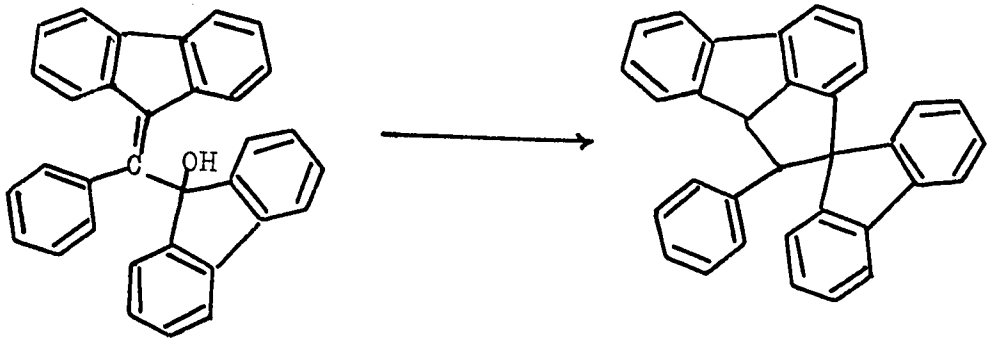
A structure which also contributes to the resonance hybrid of the above ion carries a partial positive charge on the carbon adjacent



Id

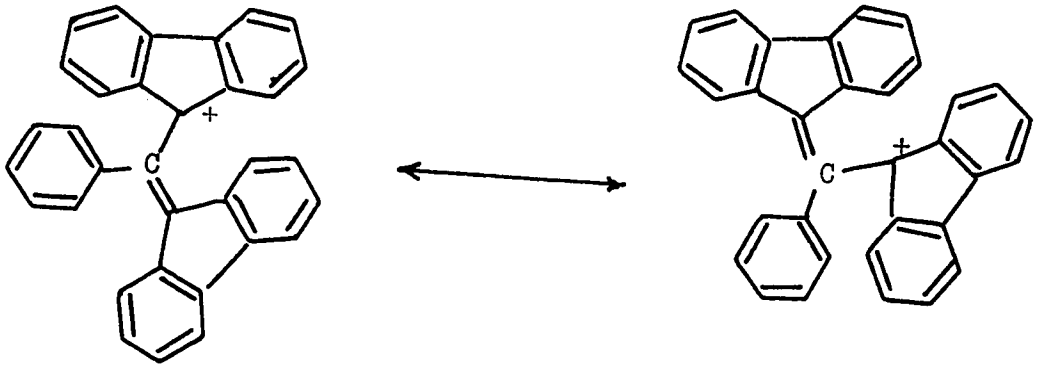
to the nitrogen (Id). It is possible for this electrophilic centre to

be in a suitable position for an attack on the benzene ring and as a result cyclization could take place. This is much like the dimerization of indole where the electrophilic centre at the α-carbon attacks the β-carbon of another indole and effects substitution (8). Another example of this type of reaction is the formation of compound Xa of Koelsch (9) from X (see also page 28). Here, an halochromic salt is obtained as



X Xa

an intermediate, and is probably a resonance hybrid of structure Xb and Xc. The electron deficient carbons are in a position to attack the ben-

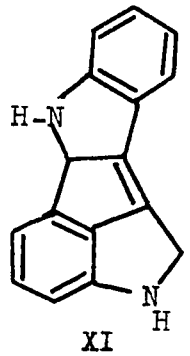


Xb Xc

zene ring. It was in fact an analogy of this type that led to the consideration of XI as a possible structure for compound II.

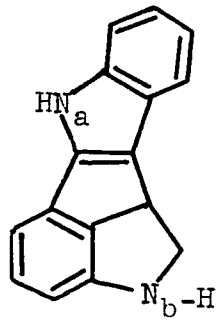
The above mechanism gives rise to the structure XI for II which should give a di-salt due to the two basic nitrogens whereas only the

mono-salt of compound II exists. By a simple 1,2-migration of the cen-



XI

tral double bond, however, a more likely structure (XII) is formed and this also accommodates the above evidence. This structure can be expected to be more stable since all the double bonds are in an aromatic



XII

system as well as being completely conjugated. A migration of this double bond in the opposite direction is unlikely since this will create two isolated systems. Structure XII can account for the formation of a mono-salt since although the nitrogen N_b is fairly basic, being like the aniline nitrogen, the other nitrogen (N_a) would be almost neutral (3b) being of the indole type.

On examination of structure XII, it is seen to contain a 2-phenylindole system. Hence the electronic spectra of this structure

should be similar to that of 2-phenylindole, though somewhat modified due to the presence of a pair of unshared electrons on the nitorgen N_b. However, since the nitrogen is in the meta position with respect to the indole substituent, the effect would be expected to be slight, as in the case of m-aminobenzoic acid (10). Indeed the ultraviolet spectra of 2-phenylindole and iso-diindolyl were found to be quite similar (Fig. 1).

A better comparison of the two spectra would be expected if the electrons on the nitrogen N_b are removed from conjugation by the formation of a salt. This comparison of the spectra is analogous to that of aniline and its salt. The spectrum of the anilinium ion has been found to be quite similar to that of benzene (11). However, the salt of iso-diindolyl gave an entirely different spectrum (Fig. 1). Thus compound II cannot have structure XII.

Further proof against structure XII was obtained from a study of the acetylation of II. According to the above structure a mono-N-acetyl derivative should be formed readily since N_b should be basic. However, acetylation was only possible under the forcing condition of refluxing with acetic anhydride in the presence of sodium acetate.

The formation of a mono-N-acetyl derivative was shown by the elemental analysis and by the ultraviolet (Fig. 2) and infrared spectral analysis. Peaks at 3310 cm^{-1} corresponding to the stretching frequency of the N-H bond and at 1690 cm^{-1} indicating the presence of an N-acetyl group (12) were obtained.

The acetyl derivative was readily hydrolyzed under the mild

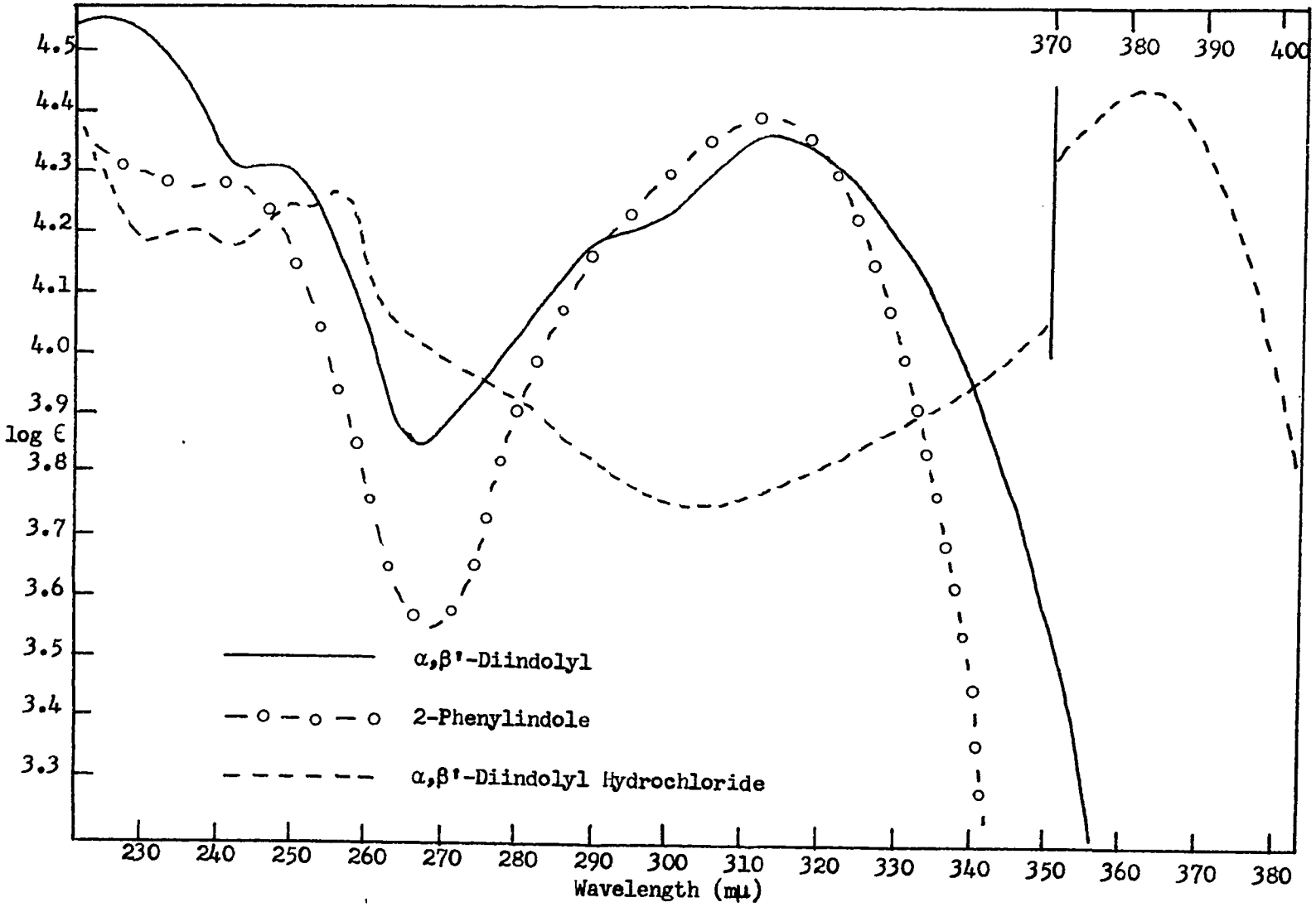

4.5
4.4
4.3
4.2
4.1
4.0
3.9
log ε
3.8
3.7
3.6
3.5
3.4
3.3
370
380
390
400
α,β'-Diindolyl
2-Phenylindole
α,β'-Diindolyl Hydrochloride
230
240
250
260
270
280
290
300
310
320
330
340
350
360
370
380
Wavelength (mμ)

Fig. 1

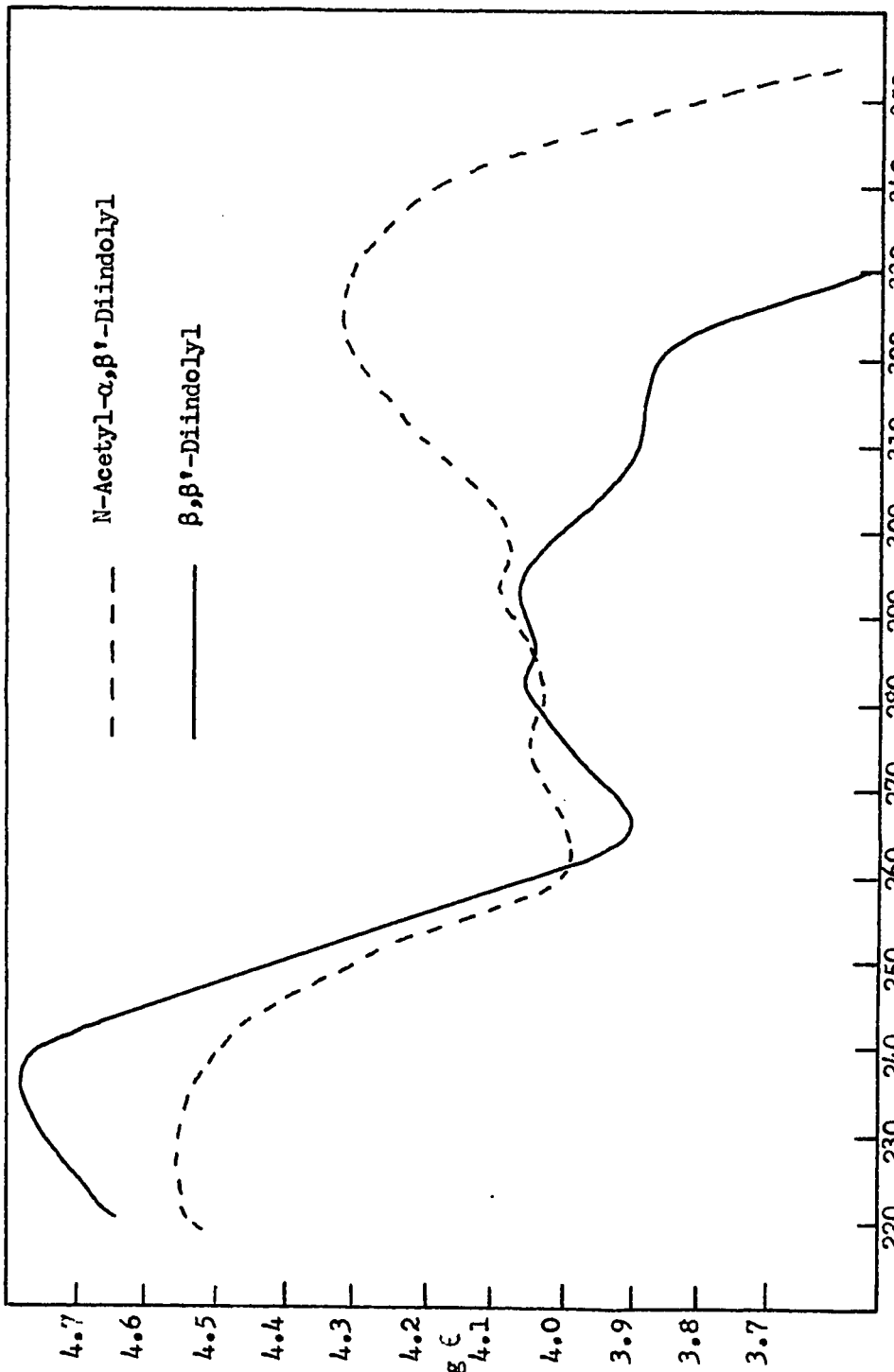
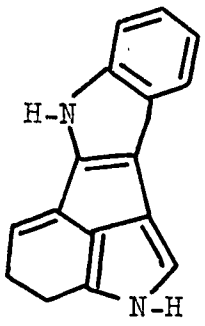

N-Acetyl-α,β'-Diindolyl
β,β'-Diindolyl
log ε
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
220
230
240
250
260
270
280
290
300
310
320
330
340
350
Wavelength (mμ)

Fig. 2

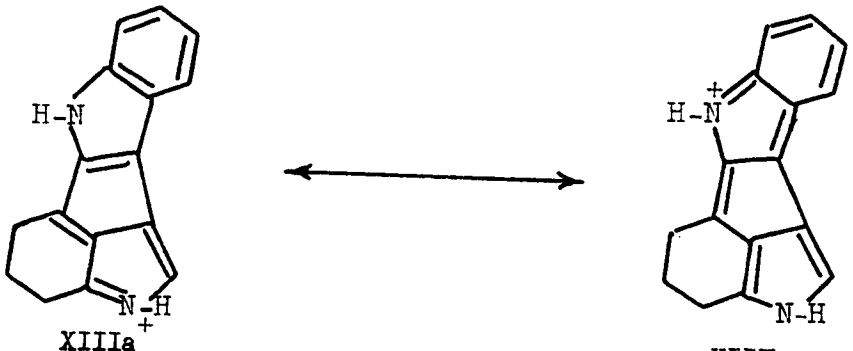
condition of allowing it to stand overnight in 1:1 ethanol-ammonia solution at room temperature. These results tend to indicate that the nitrogens are only weakly basic. The pKa of II was determined spectrophotometrically and was found to be only 1.3.

The above information caused us to look for another possibility for the structure for II. One rather simple way of modifying structure XII to accommodate the above facts, is to shift the unsaturation so as to give XIII. In order to obtain the pyrrole system, a benzene ring



XIII

must be disrupted. In doing so, a benzene resonance energy of about 39 Kcal/mole (13) is lost but most of this energy is recovered in the pyrrole system which has a resonance energy of 31 Kcal/mole (13). Also in a very strongly acidic medium, the protonated form of structure XIII can be resonance-stabilized;

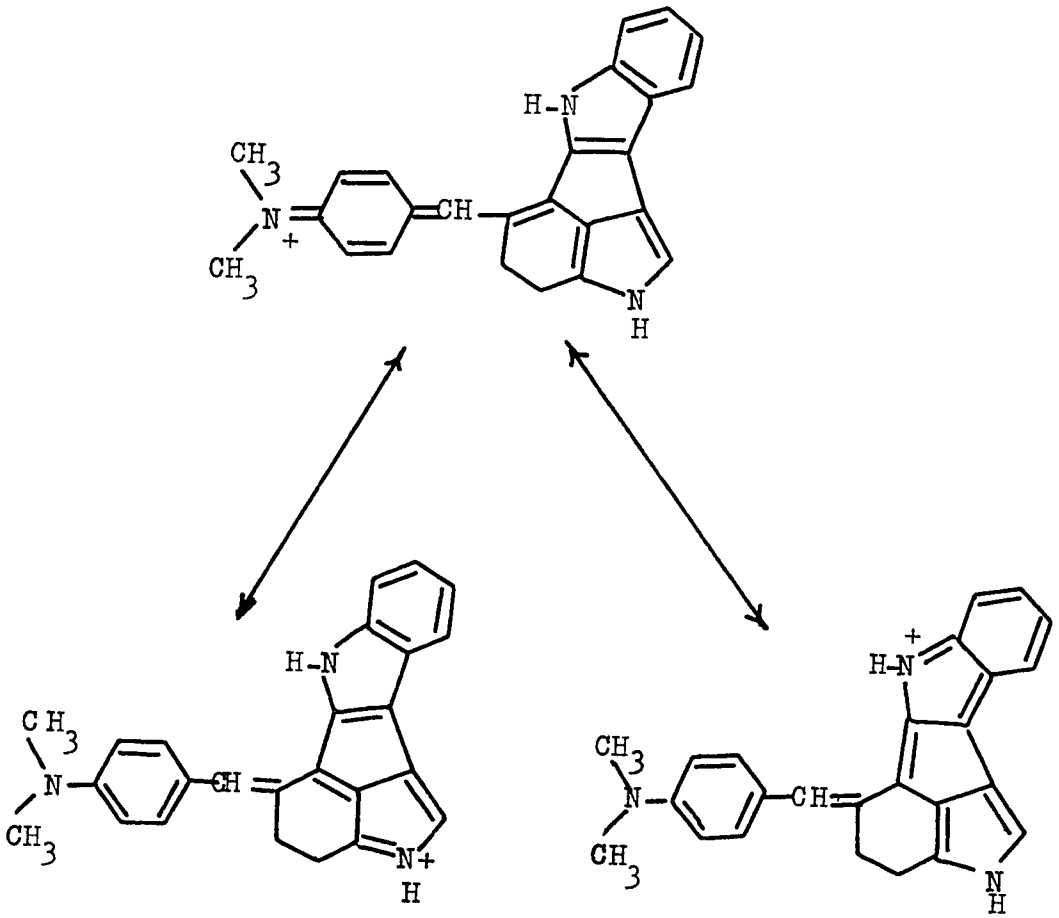


XIIIa XIIIb

An assumption of this structure for the salt also positions the remaining double bonds. The free base of the salt can give rise to structure XIII for compound II.

Structure XIII explains all the foregoing evidence. The pKa which is slightly higher than expected for the indoles or pyrroles can be explained on the basis of the resonance-stabilized ion which increases the ease of salt formation. The difficulty of formation and the ease of hydrolysis of the N-acetyl derivative is consistent with that expected of an indole.

Structure XIII also explains the formation of the intense purple



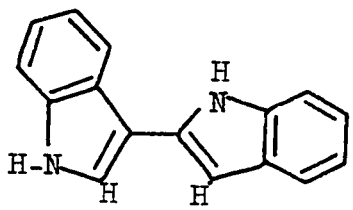
colour which is formed when II is treated with the Ehrlich reagent.

In order to obtain evidence for structure XIII dehydrogenation by various means was tried, but all proved unsuccessful. Compound II was found to be resistant to hydrogenation at atmospheric pressure using various methods. This seems to be inconsistent with structure XIII but perhaps the difficulty is due to the fact that only one hydrogen is present on the double bond which is conjugated as well.

We next attempted a potassium permanganate oxidation of II in a slightly alkaline medium using aqueous acetone as solvent and magnesium sulphate as buffer. An acid was obtained from this reaction, and found to have a neutralization equivalent of 117 and a melting point of 214-215°. A mixed-melting-point determination with N-oxalylanthranilic acid did not lower the melting point and the infrared spectrum was identical with that of N-oxalylanthranilic acid.

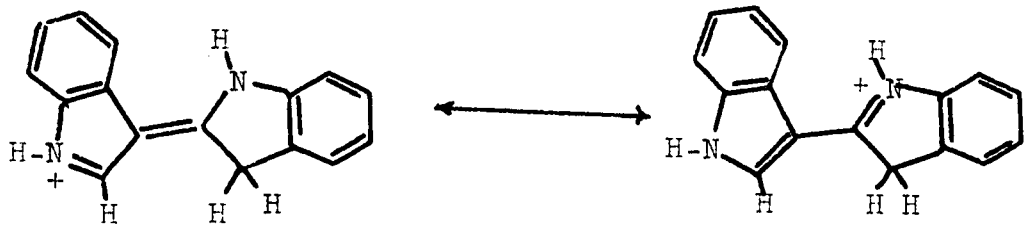
Although the oxidation reaction proved the presence of a bond on the α-carbon of an indole system, the hydrogenation and the dehydrogenation experiments were not in accord with structure XIII.

Just at this time, Faseeh and Harley-Mason (14) published a paper showing that the structure of II was simply α,β'-diindolyl, a

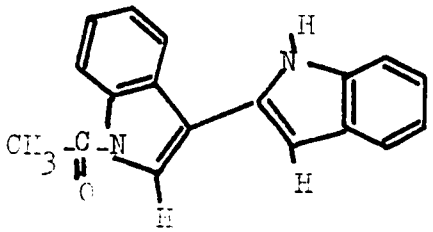


II

known compound. All the results obtained in our work are consistent with this. Unfortunately in our work we placed too much emphasis on the basic properties of II, which, as we found towards the end, are actually quite weak but much stronger than those of most indoles. The protonated form of α,β'-diindolyl is a resonance-stabilized ion;



Finally, it should be mentioned that the acetyl derivative could have two structures but most probably the acetyl group is on the less hindered nitrogen atom as shown;



The formation of α,β'-diindolyl from β,β'-diindolyl is analogous to the rearrangement of 3-phenylindole to 2-phenylindole (15). The fact that rearrangement takes place in the above manner shows that the ion Ia is formed at least to a certain extent, but not exclusively, from β,β'-diindolyl and strong acid. For the reasons previously mentioned, the ion Ib ⟷ Ic must be formed, in equilibrium with Ia, in appreciable amounts.

EXPERIMENTAL

The melting points are uncorrected. The ultraviolet spectra were measured on a Beckman DK-2 spectrophotometer.

o-Nitrophenylpyruvic Acid:

The Claisen condensation was carried out according to the method of Di Carlo (16). Diethyl oxalate (43.8 g) and o-nitrotoluene (41.1 g) were added to the cooled solution of sodium (6.9 g) in dry ethanol (80 ml). The mixture was refluxed for 10 minutes with stirring and cooled.

An equal amount of water was added to the cooled red solution and the mixture was refluxed for another 1.5 hours. The unreacted o-nitrotoluene was steam distilled (about 14 g) as rapidly as possible and after cooling, the mixture was acidified with concentrated hydrochloric acid and shaken to precipitate the acid. The crude organic acid which was dark brown in colour was filtered under suction and redissolved in hot water, treated with decolourizing charcoal, filtered and allowed to cool. Yellow crystals of o-nitrophenylpyruvic acid, m. p. 119-120^{0} were obtained. Di Carlo reports a melting point of 119-120^{0} (16). The yield was 30.3 g (75% of the theoretical based on o-nitrotoluene consumed).

N-Hydroxyindole-2-Carboxylic Acid:

The reduction of o-nitrophenylpyruvic acid was carried out according to the method of Reissert (17). The finely divided acid (4.2 g) was suspended in water and shaken with a small portion of 3% sodium amalgam until the initial dark red colour of the solution had disappeared, but not

until the solution was completely discoloured. The alkaline solution was decanted from the mercury, cooled and acidified with concentrated hydrochloric acid. The solution was cooled to precipitate greenish-grey needles of N-hydroxyindole-2-carboxylic acid, m.p. 159-160°. Reissert (17) reports a melting point of 159.5°.

Esterification of N-Hydroxyindole-2-Carboxylic Acid:

Concentrated sulphuric acid (2.5 ml) was added to a solution of N-hydroxyindole-2-carboxylic acid (8.2 g) in absolute ethanol (75 ml), and refluxed for 1 hour. The solution was cooled and poured into a previously prepared solution of sodium carbonate. The alkaline solution was extracted with diethyl ether and the ethereal extract was washed with 5% solution of sodium bicarbonate and then with water. The ether was evaporated and the residue was extracted with petroleum ether (30-65°) and cooled after treatment with decolourizing carbon. The ester V, melting at 64-65° was obtained as plates. Gabriel et al. (1) report a melting point of 64-65°. The yield was 4.1 g (42%).

Ethyl-N,N'-Dihydroxyindole-2,2'-Dicarboxylate (VI):

A 10% solution of ferric chloride was added with stirring to a hot 50% aqueous acetic acid solution containing N-hydroxyindole-2-carboxylate (10.0 g). The dropwise addition of the ferric chloride solution was stopped when the red colour was just decolourized. The solution was cooled and the precipitate was filtered and recrystallized from 50% aqueous acetic acid. The yield of the needles melting at 153-154°

was 9.1 g (93%). Gabriel et al. (1) report a melting point of 152-153° from warm acetic acid solution.

β,β'-(Ethyldiindolyl-2-Carboxylate):

The fresh reducing solution was prepared by dissolving stannous chloride dihydrate (12 g) in glacial acetic acid (35 ml) and concentrated hydrochloric acid (35 ml).

The reducing solution (60 ml) was added to a glacial acetic acid solution containing the indole-ester (11.0 g), and heated on a steam bath for 1 hour. The solution was cooled and the precipitate was filtered. The yield of the diindolyl ester, m.p. 224-225° was 8.1 g (80%). Gabriel et al. (1) report a melting point of 225-226°.

β,β'-(Diindolyl-2-Carboxylic Acid) (VII):

The ester (9.3 g) was hydrolyzed by refluxing it in ethanol (150 ml) containing 33% potassium hydroxide solution (10 ml) for 1 hour, with stirring. The white potassium salt was filtered from the yellow solution, suspended in a little hot water and acidified with concentrated hydrochloric acid. The gelatinous mass was heated on a hot plate and cooled. The yield of the acid which melted at 285° with decomposition was 7.1 g (89%). Gabriel et al. (1) report that it melts slowly at 285°.

β,β'-Diindolyl (I):

Decarboxylation of the acid was accomplished by heating the dry acid to 240°/0.2 mm. When the decarboxylation was complete, the

temperature was raised to 275°/0.2 mm at which temperature the β,β'-diindolyl sublimed to yield crystals, m.p. 285-287°. Crystallization from acetic acid raised the melting point to 286-287°. Gabriel et al. (1) report a melting point of 286-287° for this compound (X).

Preparation of α,β'-Diindolyl (II) from β,β'-Diindolyl:

Method I:

The β,β'-diindolyl (1.9 g) was dissolved in a minimum amount of hot glacial acetic acid. Hydriodic acid (10 ml) was added and refluxed for 30 minutes. The solution turned an intense red colour which gradually faded during the reaction. The solution was cooled and the orange precipitate was suspended in a little hot water, ammonium hydroxide was added to the suspension which precipitated some fluffy material. On recrystallization from 50% aqueous ethanol, crystals of α,β'-diindolyl, m.p. 210° were obtained. Gabriel et al. (1) and Raffa and Oddo (2) report a melting point of 207-208°. This compound was sublimed at 185-190°/0.5 mm. The yield was 1.6 g (86%).

Method II:

The β,β'-(diindolyl-2-dicarboxylic acid) was dissolved in a minimum amount of hot glacial acetic acid. Hydriodic acid (10 ml) was added and refluxed for 30 minutes. The solution gradually took on an intense red colour and then precipitated a yellow-orange salt. The solution was cooled, the salt filtered and suspended in a little hot water. Ammonium hydroxide was added to precipitate the α,β'-diindolyl. The dried

crude material was dissolved in hot xylene and a small amount of magnesol-celite mixture was added and filtered hot. This procedure aided in removing most of the coloured impurities. The cooled yellow solution yielded a compound melting at 209-210°. Yield, 5.1 g (75%). Calc. for $C_{16}H_{12}N_2$: C, 82.79; H, 5.17%. M. W. 232. Found: C, 82.46, 82.30; H, 5.31, 5.61% (Dr. Anet). M. W. (Rast), 222 (Dr. Anet).

N-Acetyl-α,β'-Diindolyl:

The acylation was carried out by dissolving the α,β'-diindolyl (0.5 g) in acetic anhydride (20 ml) containing freshly fused sodium acetate (0.5 g). The solution was cooled after refluxing for 1 hour, water was added and allowed to stand overnight in order to hydrolyze the acetic anhydride. The precipitate was filtered and recrystallized from absolute ethanol to give a compound which melted at 234-235°. Yield, 0.4 g (73%). Calc. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14%. Found: C, 78.57; H, 5.17%.

Oxidation of α,β'-Diindolyl:

An aqueous acetone solution, buffered with magnesium sulphate, containing α,β'-diindolyl (1 g) was warmed on a hot plate and potassium permanganate was added in small portions until the oxidation was complete. The mixture was filtered and the residue was washed five times with hot water. The combined aqueous solution was acidified and extracted with ethyl acetate. The ethyl acetate solution was washed with water, treated with Norite and allowed to cool. An acid melting at 214-215° was obtained after several recrystallizations. The neutralization equivalent was

found to be 117.

A mixed-melting-point determination with an authentic sample of N-oxalylanthranilic acid did not lower the melting point. A comparison of the infrared and ultraviolet spectra of the unknown with that of N-oxalylanthranilic acid showed the two compounds to be identical in all respects.

N-Oxalylanthranilic acid crystallizes with one mole of water which gives it an equivalent weight of 113.5 which is in fairly good agreement with the experimental value of 117.

The methyl ester of the oxidation product was prepared by treating the ether solution of it with diazomethane. An ester melting at 145° was obtained which was found to be identical with the methyl ester prepared from an authentic sample of N-oxalylanthranilic acid.

N-Oxalylanthranilic Acid:

N-Oxalylanthranilic acid was prepared by heating together a mixture of anthranilic acid (1.3 g) and oxalic acid (0.9 g). The resulting mass was cooled and recrystallized several times from water and dried in a vacuum desiccator to give a compound which melted at 214-215°.

Hoffman and Konigs (18) report a melting point of 200° whereas Claus and Collischon (19) report 210° for N-oxalylanthranilic acid.

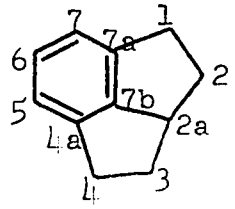
PART II

The Attempted Synthesis of a Strained Tricyclic System Containing Nitrogen

INTRODUCTION

Despite many efforts in the past to synthesize a compound having two five-membered rings fused mutually to a benzene ring, all attempts had failed. Because of these failures by numerous workers for over forty years, it was thought that such systems were excessively strained and thus incapable of existence. However, in the past three years, Rapoport et al. (24, 25, 26) have synthesized a number of such systems although physical and chemical measurements on these compounds have revealed that considerable amount of strain does exist. Therefore, the earlier belief that these compounds were strained was not altogether incorrect.

The strain in the system such as XIV can be considered to



XIV

arise from two sources. The first and probably the greater part of the strain arises from the bending of the benzene bonds when a five-membered ring is attached to a benzene ring. As Fig. 3 illustrates, the C-H bonds of the benzene molecule are in the plane of the benzene ring and form an exterior angle of 120°. Now, the cyclopentane ring which is to be fused to the benzene nucleus has an interior C-C bond angle of about 108°. Therefore, when the two rings are fused together, it is conceivable that the interior C-C bond angle of the cyclopentane is increased and at the same time the benzene molecule must also be distorted. In-

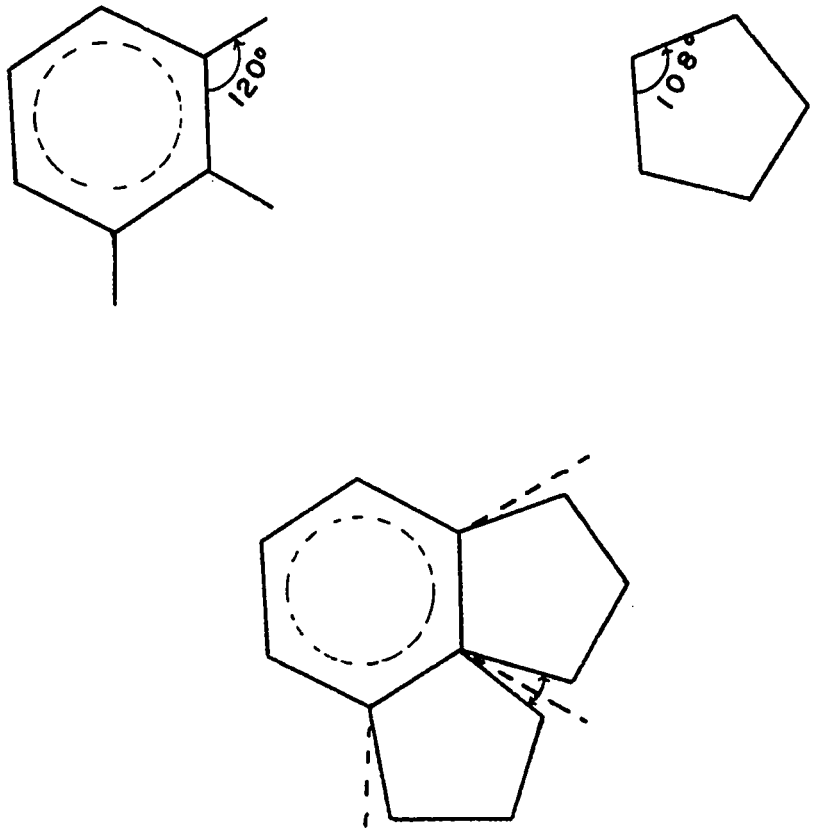


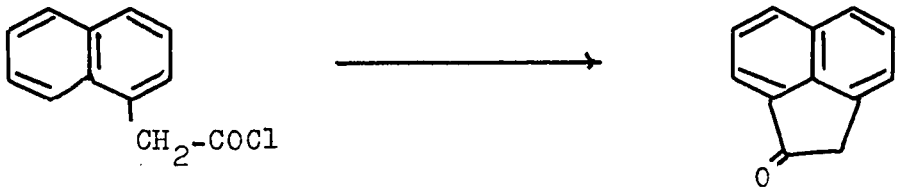
Fig. 3

deed, without doubt, there is a small amount of strain in indane but when another five-membered ring is fused mutually to these two rings to form compound XIV, the strain would be greatly increased. In fact, when a third five-membered ring is fused mutually, there is evidence (25) that the benzene ring becomes so distorted that it becomes unusually reactive.

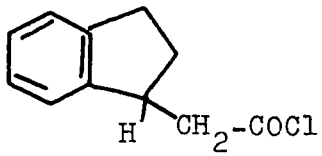
Models of the tricyclic systems show that the compound tends to be as nearly planar as possible, and consequently, the bonds on carbon 2a tend to be distorted from the tetrahedral arrangement. Hence the second type of strain is centered around this atom although it is somewhat relieved by the slight buckling of the five-membered rings. The heterocyclic analogue may be easier to synthesize as the nitrogen atom, replacing carbon 2a is flatter than the carbon atom and therefore the strain would be expected to be somewhat less. In any event, the synthesis of any of these compounds would not be expected to be easy since the main factor that must be overcome is that of bending the benzene ring.

Historically, many attempts had been made in the past to synthesize the cyclopent[cd]indene system and in the majority of the cases reported in the literature, the cyclizations were attempted by means of the Friedel and Crafts ring closure method. Although this reaction has been used effectively in many ring closure reactions, it turns out that the successful reactions were ones in which the products were not strained. Thus the failure to obtain the above mentioned tricyclic system has been attributed to the strain involved in the compound.

Perhaps the first of the many attempts was made as early as 1917 by von Braun and his co-workers (20, 21, 22). It was found that although indan-1-acetyl chloride (XVI) could not be cyclized, naphthalene-

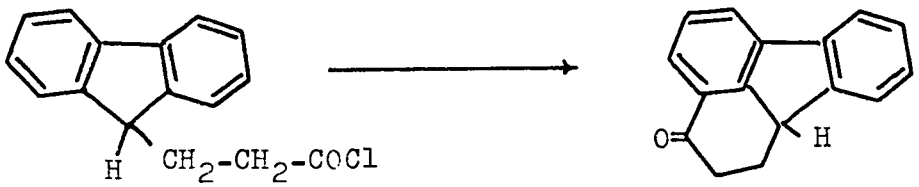


XV

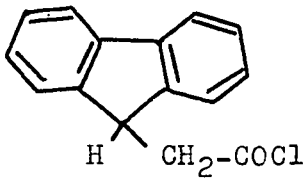


XVI

1-acetyl chloride (XV) underwent ring closure. Also, although fluorene-1-propionic acid (XVII) was readily cyclized to give XVIII, it was not possible to cyclize fluorene-1-acetic acid (XIX)

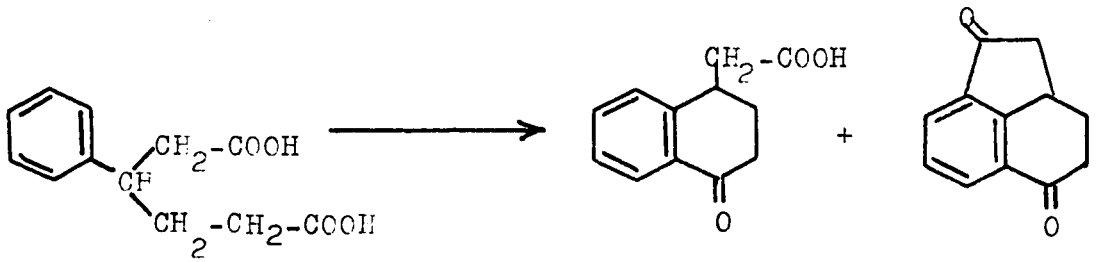


XVII XVIII

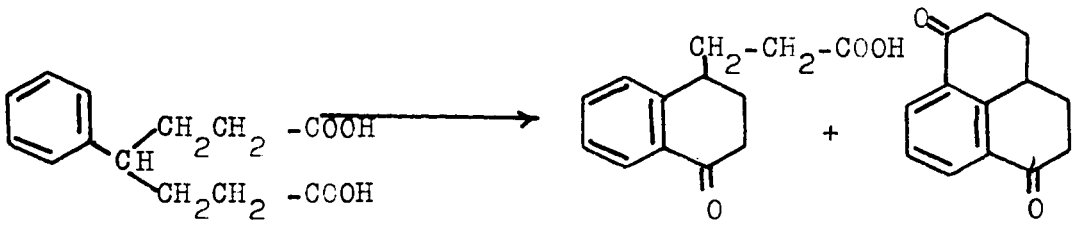


XIX

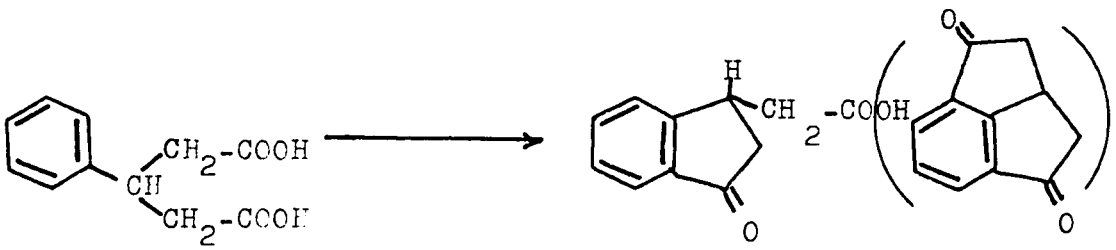
Similarly, Braun and Weissbach (23) and Manske (27) found that when XX and XXI were cyclized, the main products were the tricyclic compounds XXb and XXI b with lesser amounts of XXa and XXIa being formed. Braun and Weissbach (23) further found that although XXII could be cyclized mainly to XXIIa, they are doubtful whether any of XXIIb had formed.



XX XXa XXb



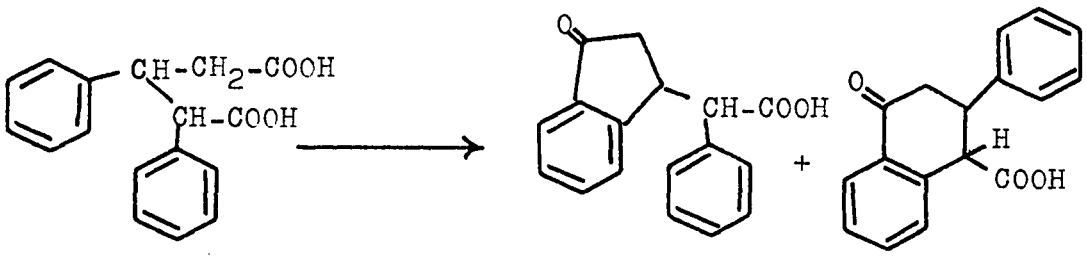
XXI XXIa XXIb



XXII XXIIa XXIIb

When diphenylglutaric acid (XXIII) was cyclized by Badger, Campbell and Cook (28), compound XXIV was obtained and not the expected compound XXV. Further cyclization of XXIV was not possible although it

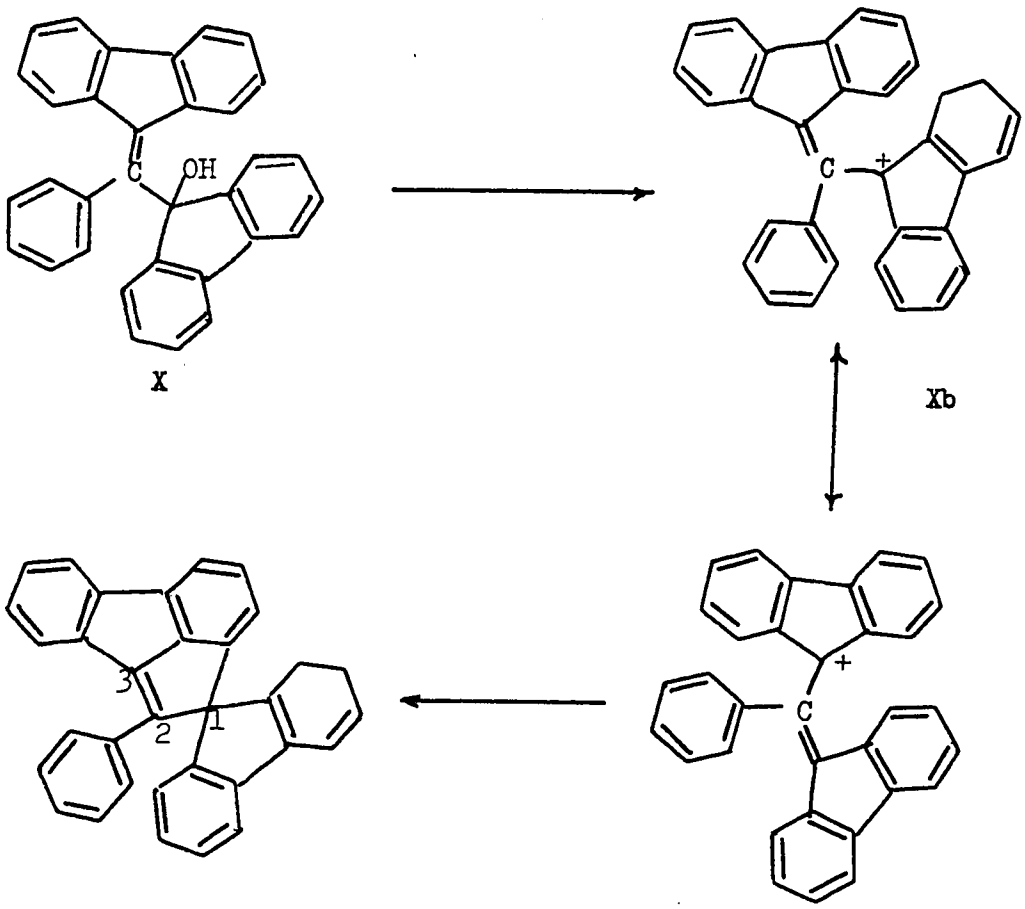
was hoped that the tricyclic ketone might form.



XXIII XXIV XXV

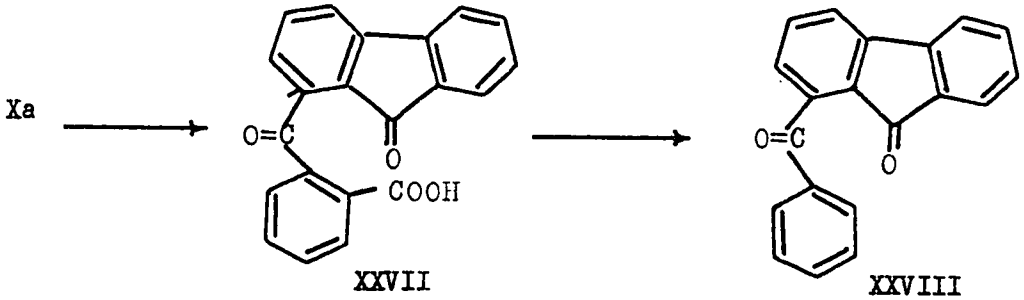
There are numerous other examples (29, 30, 31, 32) of this type of chemistry but nearly all attempts prior to 1956 to prepare the strained tricyclic system ended in failure, and thus it was thought that such a system could not exist.

There is reported, however, a synthesis of such a tricyclic system but this work has been overlooked due mainly to the complexity of the molecule in which the system occurs. The strain in this system is probably not as great as in the isolated system owing to the resonance stabilization of the compound. This compound, claimed to be 1-diphenylene-2-phenyl-3,4-phenylene indene (Xa) was prepared by Koelsch (9) in 1932. He treated α,γ-bis-diphenylenephenylallyl alcohol (X) with sulphuric acid in an acetic acid medium and obtained a halo-chromic salt which was transformed into compound Xa (see also page 8). The halo-chromic salt is probably a resonance-hybrid of structures represented by Xb and Xc. Here, the electron deficient carbons are in a position to attack the benzene ring to give 1-diphenylene-2-phenyl-3,4-phenylene indene (Xa).



X Xb Xa Xc

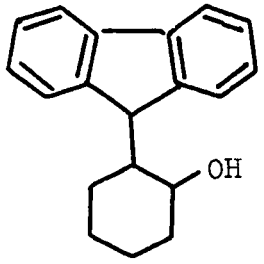
Evidence for structure Xa was obtained through degradative oxidation to give o-(fluorenone-1-carboxyl)-benzoic acid (XXVII), which on decarboxylation gave 1-benzoyl fluorenone (XXVIII). This structural proof is not conclusive but it lends strong support to structure Xa



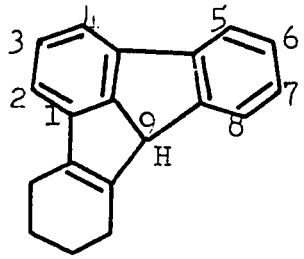
XXVII XXVIII

which contains the strained tricyclic system and thus it is the first known compound of this type. However, as mentioned earlier, the strain in Xa is probably not as great as in cyclopent[cd]indene (XIV) since carbon 3 in this compound is trigonal and also the highly conjugated system has a tendency to stabilize the molecule.

There has been another instance where the tricyclic system has been reported but the proposed structure has been proven erroneous. Hurd and Mold (33) in 1948 treated 2-fluorenylcyclohexanol (XXIX) with syrupy phosphoric acid and obtained a product which was inert towards potassium permanganate and to bromine. From these properties the authors prematurely concluded that the product was 1,9-cyclohexylene fluorene (XXX).

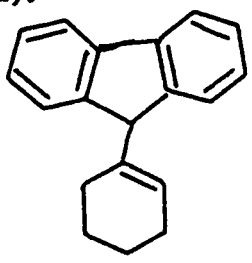


XXIX



XXX

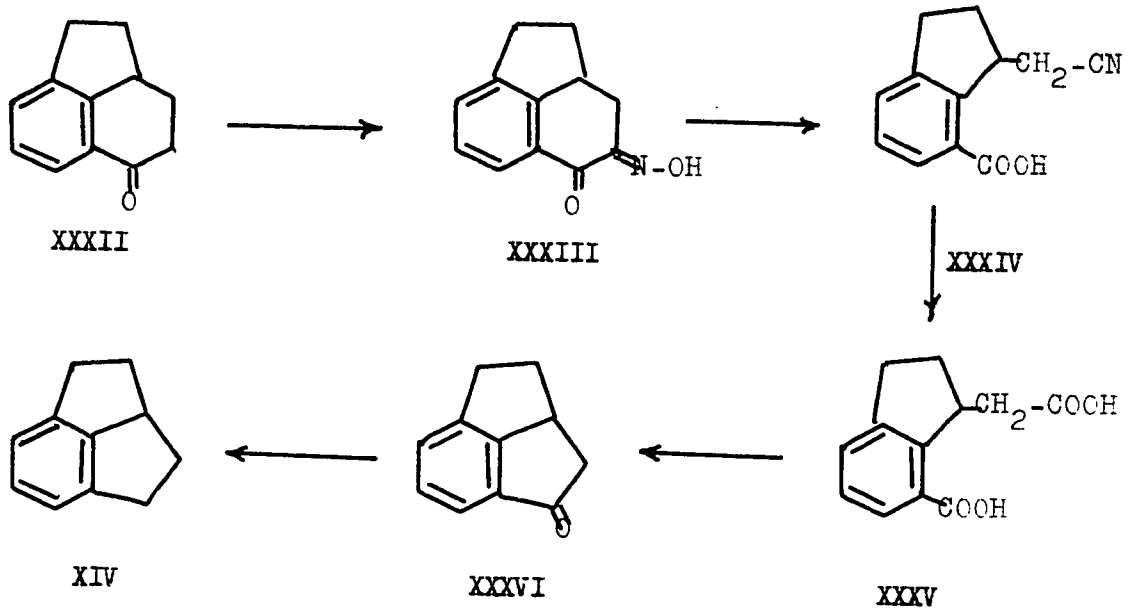
In 1952, Cook and Hunter (34) showed that this compound was not 1,9-cyclohexylene fluorene (XXX) as attested by its authors but 9-cyclohex-1'-enylfluorene (XXXI).



XXXI

The first successful synthesis of the isolated cyclopent[cd] indene came in 1956. Rapoport and Pasky (24) reasoned that the Friedel and Crafts reaction for the closure of the second five-membered ring was unfavourable due to steric requirements and furthermore to circumvent the electrophilic substitution into the benzene ring, they tried various intramolecular cyclization reactions such as the Dieckmann reaction, treatment with acetic anhydride in the presence of potassium cyanide (35) and the pyrolysis of metal salts.

Their method will be briefly outlined for it reveals the difficulty of ring closure, even at elevated temperatures, of the second five-membered ring and thus of the strain in the system. The oximino ketone (XXXIII) of 2a,3,4,5-tetrahydro-5-acenaphthalenone (XXXII) which



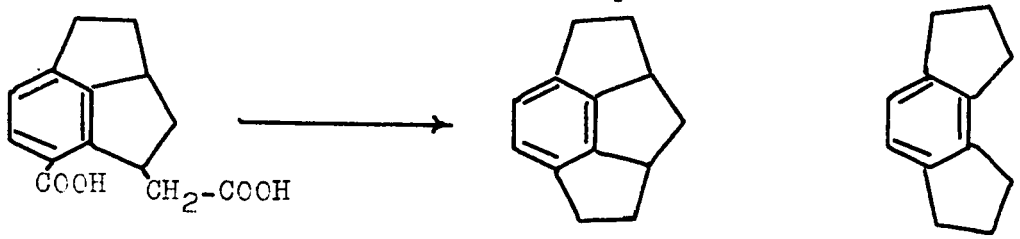
XXXII XXXIII XXXIV XXXV XXXVI XIV

was prepared by the treatment of acenaphthalenone with butyl nitrite in the presence of potassium tertiary butoxide was treated with benzenesulphonyl chloride in pyridine to give XXXIV. This was hydrolyzed to

the dicarboxylic acid (XXXV). They encountered considerable difficulty in the final ring closure to the strained system. The Dieckmann ring closure of the di-ester failed and the pyrolysis of the thorium and the calcium salts yielded only about 2-3% of XXXVI. However, when the lead salt was pyrolyzed, a fairly good yield of the ketone XXXVI (up to 50%) was obtained. Wolff-Kishner reduction of the ketone yielded the required 2,2a,3,4-tetrahydro-1H-cyclopent[cd]indene (XIV).

This compound (XIV) was found to have an ultraviolet spectrum which was not unlike that of 2a,3,4,5-tetrahydroacenaphthalene. It reacted very slowly with perbenzoic acid but not at all with maleic anhydride. It, however, reacted quite rapidly with hydrogen over palladium catalyst, and Rapoport and Pasky (24) claim that this hydrogenation being a surface reaction may be "unique in discerning small differences in stability". The compound was further characterized by oxidation to hemimellitic acid. The high volatility and the molecular weight as well as the elementary analysis were consistent with the monomeric structure.

Using the above technique, Rapoport and Smolinsky (25) were able to synthesize a tetracyclic compound, 2,2a,3,3a,4,5-hexahydro-1H-cyclopent[jkl]-As-indacene (XXXVIII) which should, from theoretical considerations, be much more strained than compound XIV. This strain was

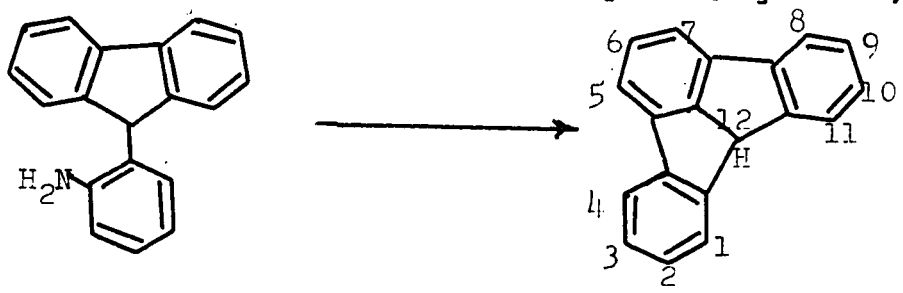


XXXVII XXXVIII XLIX

revealed in its ease of hydrogenation, perbenzoic acid absorption as well as by its unstable nature in air. These reactions, according to the authors reflect a high degree of unsaturation caused by the strain in the system which tends to bend the benzene ring and hence decrease the resonance energy.

As for the structural proof of XXXVIII, the method of synthesis and the infrared spectrum, which was found to be somewhat similar to that of the model compound, 1,2,3,6,7,8-hexahydro-As-indacene (XLIX), lends strong support.

Finally, another system which was recently synthesized by Rapoport and Smolinsky (26) has been claimed to be highly strained. They treated 9-(o-aminophenyl)-fluorene (XL) under deamination conditions and obtained a 23% yield of fluoradene (indeno[1,2,3-j,k]fluorene) (XLI).

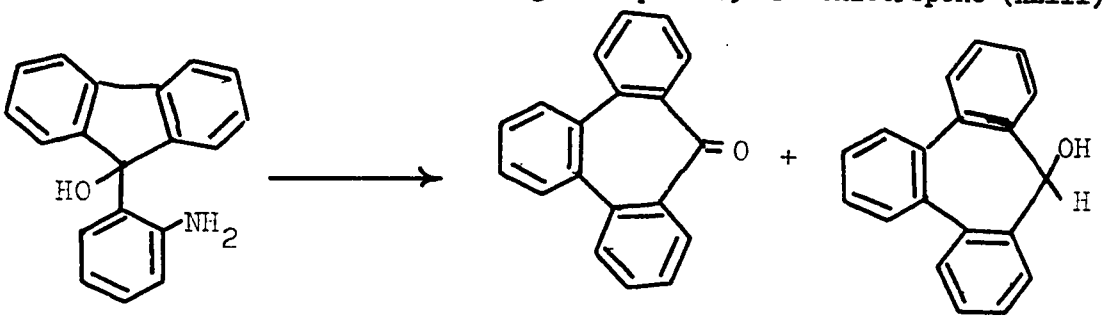


XL XLI

The structural evidence for fluoradene (XLI) was established by the method of synthesis, elementary analysis, molecular weight determination as well as by the ease of hydrogenation and consumption of perbenzoic acid. The absorption of 400 mole % of perbenzoic acid seems contradictory in the light of the reaction of 2,2a,3,4-tetrahydro-1H-cyclopent[cd]indene (XIV) which was shown to be not too reactive towards this reagent (24). However, the fact that carbon 12 probably has a

strong tendency to become trigonal due to the conjugating effect of the phenyl groups makes one of the benzene rings susceptible to hydrogenation and oxidation, whereas the tendency for 2,2a,3,4-tetrahydro-1H-cyclopent [cd]indene to do this is expected to be less. The fluoradene (XLI) was found to be appreciably acidic ($pK'a = 11 \pm 0.5$) and this has been attributed to the high degree of symmetry and to the complete conjugation that exists in the anion (26). A similar property has been observed in such compounds as 9-phenylfluorene, phenylacetylene and indene (35, 36) but these are much weaker acids having pK'a's of 21 or greater.

It is interesting to note that a similar type of reaction to that of Rapoport and Smolinsky (26) was carried out earlier by Stiles and Libbey (37). These authors treated 9-(o-aminophenyl)-9-fluorenol (XLII) under similar conditions but did not obtain the strained compound as was hoped. Instead, two rearranged compounds, tribenzotropone (XLIII)

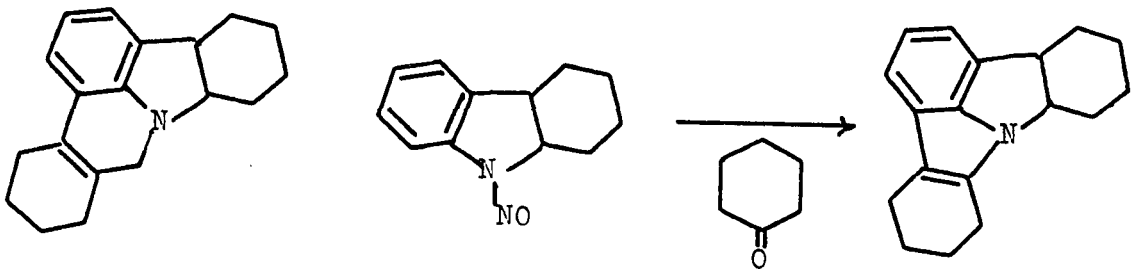


XLII XLIII XLIV

and tribenzotropyl alcohol (XLIV) were obtained.

A review of the heterocyclic series of the strained tricyclic system where the carbon 2a of cyclopent[cd]indene is replaced by a nitrogen atom reveals that this chemistry also goes back almost thirty years. Manjunath (38) in 1927 reported that the reaction between 9-nitrosohexahydrocarbazole (XLV) with cyclohexanone in the presence of

zinc dust in acetic acid gave a compound melting at 83° (picrate 138°) having the empirical formula $C_{18}H_{21}N$. Although he pictured his structure as XLVIa, he no doubt intended it to be XLVIb as his empirical formulas

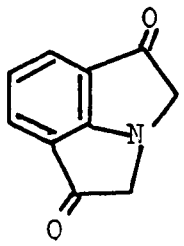


XLVIa XLV XLVIb

does not fit XLVIa. This compound contains the system under consideration here although Manjunath's compound is probably more stable due to the resonance-stabilized tetrahydrocarbazole moiety. No structural evidence is given for XLVIb except for the analysis but later work (see below) shows that the designated structure is probably correct.

At around this period, there was much interest in trying to isolate the optical isomers of nitrogen containing compounds since there was considerable evidence that the tervalent nitrogen atom was not planar. Jackson and Kenner (39) took much interest in this work and reasoned that the failure to isolate such isomerides was due to the fact that the non-planar form readily passed into the planar form or else that the natural configuration was a plane. In order to show which was actually the case, they set about to synthesize a compound in which the nitrogen atom would be common to two rings which are at the same time planar and coplanar. One such compound would be XLVII, but they were unable to synthesize this compound although mention is made that a "small amount of material of the expected composition" was isolated. However,

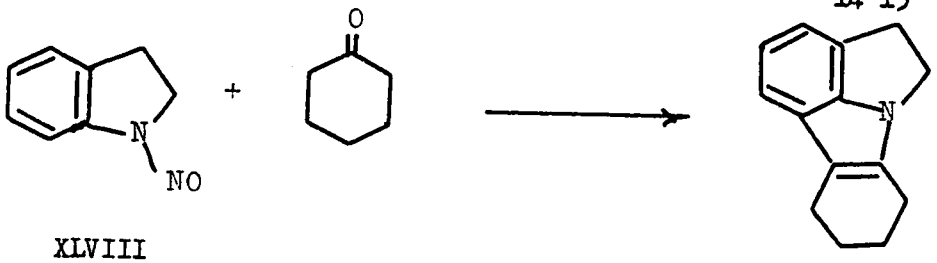
they admit that their product was probably not XLVII.



XLVII

Lions and Ritchie (40, 41) repeated Manjunath's work (38) and obtained a similar compound having "slightly different constants" and although Manjunath reported a picrate, Lions and Ritchie (40, 41) were not able to prepare a picrate of their compound. In support of structure XLVIb, Lions and Ritchie report that they were not able to cyclize 8-methylhexahydrocarbazole which has the 8-position blocked.

Using Manjunath's (38) method, Lions and Ritchie (40, 41) treated N-nitrosoindoline (XLVIII) with cyclohexanone in glacial acetic acid in the presence of zinc dust and obtained a neutral compound (XLIX) having a melting point of 154° (picrate 141°). Although no structural evidence is presented for XLIX, the elementary analysis ($C_{14}H_{15}N$) agrees



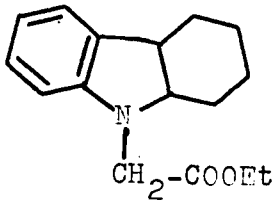
XLVIII

XLIX

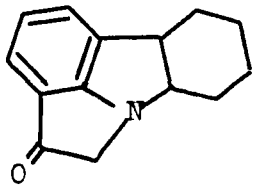
with the proposed structure. Similar condensations of N-nitrosoindoline (XLVIII) with (a) pyruvic acid and (b) ethylpyruvate failed to yield an indole derivative.

Perkin and Reilly (42) had tried to cyclize the hexahydrocarbazole-

9-acetic acid but failed and Lions and Ritchie, repeating the experiment with ethylhexahydrocarbazole-9-acetate (L) with concentrated sulphuric acid under varying conditions could not get the cyclization to



L

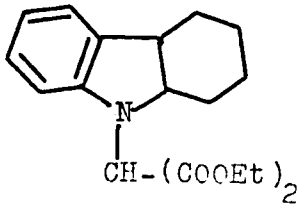


LI

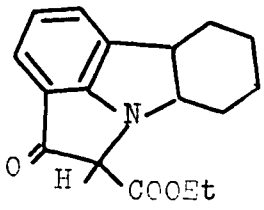
LI to take place.

Lions and Ritchie (41) attempted several other cyclizations but failed to obtain a compound containing the tricyclic system in which we are interested.

1. They tried to convert hexahydrocarbazole-9-malonic ester (LII) by heating it to 280° but the expected compound (LIII) was not isolated.



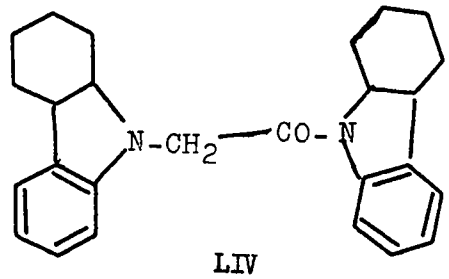
LII



LIII

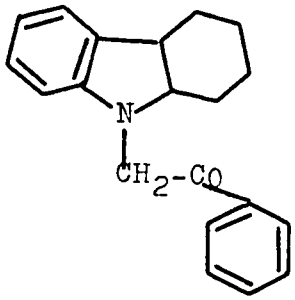
2. They attempted to obtain the oxindole by the interaction in hot aqueous-alcohol solution of cis-hexahydrocarbazole and glyoxal-bisulphite, the method Hinsberg (43) developed for the preparation of oxindole sulphurous ester which can be readily hydrolyzed to the oxindole. As this lead to a

a very low yield of the amide LIV, they made no further attempt to cyclize it.

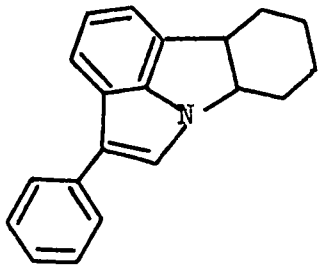


LIV

3. The cyclization of 9-phenacyl hexahydrocarbazole (LV) could not be effected to give (LVI) with concentrated sulphuric acid, anhydrous zinc chloride, phosphorus pentoxide or by simple heating.

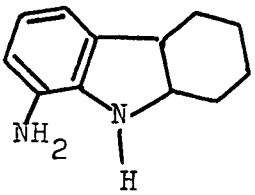


LV

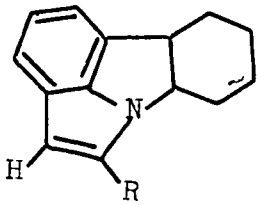


LVI

4. Finally, the treatment of 8-aminohexahydrocarbazole (LVII) with carboxylic acids followed by treatment with sodium nitrite in acetic acid "led only to the formation of tarry material" and not to the expected LVIII.

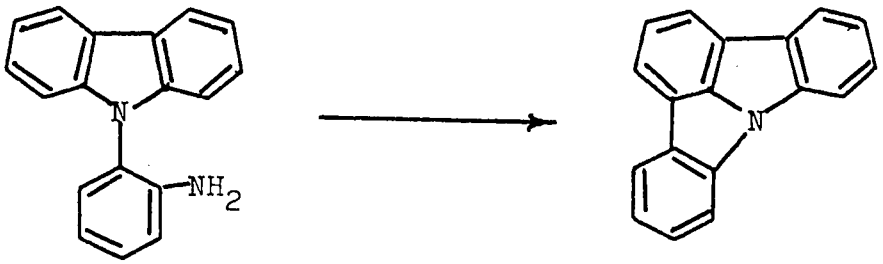


LVII



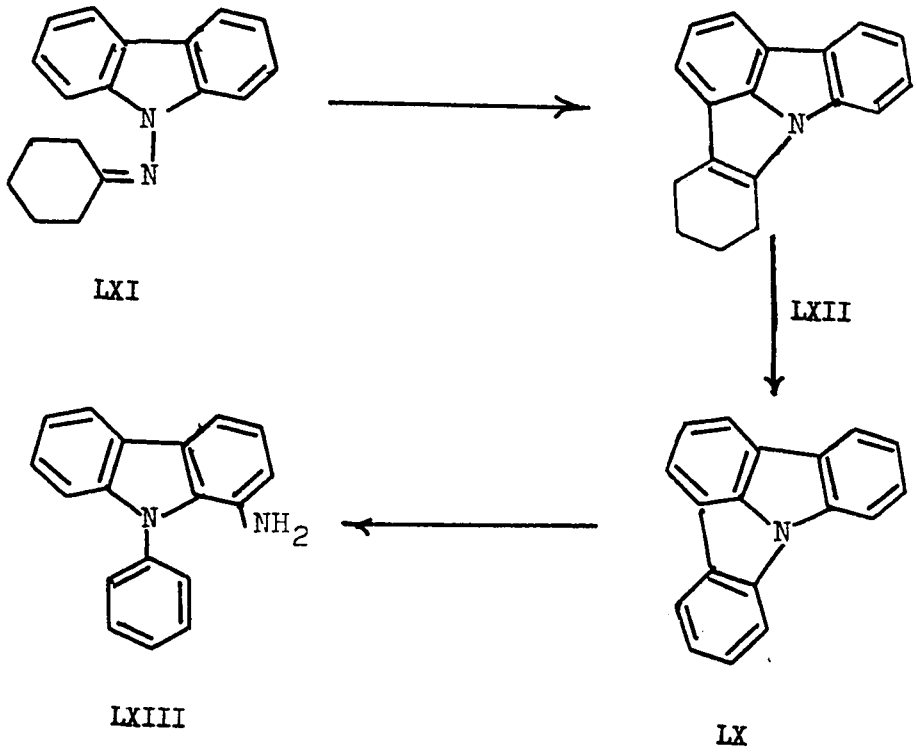
LVIII

In 1939, Dunlop and Tucker (44) reported the cyclization of 9-(o-aminophenyl) carbazole (LXIX) by heating it in glacial acetic acid and concentrated sulphuric acid, diazotizing at 0° with sodium nitrite



LXIX LX

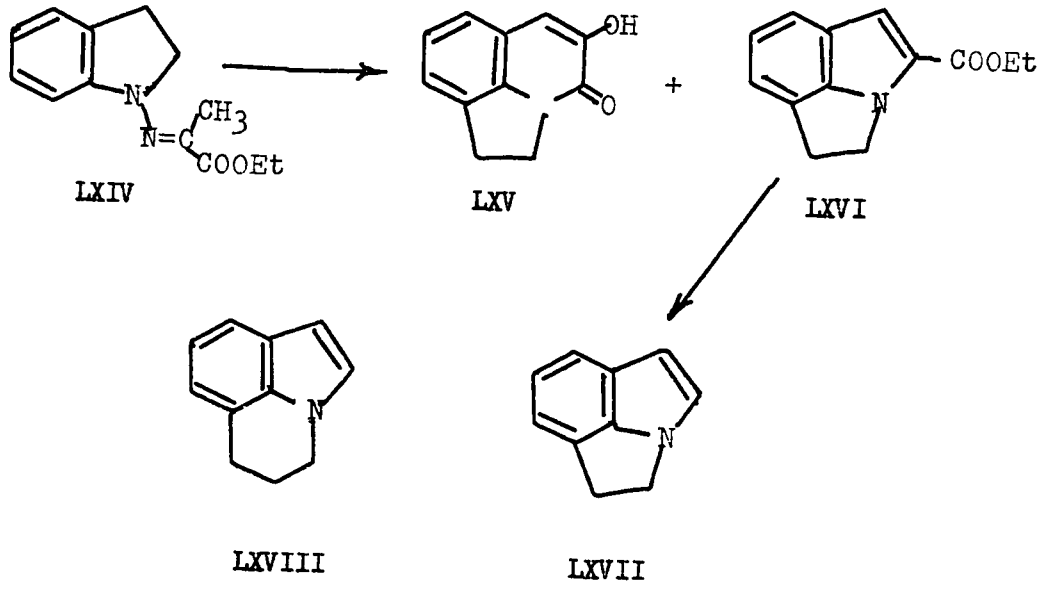
and then boiling for thirty minutes to give 1,9-phenylenecarbazole (LX). The same compound, LX, was obtained by Preston and Tucker (45) by heating carbazolehydrazone of cyclohexanone (LXI) in tetralin at 160° while



LXI LXII LXIII LX

bubbling dry hydrogen chloride gas through the solution. As this reaction is similar to that of Manjunath (38) and to that of Lions and Ritchie (41) it may be taken as further evidence for the structures XLVIb and XLIX. Upon dehydrogenation of the cyclized product (LXII), 1,9-phenylenecarbazole (LX) was obtained. Further, 1,9-phenylenecarbazole (LX) was obtained by the diazotization of 1-amino-9-phenylcarbazole (LXIII) in acetic-sulphuric acid mixture at 0°. Preston and Tucker (45) were not, however, able to cyclize the diphenylenehydrazone of acetone, pyruvic acid, methyl pyruvate, ethyl acetoacetate and ethyl oxaloacetate in a similar manner as for compound LXI.

Rapoport and Tretter (46) have reported that they were able to cyclize the indolinehydrazone of ethyl pyruvate where Lions and Ritchie (41) had not succeeded. Perhaps the yield obtained by the latter authors were too small to be detected in the reaction mixture. The former authors treated the hydrazone (LXIV) under conditions of Fischer indole synthesis and obtained two products, one of which was shown to

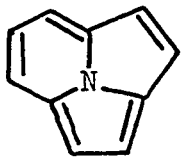


LXIV LXV LXVI

LXVIII LXVII

be the hydroxyquinoline (LXV) and the other which was present in very small amount was claimed to be the α-carbethoxy indole (LXVI). The structure of the latter compound was demonstrated by saponification to the acid of equivalent weight 188 and then by decarboxylation to 1,2-dihydropyrrolo-3,2,1-h,i indole (LXVII). The ultraviolet spectrum of the indole (LXVII) was found to be similar to that of the corresponding six-membered ring compound (LXVIII).

Recently, Boekelheide et al. (47) have reported a synthesis of a new class of aromatic heterocycle (LXIX) which is somewhat analogous to the compound of Rapoport and Tretter (46). Both of these compounds are probably resonance stabilized, particularly that of Boekelheide. The stability is evidenced by the ease of cyclization and the stability of the compound towards light, heat and air. The aromatic properties



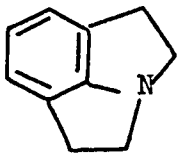
LXIX

of LXIX have been indicated by the normal substitution reactions which it undergoes with bromine and in the Friedel and Crafts reaction.

DISCUSSION

As mentioned above, the existence of a strained polycyclic system consisting of two five-membered rings fused mutually to a benzene ring was not known and thus, the problem of synthesis of such a system was a challenging one. If such a system could be synthesized, its physical and chemical properties would most certainly be of interest. The initial program was to synthesize a homocyclic system in which two five-membered rings were mutually fused to a benzene ring. However, after some preliminary work had been done on this problem, in 1956, Rapoport and Pasky (24) reported the synthesis of the compound we had in mind. Hence, although our approach to the problem was different, this project was terminated and the analogous heterocyclic system was investigated.

The heterocyclic system which we hoped to synthesize was one in which the carbon 2a of the cyclopent[cd]indene (XIV) was replaced by a nitrogen. Such a compound (LXX) would be expected to be somewhat less



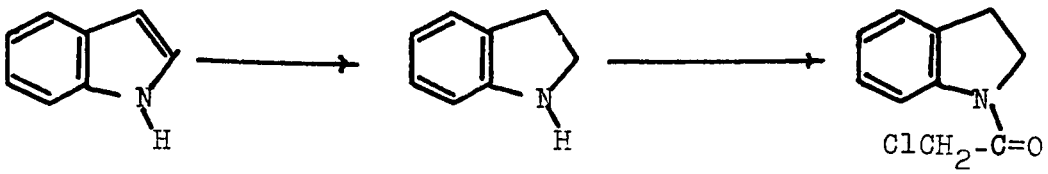
LXX

strained due to the flatter nature of the nitrogen atom.

Although numerous attempted cyclizations to the strained system via the Friedel and Crafts reaction in the homocyclic series are exemplified in the literature (see above), it was felt that the same restrictions did not apply to the heterocyclic system, at least not to

as great an extent. This might be expected since the nitrogen atom is flatter than the carbon atom and also because the nitrogen would be expected to assist in the activation of the ortho-carbon in the benzene ring.

The first compound which we hoped to cyclize was N-chloroacetylindoline (LXXIII). Cyclization of such a compound followed by reduction of the cyclic amide would lead to the desired compound (LXX). N-Chloroacetylindoline (LXXIII) was chosen as the precursor for several reasons; firstly, the precursor is available in good yields from indoline (LXXII)



LXXI LXXII LXXIII

and chloroacetyl chloride, secondly, indoline (LXXII) can be obtained from indole (LXXI) of which a plentiful supply was available, thirdly, it was possible to follow the course of the reaction spectroscopically, and furthermore, this is the simplest possible compound containing the required system. The starting material contains an open chain amide, whereas the cyclized product would have a five-membered cyclic amide. These functional groups would normally have different absorptions in the infrared and therefore, it would be very convenient in detecting any cyclization that might take place.

There are numerous electrolytic (48, 49) and catalytic methods (50-55) for the reduction of indoles but the disadvantages of these methods are that they require either an high hydrogen pressure (300 atmos.) and/or a high reaction temperature (225^{0}) as well as special

apparatus in some cases. Furthermore, from the point of view of yield, the formation of other hydrogenation products such as the octahydro-compound (51, 53) is not desirable. Also, in some cases, the drastic reduction conditions yielded aminoethylbenzene (50, 54). The best method was found to be a slight modification of the method used by Little et al. (56) for the reduction of 1-methyl-7-phenylindole.

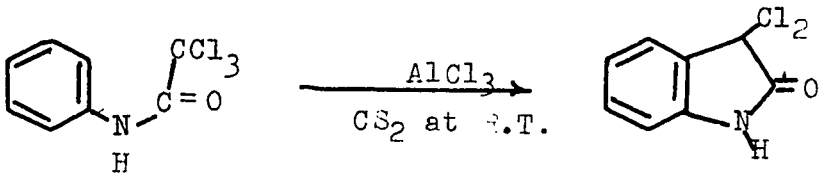
When the Friedel and Crafts reaction with purified aluminum chloride was carried out on N-chloroacetylindoline, the reaction did not yield the desired product. Under mild conditions, the starting material was recovered unchanged whereas under more drastic conditions, a discouraging, dark intractable tar was obtained. A careful examination of the ethanolic and ethereal extracts yielded the unchanged starting material and some N-acetylindoline but no product containing the five-membered cyclic amide was detected. The tar, presumably a polymer, was chloroform soluble. An infrared analysis of the chloroform solution of the tar showed an absorption at 1720 cm^{-1} indicating the presence of a five-membered cyclic amide. An Ehrlich reagent for active hydrogens gave a test indicative of the presence of an indole structure. However, despite much effort, no identifiable substance could be isolated from the tar.

It is interesting to note that in all the experiments, (Table I), varying amounts of the starting material was recovered unchanged. This must indicate that the cyclization proceeded only when the reverse Friedel and Crafts reaction had taken place at the high reaction temperature or that the two reactions, cyclization and ring cleavage, both promoted by aluminum chloride was taking place simultaneously.

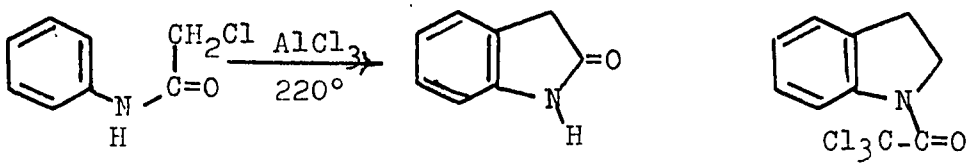
As the drastic reaction conditions were no doubt responsible for the formation of the polymer, several cyclizations were attempted under milder conditions. Firstly, aluminum bromide, a more active Friedel and Crafts reagent, was chosen as it should be possible to carry out the reaction at a lower temperature with such an active reagent. However, when the chloroacetyl derivative was heated with this reagent for 50 minutes at 180°, only unchanged starting material was obtained. When the temperature was raised to 200°, large amount of tar was obtained from which no identifiable product could be isolated.

Secondly, it was felt that perhaps the cyclization may take place by heating the N-chloroacetyl or the more active N-iodoacetylindoline in 98% formic acid. Samples were taken every hour for the first six hours and then two more samples at eight hour intervals but no compound showing an infrared absorption corresponding to the cyclic amide was obtained. Hence no effort was made to isolate the products, if any, of this reaction.

Thirdly, it has been reported by Julian et al. (57) and Bergdoll et al. (58) that the cyclization of trichloroacetylaniline (LXXIV) proceeds much more readily than the corresponding monoacetyl derivative (58). Although the monochloroacetylaniline (LXXV) required strong heating, it was found that the trichloroacetyl derivative of aniline (LXXIV) could be cyclized at room temperature (57, 58). When



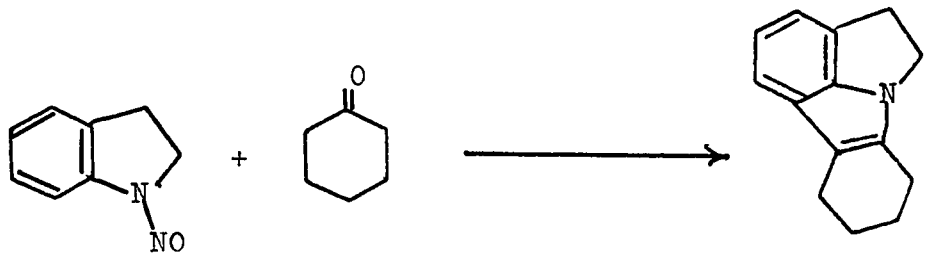
LXXIV



LXXV LXXVI

N-trichloroacetylindoline (LXXVI) was stirred at room temperature in carbon disulphide in the presence of aluminum chloride, the unchanged starting material was isolated in good yield. However, upon heating N-trichloroacetylindoline with aluminum chloride at 110° or when the carbon disulphide solution was refluxed in the presence of aluminum chloride, only an amorphous compound melting above 310° was obtained.

Finally, a Fischer indole synthesis was attempted with N-aminoindoline and cyclohexanone. This type of cyclization is expected to take place readily since it is reminiscent of the formation of tetrahydrocarbazole, which is known to proceed with extreme ease and in almost quantitative yields. In fact, Lions and Ritchie (40, 41) had reported

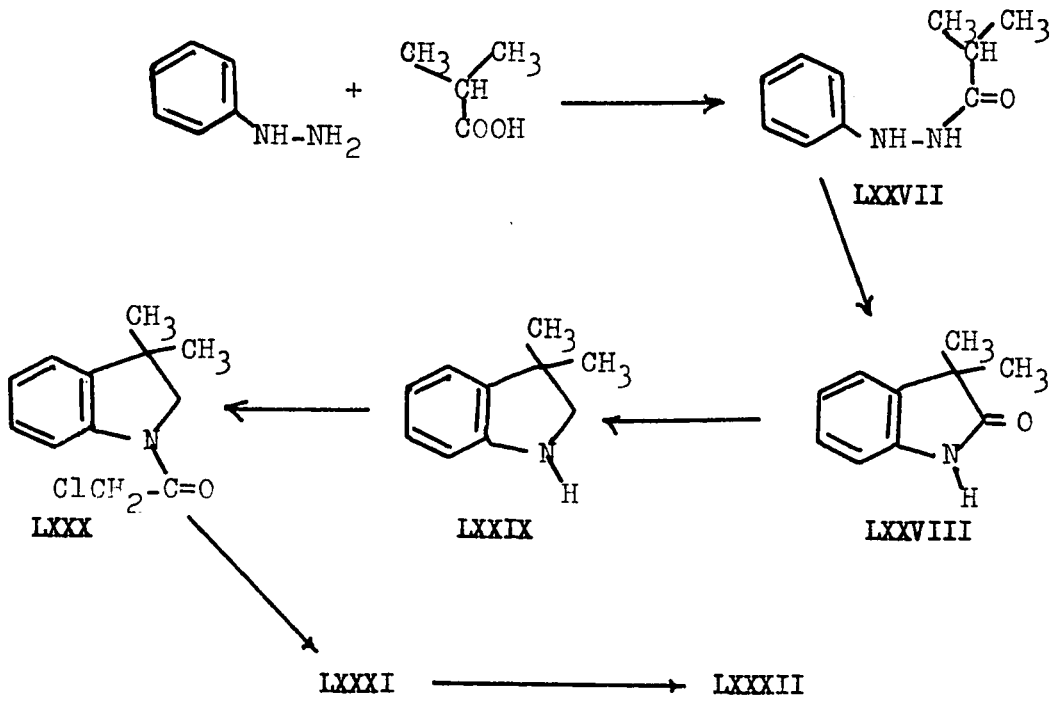


LXIX

the preparation of XLIX by the treatment of nitrosoindoline and cyclohexanone under reducing conditions. A sample prepared by this method given by the above authors and the compound prepared by the treatment of N-aminoindoline and cyclohexanone proved to be identical in all respects. However, this compound as well as that of Rapoport and Tretter (46) is

expected to be formed more readily and is more stable than the compound which we intended to synthesize since they are probably resonance stabilized.

As the formation of the tars was believed to be due to the active hydrogens on the β-carbon of the indoline, a compound having this position fully substituted was next tried. The simplest compound of this type, 3,3-dimethylindoline (LXXIX) was prepared by the cyclization, followed by reduction, of phenylisobutyrohydrazide (LXXVII) (59). Cyclization of the N-chloroacetyl-3,3-dimethylindoline (LXXX) in the



Friedel and Crafts reaction yielded a compound (LXXXI) which melted sharply at 54-55°. However, upon storage in the refrigerator under petroleum ether (30-65°) or repeated crystallizations from petroleum ether (30-65°), a higher melting (76-77°) compound was obtained. The

analyses of these two compounds were identical and corresponded to $C_{12}H_{13}ON$. Furthermore, the ultraviolet and infrared spectra were also identical and hence it appears that the cyclized compound had undergone a change in crystal structure. This compound (LXXXI) had a carbonyl absorption band at 1692 cm^{-1} (Nujol) corresponding to an oxindole ring and another band at 1376 cm^{-1} (CCl_4), due to the methyl deformation vibration (60). The ultraviolet spectrum was similar to that of an oxindole having λ_{max} at 253 mμ, log ϵ = 4.00 and 284 mμ, log ϵ = 3.27 (Fig. 4).

The reduction of the oxindole (LXXXI) was accomplished with lithium aluminum hydride. There have been several earlier reports of lithium aluminum hydride reduction of amides (61, 62) and of oxindoles (61, 63, 64) in the literature and from analogy this reaction seemed favourable. To be sure, the reduction of the oxindole (LXXXI) yielded an oily base (LXXXII) having an empirical formula $C_{12}H_{15}N$. The base formed a hydrochloride as well as a picrate ($C_{18}H_{18}O_7N_4$) and had pKa of 4.90 (in water) determined spectroscopically.

The infrared spectrum of the base showed the absence of N-H and carbonyl groups. It gave a methyl absorption band at 1377 cm^{-1} (60). The ultraviolet spectrum gave λ_{max} at 251 mμ, log ϵ = 3.81 and 301 mμ, log ϵ = 3.33 which is similar to that of 3,3-dimethylindoline (LXXVIX), except that the peaks of the base are shifted slightly to the longer wavelength, as might be expected (Fig. 5). According to Remington (65) the increase in planarity of the molecule is expected to shift the λ_{max} to a higher wavelength accompanied by an increase in absorption.

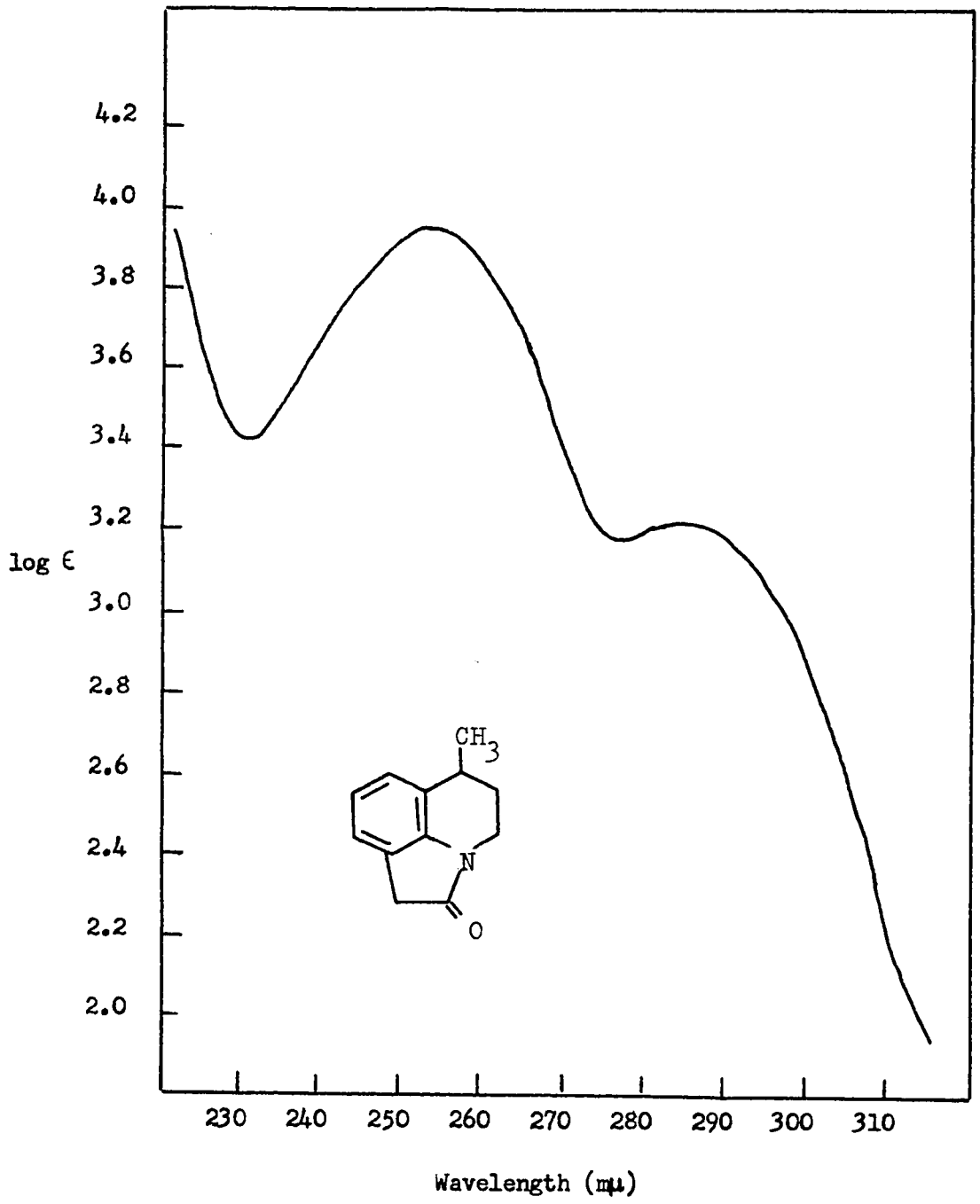

4.2
4.0
3.8
3.6
3.4
3.2
log ε
3.0
2.8
2.6
2.4
2.2
2.0
CH3
N
O
230
240
250
260
270
280
290
300
310
Wavelength (mμ)

Fig. 4

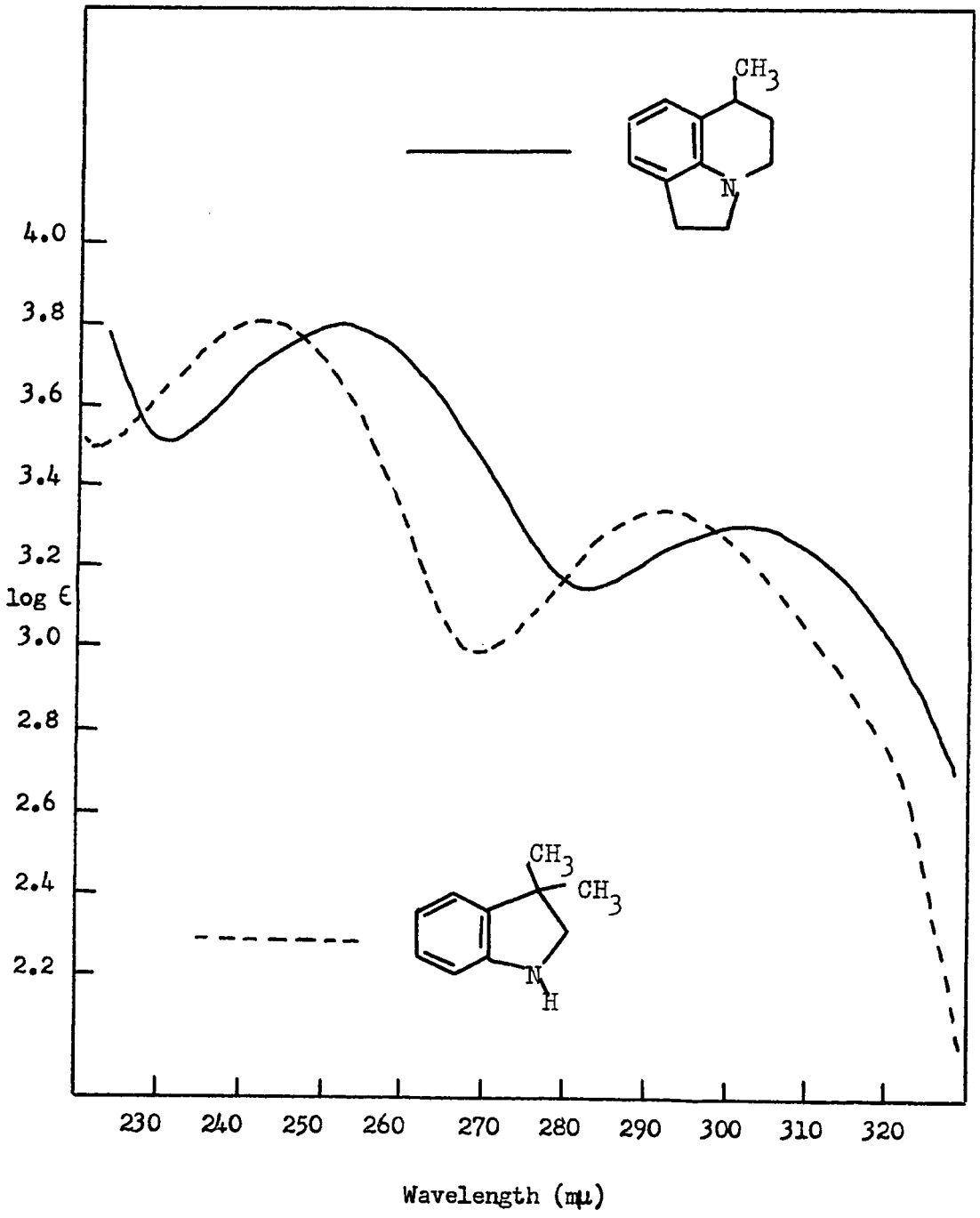
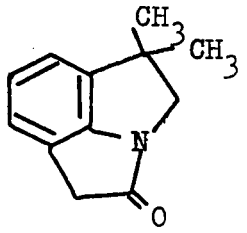
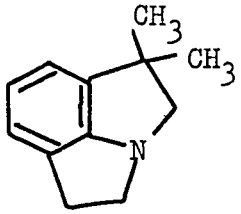

CH3
N
4.0
3.8
3.6
3.4
3.2
log ε
3.0
2.8
2.6
2.4
2.2
CH3
CH3
N
H
230
240
250
260
270
280
290
300
310
320
Wavelength (mμ)

Fig. 5

When the above data are scrutinized carefully, they do not seem to agree with the required structure. From the course of the reaction, compound LXXXI and consequently compound LXXXII would be expected to have the following structures; LXXXIa, LXXXIIa respectively. A base of this type should have a lower pKa value since, from the models, this



LXXXIa



LXXXIIa

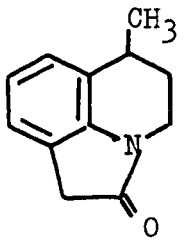
compound has a rigid planar structure. In a planar structure, the unshared pair of electrons on the nitrogen atom can couple with the π-electrons of the benzene ring more effectively than when the substituents on the nitrogen are out of plane of the benzene ring. This phenomena is evidenced, for example, in the pKa's of N,N-dimethylaniline and N,N-dimethyl-o-toluidine. The former has a pKa value lower (4.26) than that of the latter (5.07) (66) showing that the two methyl groups on the nitrogen of the N,N-dimethyl-o-toluidine are twisted out of plane from the benzene ring by the bulky ortho-methyl groups on the benzene nucleus (66, 67).

The absence of N-H and carbonyl absorption bands in the infrared might be expected on the basis of the reaction scheme outlined above but the C-methyl absorption band at 1377 cm^{-1} is disturbing since the expected compound should have a gem-dimethyl group which should give two absorptions of equal intensities on either side of 1377 cm^{-1} (60).

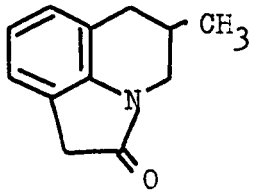
The ultraviolet spectrum appears satisfactory although the

shift of the maxima of the base (LXXXII) obtained was expected to be greater than was observed, and also the intensity of absorption should have increased (Fig. 4).

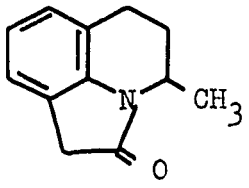
In order to get more data to help in determining the structure of compound LXXXIa, a nuclear magnetic resonance spectrum was obtained with a Varian Model V-4300 NMR spectrometer at a fixed frequency of 40 Mc./sec. This spectrum which was essentially the same as that in Fig. 6 could not be reconciled with structure LXXXIa since a gem-dimethyl group in such a compound would be expected to give a single peak having an intensity corresponding to six hydrogens in the high field region. In view of the fact that the carbon-hydrogen analysis and the molecular weight of the compound agree with that of the structure LXXXIa, the only plausible explanation for the above discrepancies is that some rearrangement had taken place. This rearrangement must be taking place during the drastic reaction conditions of the Friedel and Crafts reaction rather than during the reduction stage. Furthermore, since the infrared spectrum shows an absorption corresponding to the five-membered cyclic amide, the rearrangement must involve either a migration of the methyl group or a ring opening reaction followed by a ring closure to give a six-membered ring. The former is ruled out from our pK_a measurements as well as by the nuclear magnetic resonance spectrum and in the light of the nuclear magnetic resonance studies and the consideration of the postulated Friedel and Crafts reaction mechanism, (68-71) the ring expansion reaction is very appealing. Such a rearrangement could result in three possible isomers;



LXXXIII

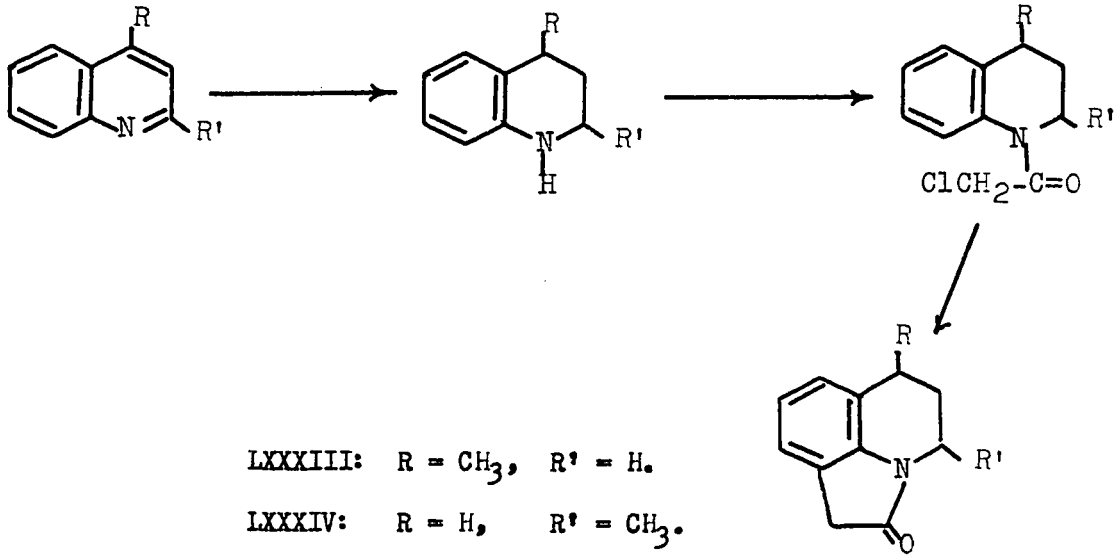


LXXXIV



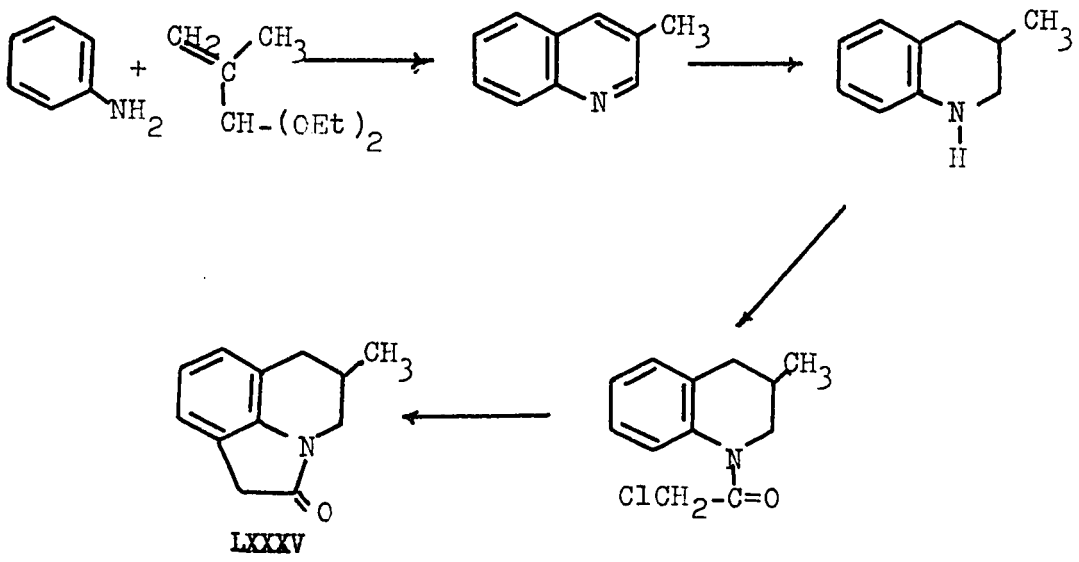
LXXXV

In order to ascertain the structure of compound LXXXI, we proceeded to synthesize these compounds for comparison. As it was felt that, as mentioned earlier, the rearrangement took place in the cyclization step, the actual comparison was made on the oxindole derivatives rather than on the free base. Although the 2- and the 4-methylquinolines were available, it was necessary to synthesize the 3-methylquinoline. This was accomplished by treating aniline with α-methylacrolein. The methylquinolines were reduced to the corresponding methyl-1,2,3,4-tetrahydroquinolines and then chloroacetylated with chloroacetyl chloride.



LXXXIII: R = CH_3, R' = H.

LXXXIV: R = H, R' = CH_3.



LXXXV

Cyclization of these N-chloroacetyltetrahydroquinolines gave the respective methyldihydrolilolones (LXXXIII, LXXXIV, LXXXV). The cyclizations proceeded under much milder conditions than that of LXXX.

The crystallization habits and the melting point of the 4-methyl derivative (LXXXIII) were identical with that of compound LXXXI. The identity was confirmed by mixed-melting-point determination and the comparison of the ultraviolet and infrared spectra. Furthermore, the nuclear magnetic resonance spectrum of compound LXXXI was the same as that for compound LXXXIII (Fig. 6).

The nuclear magnetic resonance spectra of the other two isomers (LXXXIV and LXXXV, Figs. 7 and 8 respectively) are also included to show that the subtle differences in the three isomers can be shown by this method. The chemical shifts of the assigned bands are consistent with what would be expected theoretically, Pople et al. (72).

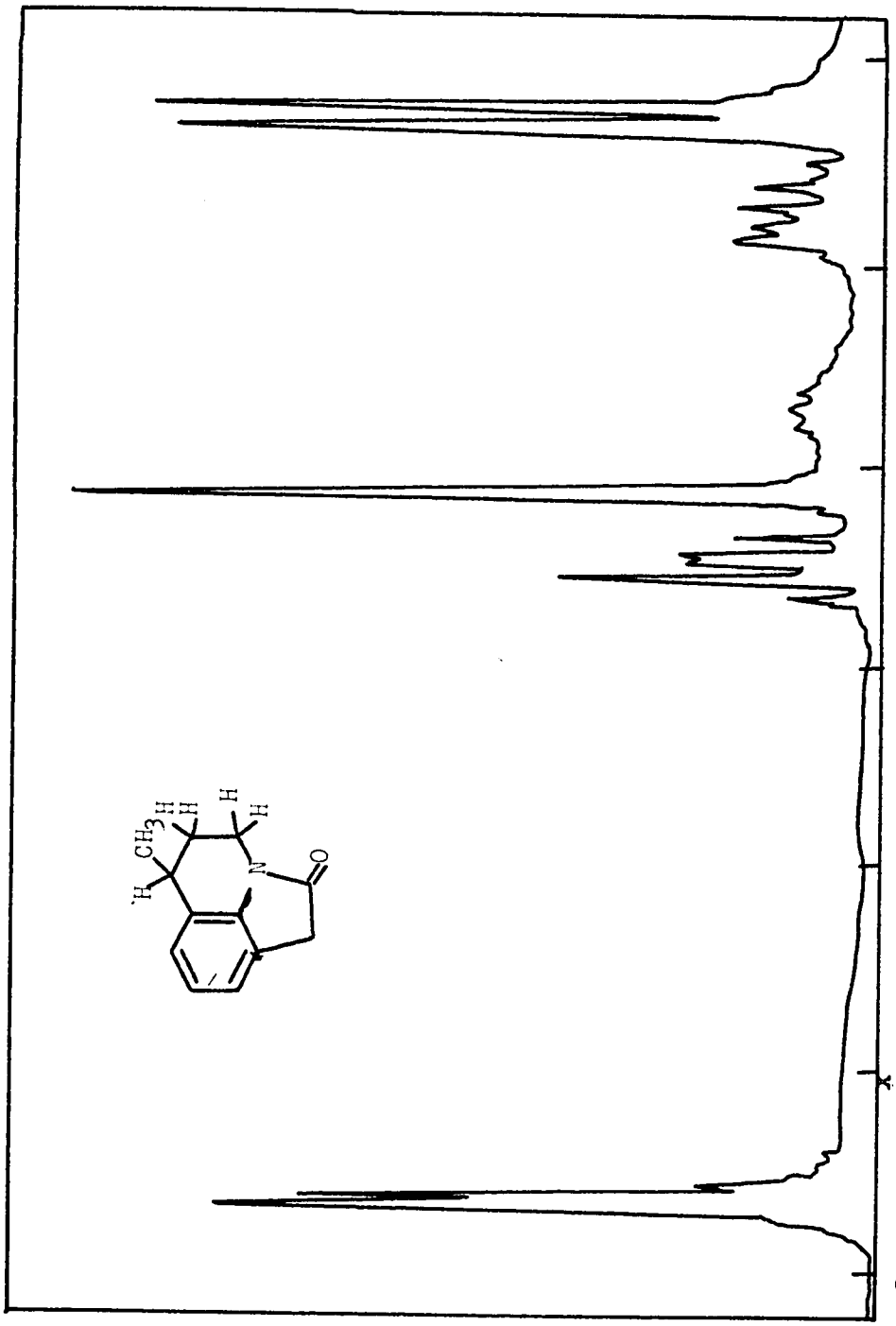


Fig. 6

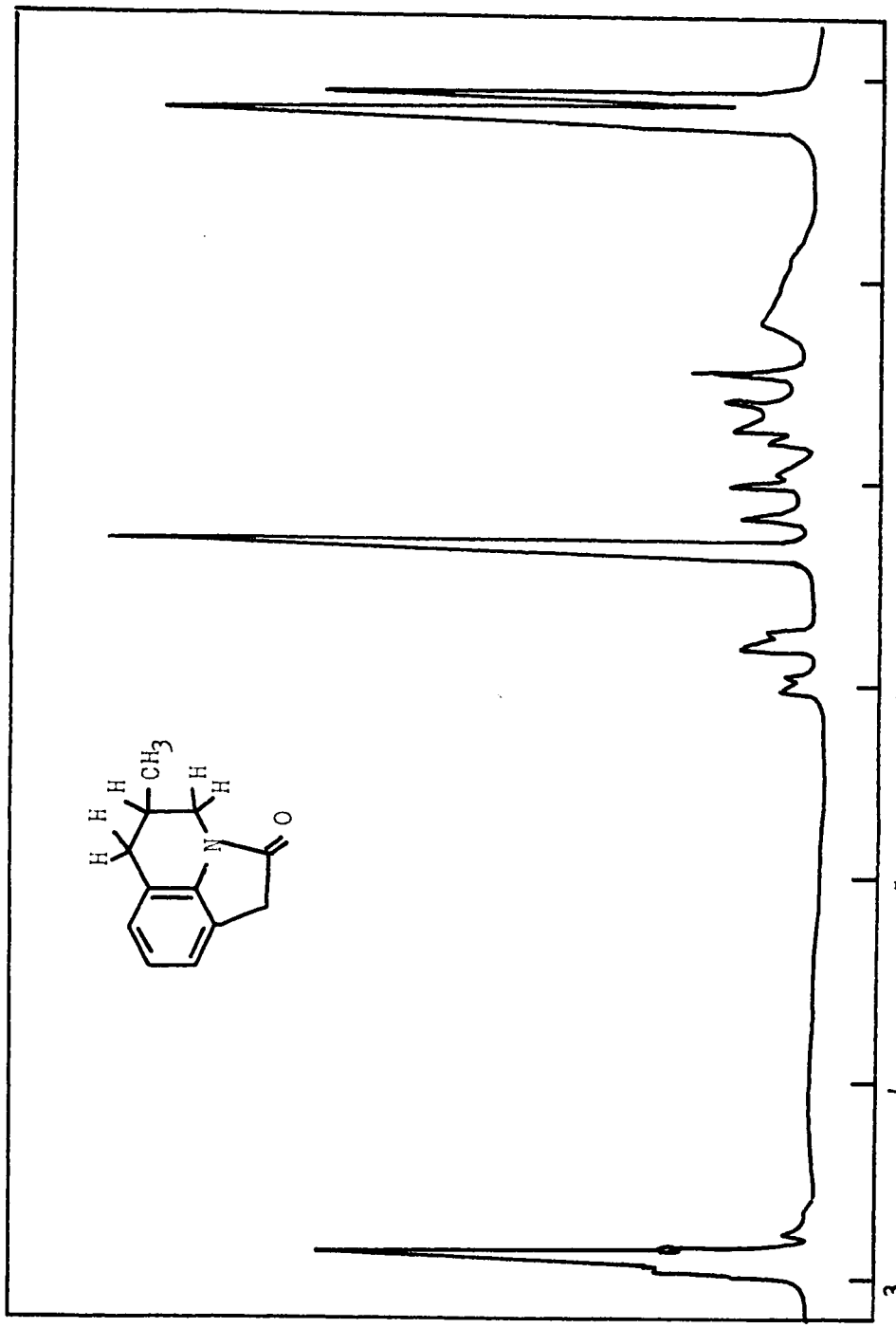


Fig. 7

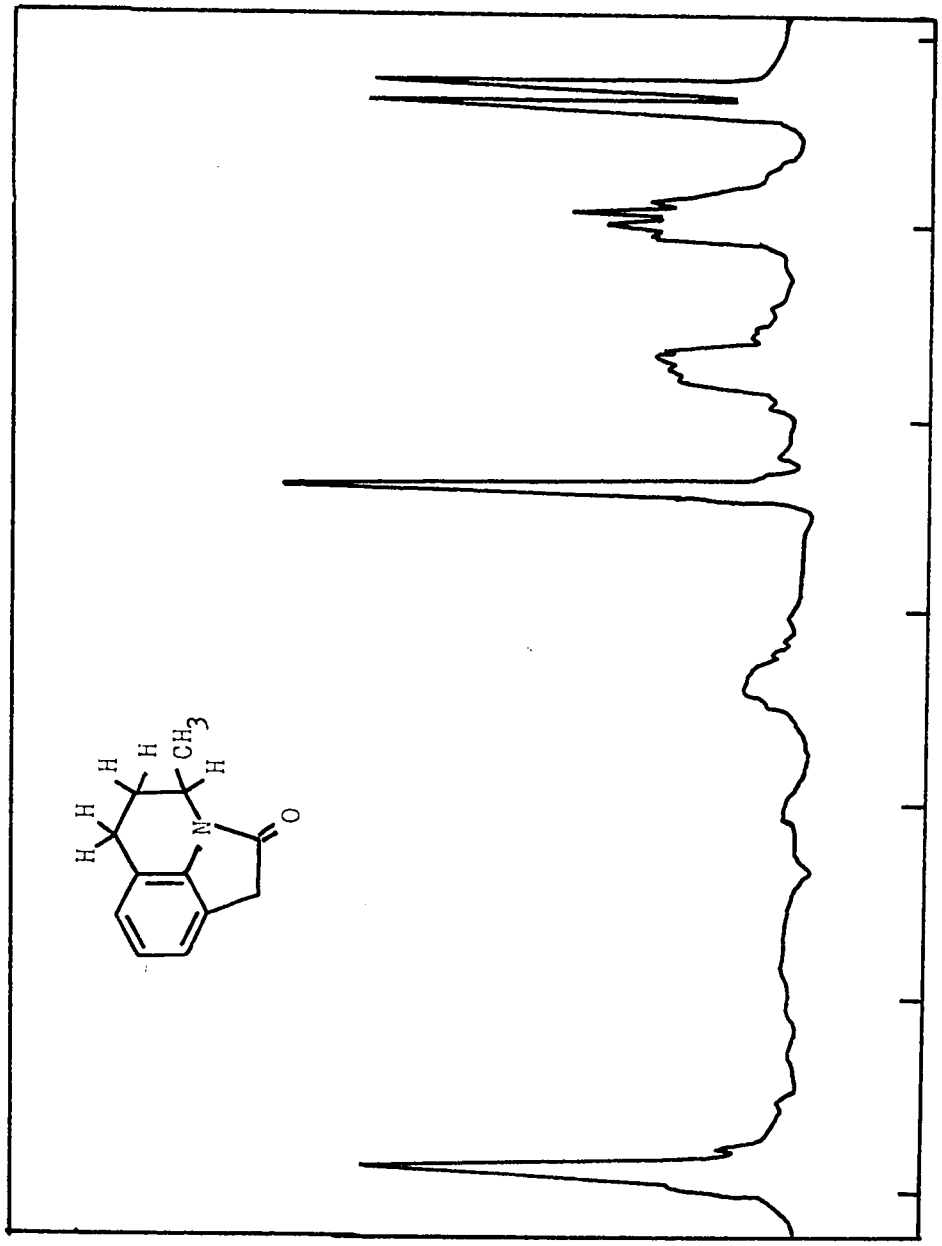
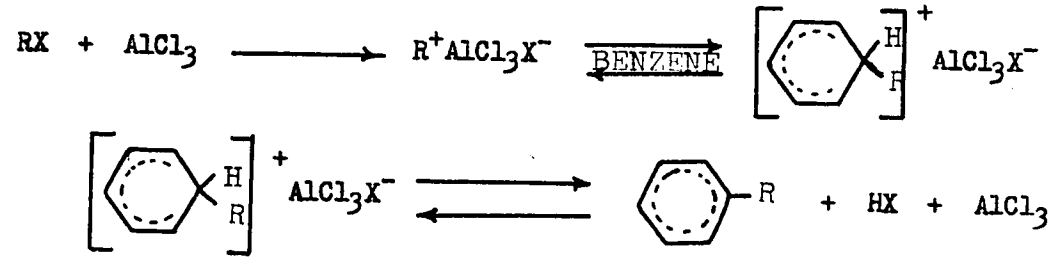


Fig. 8

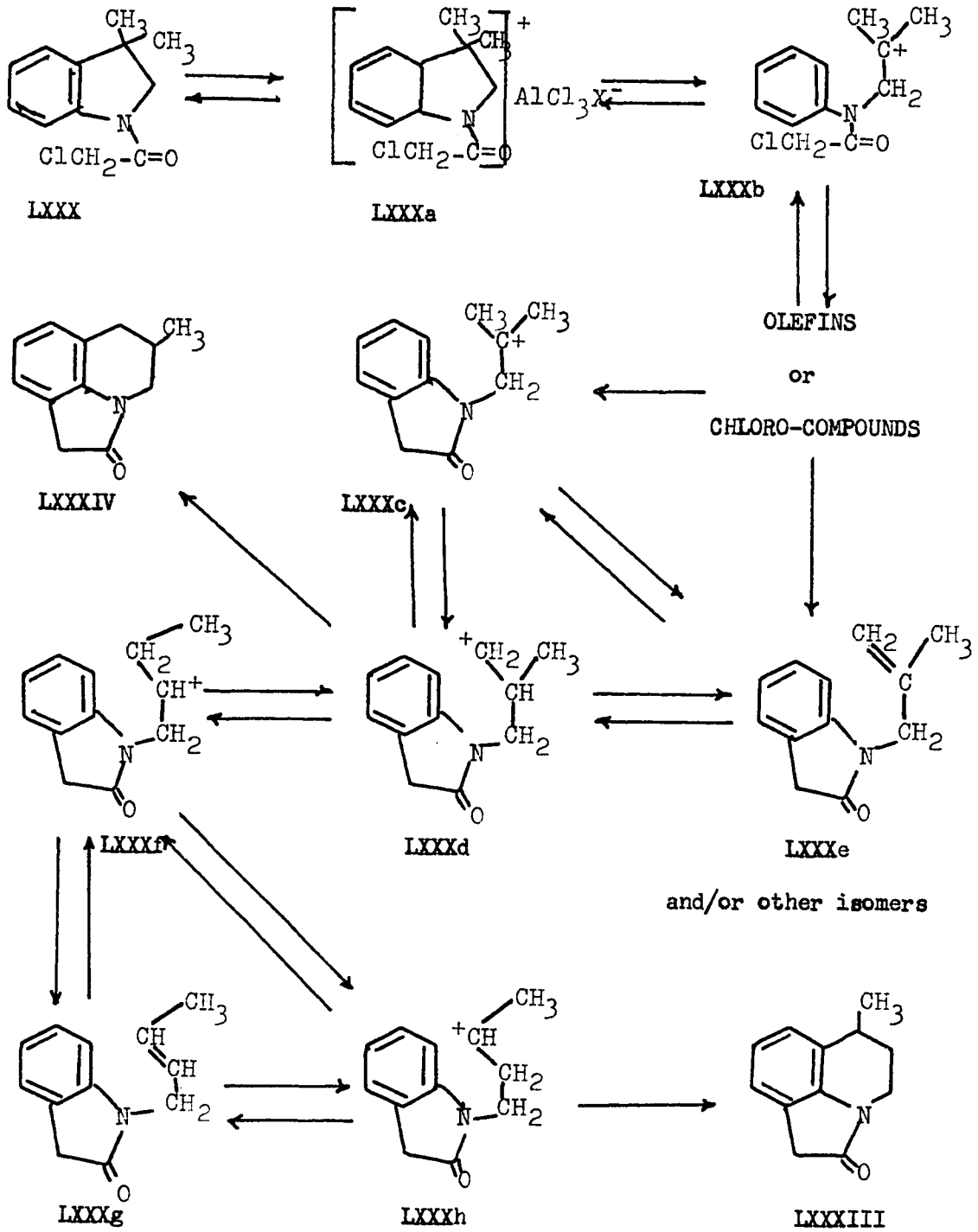
The question then arises as to how such a compound can be formed. It is possible that the tricyclic compound may have formed at one stage but due to the strain in the molecule and the drastic reaction conditions, it subsequently underwent a ring opening. It is also possible, however, that the ring opening took place before the cyclization step. Dealkylation or reverse Friedel and Crafts reaction has been observed in many cases (68, 73), especially at high temperatures. The mechanism of the Friedel and Crafts reaction is thought to be bimolecular at low temperatures but at higher temperatures, a carbonium ion intermediate is thought to exist (69-71). Accordingly then, the generalized Friedel and Crafts reaction at high temperatures can be formulated as;



The reverse of the alkylation is then promoted by the attack by the cation to give the complex which then dissociates (68, 69, 74).

It has been previously mentioned that at lower temperatures, even with an active Friedel and Crafts catalyst, no reaction took place even on prolonged heating. At the higher temperature, however, where dealkylation (68, 73) might very well occur, the reaction proceeds to yield a variety of compounds. One of these being N-acetyldimethylindoline, which is only formed in the high temperature reaction, must be the result of a disproportionation reaction with a ring opened species LXXXb. The yield of this compound was low as might be expected since once the ring opens, the cyclization to the cyclic amide would take place rapidly

to give LXXXc. Of course, the ring opened species can recyclize again to the original starting material but a ring closure to the cyclic amide would drive the reaction to the right.



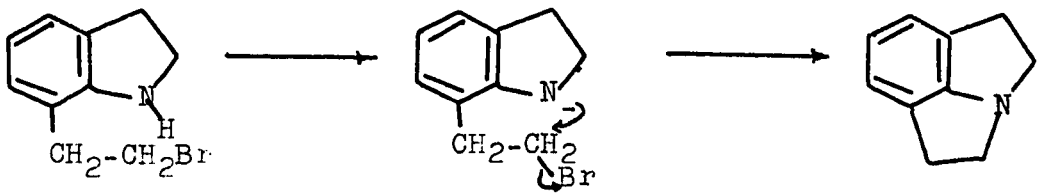
The mechanism for the formation of the rearranged product can therefore be postulated as being the result of the following series of reactions. N-Chloroacetyldimethylindoline can be attacked by HX---$AlCl_3$ (75) to give the complex LXXXa. It has been observed that protonation takes place preferentially such that the tertiary group is dealkylated (73). The dealkylated species LXXXb can then undergo cyclization to give the cyclic amide LXXXc. This ion can undergo cyclization to give the strained tricyclic compound but the fact that such a compound is not isolated would indicate that the strain is too great. The ion LXXXc, however, can undergo a number of reactions such as the formation of tar and thus explains the low yield of the product isolated.

The first possibility is that it can undergo a hydride shift to give LXXXd which may undergo disproportionation to give LXXXe. Species LXXXe can then enter into a polymerization reaction. The concentration at any given time of species such as LXXXd which is a primary carbonium ion would be expected to be very low but such a carbonium ion would rapidly cyclize to give LXXXIV. Although this compound was not isolated, it is possible that a small amount of this could have formed. Cation LXXXd can also undergo methyl migration to give LXXXf, which can give rise to species LXXXh. The cation LXXXh can then readily undergo cyclization to give LXXXIII.

Thus the structure of the cyclization product (LXXXII) was shown to be 4-methyl-3,4-dihydrolilolone (LXXXIII) and not 3,3-dimethylcyclopent[cd]indoline (LXXXII) which was the desired compound. This rearrangement may be taken as further evidence for the existence of

strain in the tricyclic system.

Another approach to this problem of synthesis of the strained tricyclic system was next considered. It does not appear unreasonable to assume that the anion of 7-(2'-bromoethyl) indoline (LXXXVIa) should undergo cyclization by an internal displacement reaction. Although this



LXXXVI LXXXVIa LXX

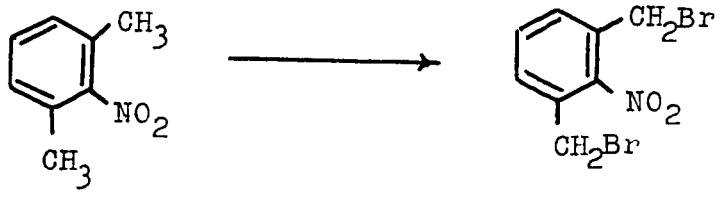
anion would not be expected to cyclize as readily as the aniline analogue (76), the prospect is attractive since the carbon bearing the bromine atom can approach fairly close to the negatively charged nitrogen atom for it to be attacked. However, it may be that the distance between these two atoms are just a little too large for bond formation. After all, if the predicted strain is present, it would tend to prevent such a reaction.

There are other reasons why the cyclization reaction would be difficult, even if the strain is not large enough to prevent such a reaction. Any strain would tend to slow down the cyclization reaction and this would increase the extent of side reactions. One of these side reactions may be the formation of a styrene type compound by the elimination of hydrogen bromide. In an aqueous medium, it is possible that hydrolysis may occur to give the alcohol or if the reaction conditions are such that there is a large concentration of 7-(2'-bromoethyl)

indoline (LXXXVI) at any time, a dimerization or even polymerization may take place.

Since many competitive reactions were anticipated, it was desirable to have a large quantity of 7-(2'-bromoethyl) indoline (LXXXVI). However, this compound was not known at the beginning of this investigation, and although a synthesis was devised, the number of steps were numerous and the yield rather low.

The starting material for the synthesis was 2,6-dimethyl-nitrobenzene (LXXXVII). Homologation was first attempted by the bromination of the methyl groups with N-bromosuccinimide. It was thought that the nitro group would activate the methyl groups in the



LXXXVII

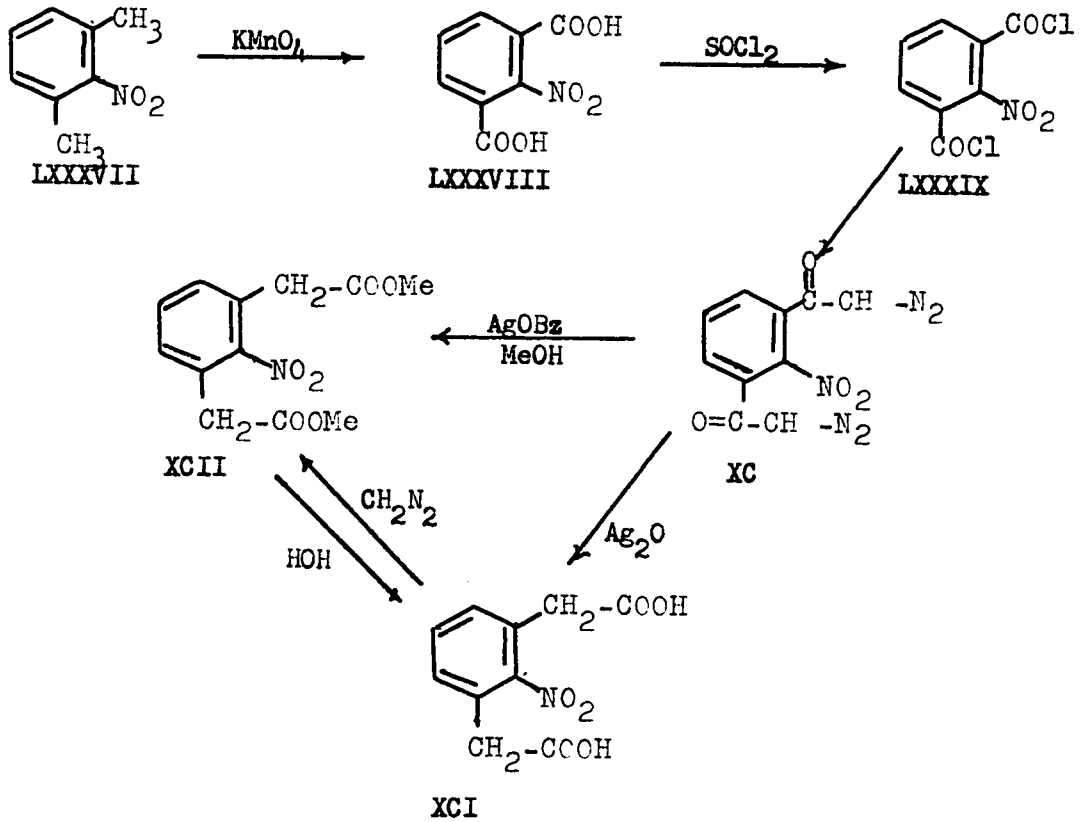
ortho position to facilitate the bromination. Although a large excess of N-bromosuccinimide was used, the product gave an analysis showing only 1.3 bromine atoms. A retreatment of the partially brominated compound with more N-bromosuccinimide did not appear to increase the bromine content appreciably. Although the second bromine would be expected to attack the second methyl group, this was not established. In any case, since it was found that the dibromo-compound could not be readily obtained and also because the brominated compound was found to

be extremely lachrymatory, the Arndt-Eistert method of chain lengthening was investigated.

2,6-Dimethylnitrobenzene (LXXXVII) was oxidized with alkaline potassium permanganate to 2-nitroisophthalic acid (LXXXVIII) as described by Noelting and Gachot (77). The melting point of the acid obtained was found to be considerably higher than that reported in the literature (77, 78). However, the chlorine analysis of the nitroisophthalyl chloride (LXXXIX) was consistent with the expected compound. It is not possible for the acid to be any of its several isomers, all of which are known, since none of these have melting points above 280°. Consequently, it seems likely that the dicarboxylic acid obtained by us is indeed the one required and it may be that the reported melting point of Noelting and Gachot (77) and of Huising (78) may have been low due to impurities.

The first stages of the Arndt-Eistert reaction proceeded without difficulty. The acid chloride of 2-nitroisophthalic acid was obtained in good yields by the treatment of the acid with purified thionyl chloride. The addition of the tetrahydrofuran solution of the acid chloride to the ether solution of diazomethane at 0° yielded 1,3-bis-diazoacetyl-2-nitrobenzene (XC). The nitrogen analysis of the diazotized compound gave N, 23.17%. Calc. for $C_{10}H_5N_5O_4$: N, 27.02%. The discrepancy in the nitrogen content is probably due to the decomposition of the diazoketone as this compound was not very stable. Some difficulties were encountered in the Wolff rearrangement of the bis-diazoketone (XC) and some experimentation was necessary. The silver oxide method in aqueous dioxane (79a) gave a low yield of an acid (XCI)

melting at 215°, although in absolute methanol (80) a fairly good yield (50%) of the ester (XCII) was obtained. This ester was found to be identical with the methylated product of the dicarboxylic acid (XCI). Low yields of the rearranged acid was also obtained by heating the diazoketone (XC) in benzyl alcohol alone and in the presence of dimethylaniline (81). Finally, Newman and Beal (82) were able to obtain good yields from the Wolff rearrangement by using silver benzoate dissolved in triethylamine. This method appeared to be advantageous because the reaction medium was homogeneous. However, it was not suitable for our purpose as, for some unknown reason, a compound melting at 89-90° was obtained, the nature of which was not fully investigated. A slight modification of this procedure, using silver benzoate dissolved in absolute methanol yielded a 54% yield of an ester (XCII) melting at



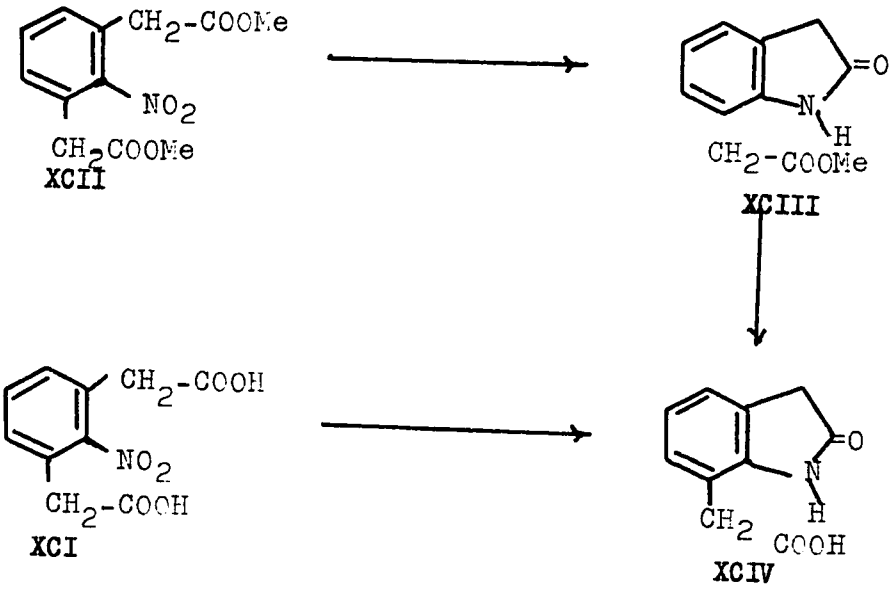
145°. The analysis gave an empirical formula $C_{12}H_{13}NO_6$. Hydrolysis of this ester yielded the acid (XCI) obtained in the reaction using silver oxide in aqueous dioxane.

Difficulties were encountered in reducing the nitro group of the dimethyl ester of 2-nitrophenyl diacetic acid (XCII). Reduction with Adams' catalyst or rhodium on carbon in an acidic medium was not very successful, the yield of product melting at 149-153° was in the neighbourhood of 30%. The product obtained from this reaction, carried out at room temperature and for 30 minutes under a hydrogen pressure of 50 psi was badly contaminated with the starting nitro compound (XCII), and as the two compounds had similar solubilities, they were difficult to separate. The same reaction, run at an elevated temperature for a longer duration did not completely reduce the starting compound.

It has been reported by Fletcher and Namkung (83) that reductions of nitro groups which occur in low yields by ordinary methods were often reduced in excellent yields at steam bath temperature if the reaction was carried out with Raney nickel and hydrazine in ethanol. When this method was employed, no compound similar to the one isolated from the reaction using Adams' catalyst was formed, and in fact, only a red neutral tar could be obtained. Finally, the reduction was carried out in methanol with an especially active ("W-6") Raney nickel (84) at a hydrogen pressure of 50 psi. This method gave a good yield (76%) of the oxindole-ester (XCIII) melting at 154°. This compound could be hydrolyzed to the acid (XCIV), having a melting point of 225°. When the nitro-acid (XCI) rather than the nitro-ester (XCII) was reduced,

the high melting (225°) compound (XCIV) was obtained which was identical in all respects with the hydrolyzed ester. Ultraviolet spectrum of the reduced compound gave a typical oxindole spectrum (Fig. 9).

The formation of the oxindole is to be expected from the reduction of the nitro group as the amine first formed would react with the ester group to give the oxindole. This oxindole ester (XCIII) was found to be very stable even at the sublimation temperature, and did



not undergo further cyclization.

The oxindole-ester (XCIII) was reduced with lithium aluminum hydride in tetrahydrofuran and although the reduction of the oxindole part of the molecule as well as the ester was anticipated, only the ester group was reduced. Among solvent systems used, dioxane-ether, ether, 1,2-dimethoxyethane and tetrahydrofuran, tetrahydrofuran was found to be the best. Three products were isolated from this reaction

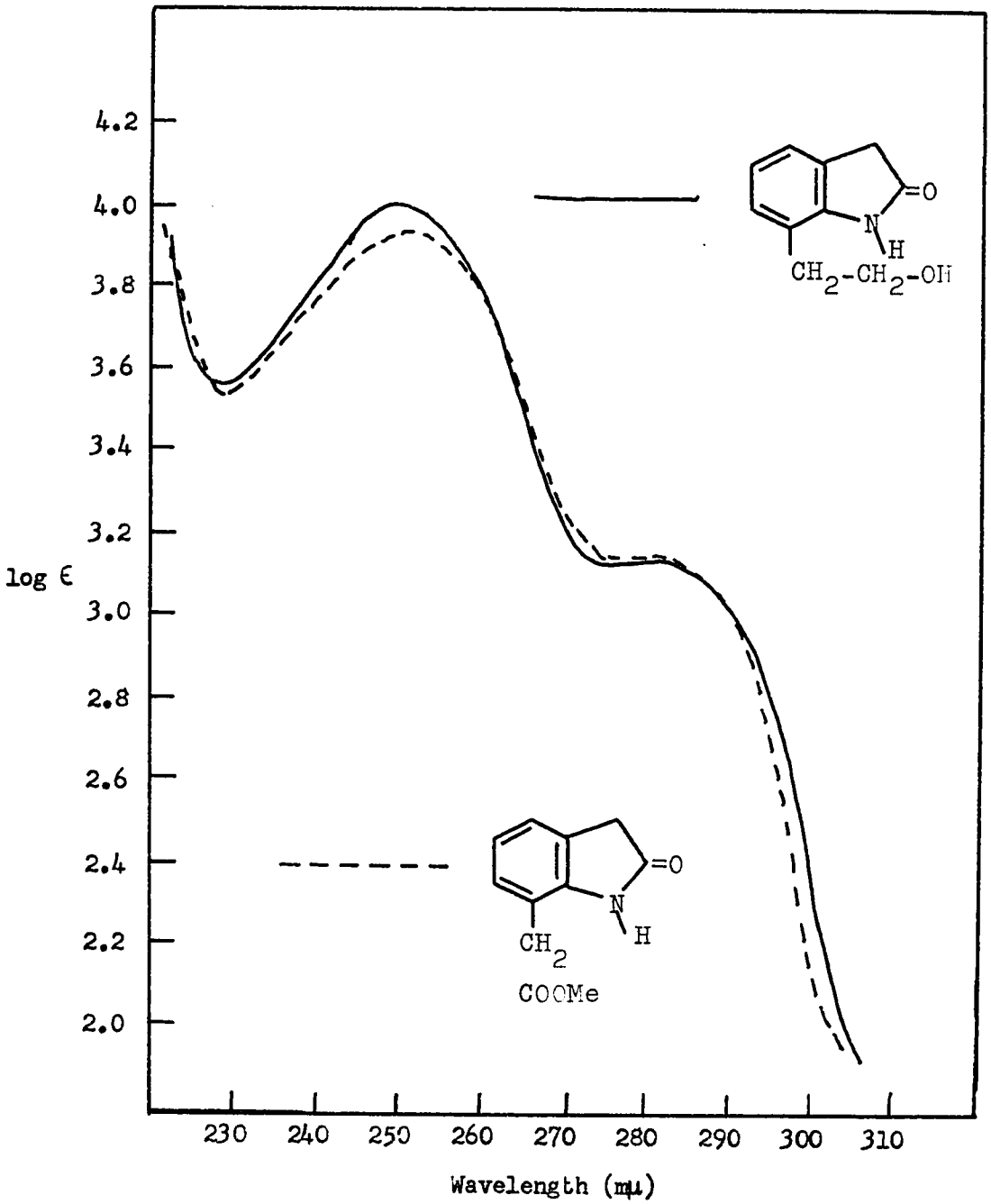
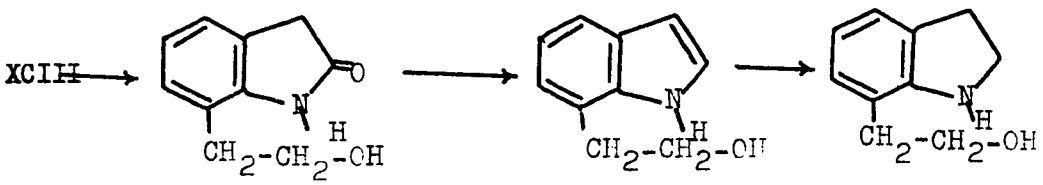

4.2
4.0
3.8
3.6
3.4
3.2
log ε
3.0
2.8
2.6
2.4
2.2
2.0
230
240
250
260
270
280
290
300
310
Wavelength (mμ)
=O
N
H
CH2-CH2-OH
=O
N
H
CH2
COOMe

Fig. 9

mixture, these being the various stages of the reduction of the oxindole ester. Very little of 7-(2'-hydroxyethyl) indole (XCVI) was obtained, the 7-(2'-hydroxyethyl) oxindole (XCV) being the main product. The other compound was a base having a melting point of 96-97° which was crystallized from benzene in small yield. This compound was not investigated further as the yield was very low and it could not be obtained again after the first experiment.

Although numerous examples are available (61, 63, 64) where reduction of amides and oxindoles are accomplished with lithium aluminum hydride, 7-(2'-hydroxyethyl) oxindole (XCV) could not be reduced further with this reagent. The reason for this may be due to the formation of insoluble salts but this was not fully investigated. We then attempted to reduce the oxindole (XCV) with sodium and alcohol followed by treatment with amalgamated zinc and hydrochloric acid. This reduced the oxindole ester (XCIII) in an overall yield of 26% to hydroxyethylindoline (XCVII). The 7-(2'-hydroxyethyl) indoline (XCVII) gave a typical aniline-type spectrum; λ_{max} at 292 mμ, log ϵ = 3.32 and 242 mμ, log ϵ = 3.77 (Fig. 10). It also gave two distinct peaks, one for O-H absorption and another for N-H absorption in the near infrared (Fig. 11).



XCV XCVI XCVII

The 7-(2'-hydroxyethyl) indoline (XCVII) was treated with

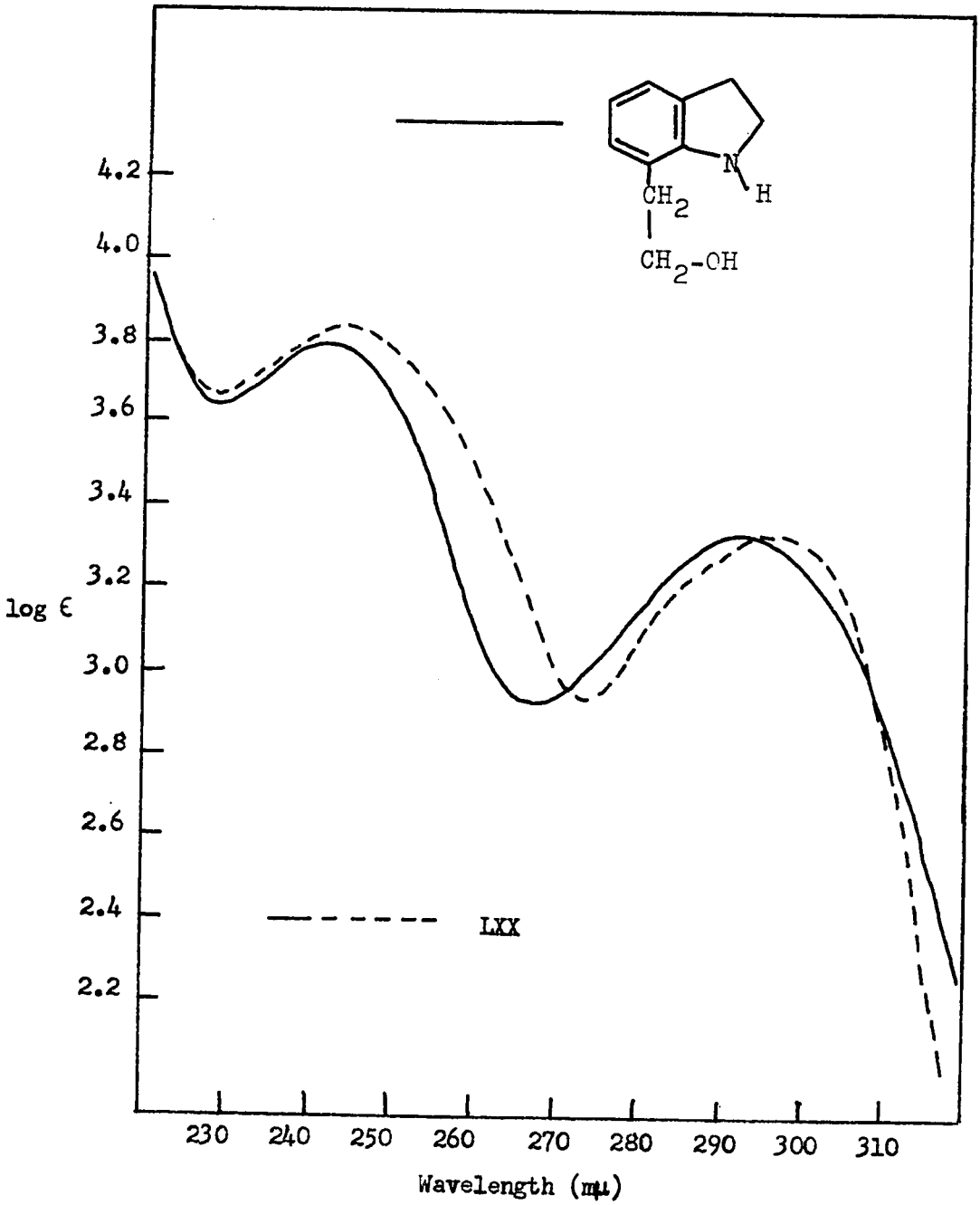

4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
log ε
230
240
250
260
270
280
290
300
310
Wavelength (mμ)
CH2
CH2-OH
N
H
LXX

Fig. 10

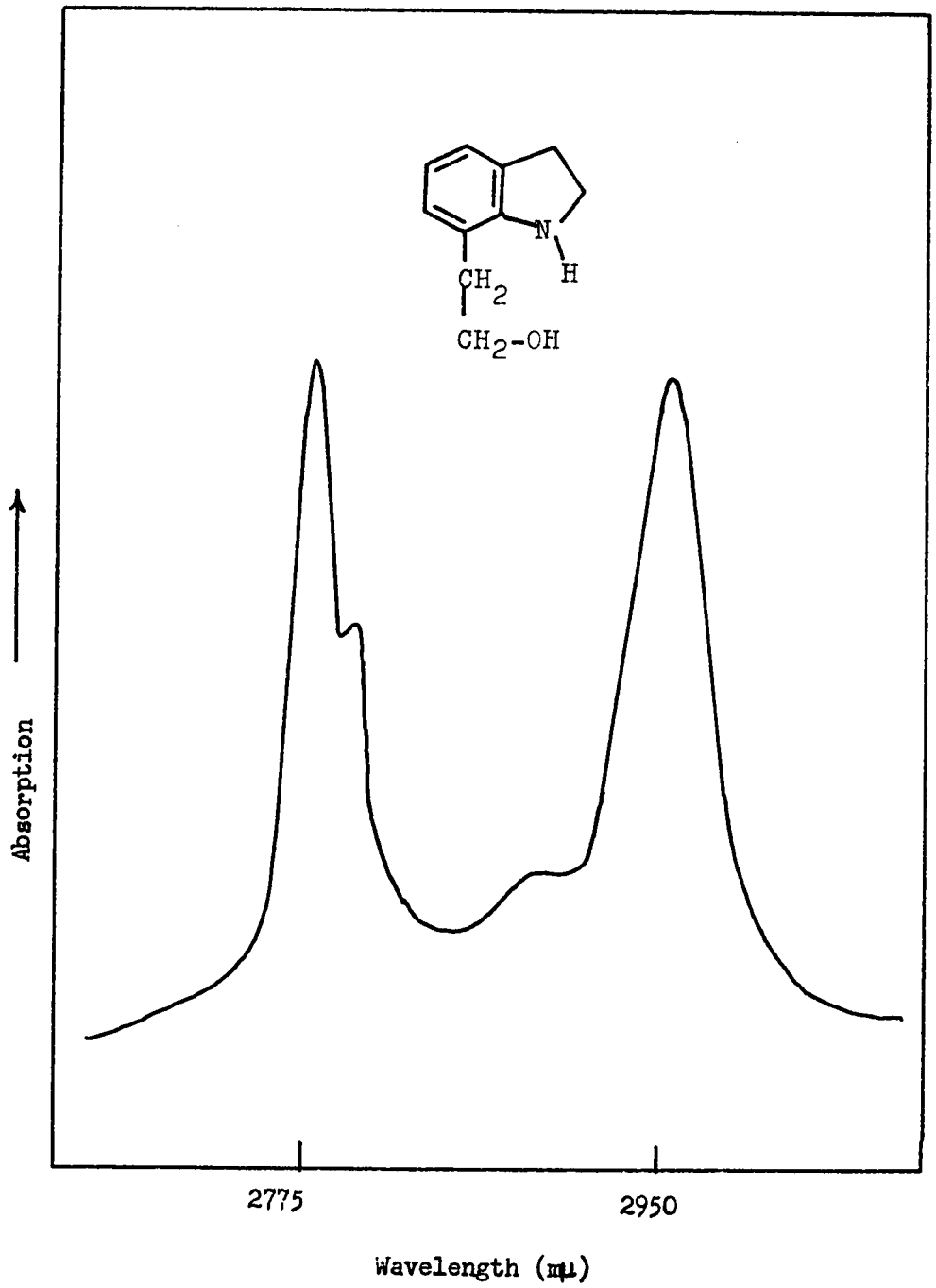
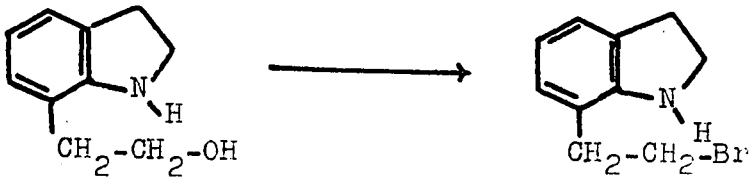


Fig. 11

hydrobromic acid to yield the bromide (LXXXVI) which was isolated as the hydrobromide. This compound was crystallized from methanol as the salt and kept in this form as the free bromide was not very stable.



XCVII LXXXVI

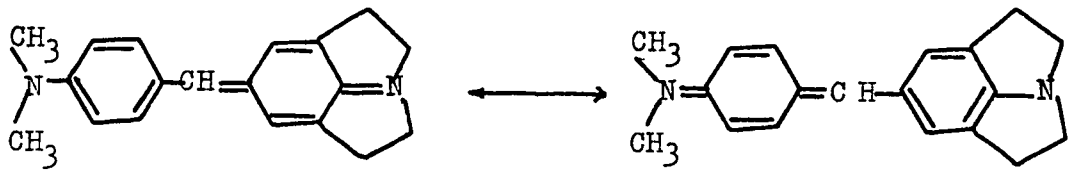
As the cyclization of the bromoamine was thought to be best accomplished in a dilute, non-polar solvent, triphenylmethyl sodium in ether was used in the first instance. This did not yield any volatile basic compound, the only product obtainable being triphenylmethane and a pale yellow glassy substance.

Bennet and Hafez (85) have reported the cyclization of o-(β-hydroxyethyl) aniline in aqueous alkaline medium and thus this method was attempted. A very slow dropwise addition of the hydrobromide solution was employed in order to maintain the concentration of the bromoamine (LXXXVI) as low as possible and thus prevent polymerization. Upon steam distillation, extraction with ether and distillation, an oil was obtained which distilled at 60-65°/0.05 mm. This oil showed either an O-H or N-H absorption band in the infrared and a λ_{max} at 318 mμ and was probably the corresponding styrene derivative. As might be expected, the yield of this product was very low, the majority of the product being the amino-alcohol.

When the bromide (LXXXVI) dissolved in dry toluene was added

to a refluxing solution of toluene containing a large excess of sodium hydride, a basic product was obtained which had an odour reminiscent of substituted amines. Upon distillation under reduced pressure, a small amount of oil was obtained but the majority of the mixture could not be distilled below 100°/.05 mm (air bath temperature). The ultraviolet spectrum of the residue resembled that of a styrene and this spectrum remained unchanged upon making the solution acidic.

The pale yellow oil which distilled at 60-70°/.05 mm (air bath temperature) solidified upon cooling and melted at 22.5-23°. This compound was found to be unstable and exposure to air slowly decomposed the compound to a brown oil which could not be redistilled. This may explain the poor elemental analysis obtained for the base, whereas the analysis of the picrate appears to be much better. The homogeneity of the freshly distilled base was determined by gas chromotography which gave a single eluted peak. It also gave a strong Ehrlich test indicative of a reactive position. It might be expected that a compound of structure LXX should be more reactive than aniline and give a product of the following structure;

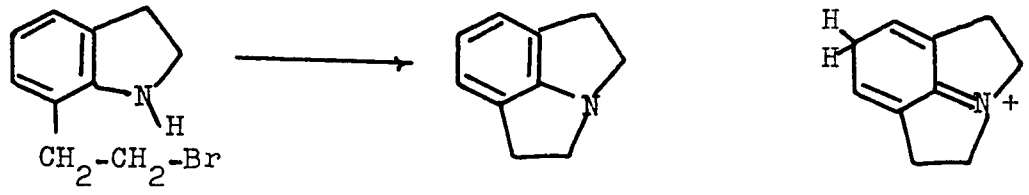


The infrared spectrum of the basic oil showed the absence of the O-H and N-H groups and the ultraviolet spectrum showed a slight shift of the λ_{max} to the longer wavelength as compared with that of

7-(2'-hydroxyethyl)-indoline (XCVII) (Fig. 10). This type of a shift might be expected of a compound such as LXX which is planar but at the same time, an increase in the intensity of absorption is also anticipated.

Potentiometric titration of the base gave an equivalent weight of 152 which is in good agreement with the equivalent weight (145) of the expected compound (LXX). Although the molecular weight was not directly measured, the high volatility of the base is only consistent with a monomeric structure. The pKa was found to be 4.9 (in water).

A disturbing piece of evidence was obtained upon making the solution strongly acidic. A yellow solution resulted and the ultraviolet spectrum indicated that the peak at 296 mμ had diminished and a strong absorption developed in the visible region at 370 mμ (Fig. 12). The intensity of this peak varied considerably over a period, increasing with time. This increase in intensity was greater during the first ten minutes and gradually slackened although even after 4 hours, the absorption seemed to be still rising. This abnormal behavior does not



LXXXVI LXX LXXa

appear to be due to a formation of a fulvene type (86, 87) ion (LXXa). The ultraviolet spectrum of the acidified solution of compound LXX (Fig. 12) shows that the protonated form has the proton on the nitrogen

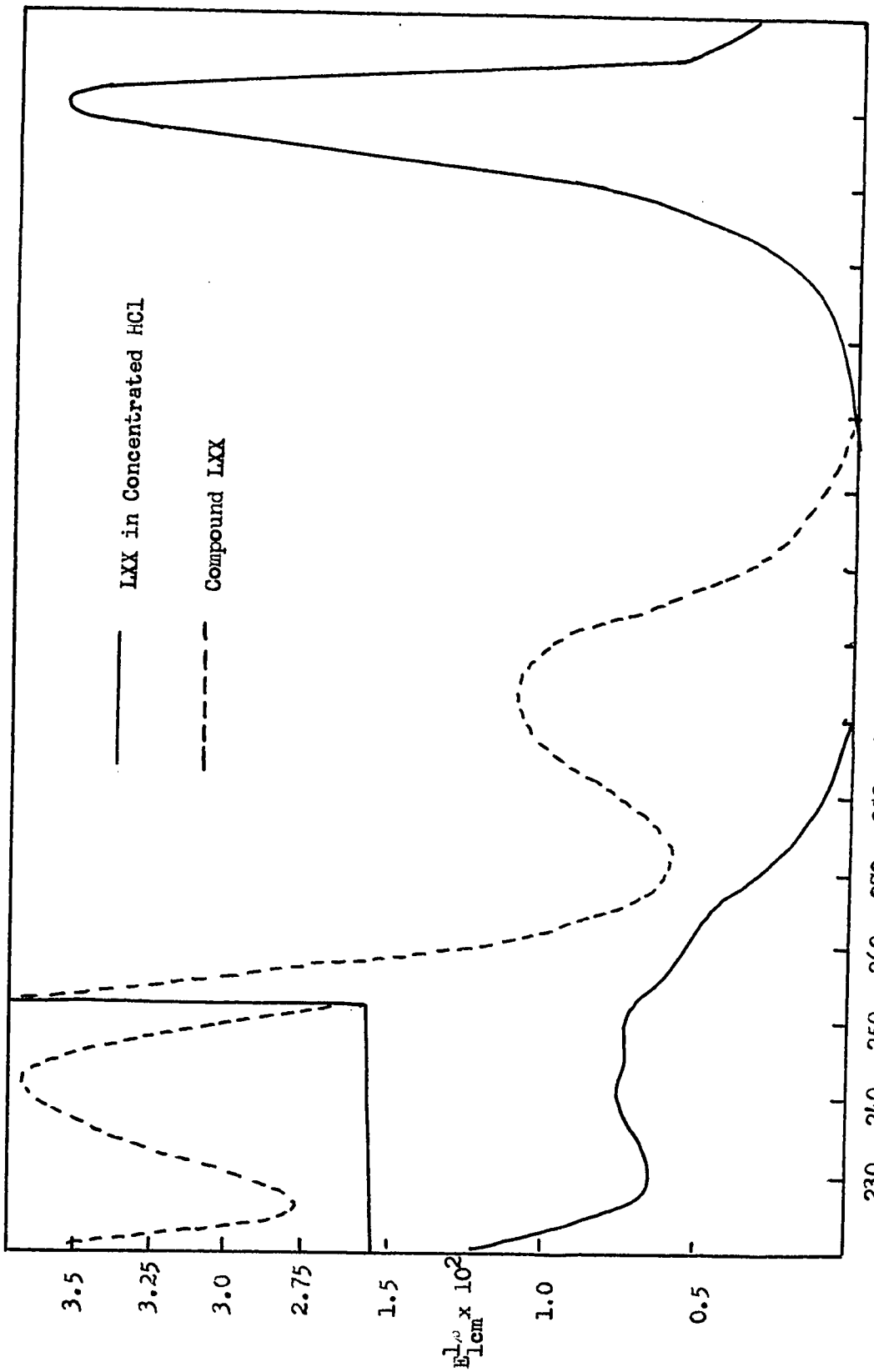

LXX in Concentrated HCl
Compound LXX
$E^{1\%}_{1cm}$ x 10^2
3.5
3.25
3.0
2.75
1.5
1.0
0.5
230
240
250
260
270
280
290
300
310
320
330
340
350
360
370
Wavelength (mμ)

Fig. 12

since the spectrum of the base disappears and only a weak absorption due to the benzene ring remains. It is difficult to explain why the yellow colour is only produced in strongly acidic solution and disappears on decreasing the pH to 0-1. The only possible explanation is that a diprotonated species is formed but this introduces other difficulties which can only be resolved by further work.

Thus, although we did not obtain enough of the base to characterize it completely, the substance obtained may well be the expected compound. The yield in the final stage was exceedingly low, but this may be expected from the numerous side reactions that can take place. It is also possible that the final product contained a small amount of the unchanged bromide which catalyzed the polymerization during the distillation giving rise to an apparent low yield. However, there is no doubt that the overall yield can be increased perhaps by another approach to the synthesis of 7-(2'-bromoethyl) indoline (LXXXVI) or of a similar compound suitable for cyclization. A fairly substantial amount of this bromoamine is necessary as the competitive reaction in the final stage is high regardless of the method employed.

EXPERIMENTAL

The ultraviolet spectra were measured on a Beckman DK-2 spectrophotometer. The infrared spectra were measured on a Perkin-Elmer single-beam double-pass instrument. The NMR spectra were recorded in carbon tetrachloride with a Varian Model V-4302 spectrometer at a fixed frequency of 60 Mc./sec. using tetramethylsilane as an internal standard (88). Signal separations were measured by the side-band technique in the usual manner.

Indoline (LXXII):

The hydrogenation of the indole was accomplished by the Clemensen reduction method (56). Amalgamated zinc was prepared by shaking a mixture of zinc dust (240 g), mercuric chloride (24 g), water (200 ml) and concentrated hydrochloric acid (10 ml) for 5 minutes. The solution was decanted and the amalgamated zinc was washed with three portions of water (100 ml).

The following reagents were added in the order given in a two-litre round bottom flask containing the amalgamated zinc; water (150 ml), concentrated hydrochloric acid (350 ml) and indole (58.5 g). The flask was fitted with a condenser with a gas absorption trap and the mixture boiled at reflux. At the beginning, the reaction was quite violent but it soon subsided to a vigorous boil. During the refluxing period of 24 hours, concentrated hydrochloric acid (50 ml) was added at 8 hour intervals.

The mixture was allowed to cool overnight and the unreacted zinc was filtered. The solution was made alkaline with concentrated ammonia and then with a solution of 50% sodium hydroxide. The alkaline solution was extracted five times with 150 ml portions of diethyl ether. The combined ether extract was dried over magnesium sulphate and the ether evaporated. The residue was distilled under reduced pressure and the fraction boiling at 115-120°/30 mm was collected. Yield, 32 g (54%). The N-benzoyl derivative melted at 119-120°. Ferber (89) reports a melting point of 118° for N-benzoylindoline.

Chloroacetyl Chloride:

Chloroacetyl chloride was prepared according to the method given by Vogel (79b) for the preparation of acid chlorides.

To monochloroacetic acid (43 g) in a cold water bath was added phosphorous trichloride (14 ml) in small portions through a dropping funnel. The flask was shaken frequently to ensure mixing of the reagents. After completion of addition, the mixture was heated in a water bath at 40-50° for 30 minutes. The product was distilled until the distilling temperature reached 110°.

The distillate was redistilled and the fraction boiling at 105-108° was collected. Yield, 10.7 g (21%). N-Chloroacetylaniline melted at 134-135°. Zincke and Kegel (90) report a melting point of 134° for this compound.

N-Chloroacetylindoline (LXXIII):

The chloroacetyl derivative of indoline was prepared according to the method of Hach and Protiva (75). Cold acetone solutions of indoline (7.2 g) and chloroacetyl chloride (2.5 g) were mixed and the resulting solution was poured into a previously prepared saturated solution of sodium acetate and stirred. The acetone layer was separated and the aqueous solution was extracted once with acetone. The combined acetone solution was dried and evaporated. The residue was crystallized from ethanol to give 10.5 g (89%) of N-chloroacetylindoline, m. p. 133-134°. Hach and Protiva (76) reported a quantitative yield of the compound, m. p. 134-135°.

Attempted Cyclization of N-Chloroacetylindoline:

Method I:

The reaction was carried out according to the method of Stolle (58) for the cyclization of chloroacetanilide.

Chloroacetylindoline (0.25 g) was mixed with purified aluminum chloride (0.25 g) and heated to 220° and held at this temperature until no further evolution of gas was noticed --- approximately 10 minutes. The dark reddish mass was cooled and crushed ice was added and stirred until the solid had completely dissolved. The mixture was extracted with chloroform and the extract was washed with water, dried and the solvent evaporated. The residue was taken up in hot ethanol and cooled to yield crystals, m. p. 130-133°. After several recrystallizations, the crystals had m. p. 134°. This compound was found to be identical in all respects with the starting material.

The residue from the hot ethanol extraction was soluble in chloroform but not in ether. Efforts to obtain a crystalline product by means of column chromatography failed. This amorphous material gave a positive test for indole (Ehrlich test) and the infrared spectrum had an absorption band (1692 cm^{-1} in Nujol) characteristic of a five-membered cyclic amide. The amorphous substance was non-volatile and thus it was probably polymeric in nature.

The ethanol solution, after precipitation of the N-chloro-acetylindoline was evaporated and the residue was taken up in a small amount of methanol. After five recrystallizations, a small amount of crystals, m. p. 101° was obtained. Admixture of this substance with N-acetylindoline caused no depression in the melting point.

The other Friedel and Crafts reactions were carried out in

TABLE I

Trial	Reaction Time	Weight Chloro Compd.	Weight $AlCl_3$	Temp.	Products
1	140 min.	0.2 g	0.1 g	160°	S
2	140	0.2	0.15	160	S
3	140	0.2	0.2	160	S
4	50	0.2	0.1	220	S T A
5	50	0.2	0.2	220	S T A
6	50	0.2	0.4	220	S T A
7	30	0.2	0.4	220	S T A
8	5	0.2	0.2	220	S T A
9	30	0.2	0.2	250	S T A

S - Starting material, T - Tar, A - N-acetylindoline

the analogous manner except for the change in reaction temperature, duration of heating and the ratio of the aluminum chloride to the chloroacetylindoline, as shown in Table I. The tar was repeatedly trituated with ethanol and diethyl ether and the extracts were carefully examined for a product containing the five-membered cyclic amide but none was detected.

Method II:

N-Chloroacetylindoline (0.2 g) was refluxed in 99% formic acid but there was no evidence of chloride ions after two hours. Potassium iodide was added to the reaction mixture and the solution refluxed for another 22 hours. It was cooled and made slightly acidic by the slow addition of concentrated hydrochloric acid. The solution was extracted with chloroform and washed with water. The chloroform extract was dried and evaporated. An infrared analysis of the crude showed no absorption corresponding to the five-membered cyclic amide. Consequently, the tar was not worked.

N-Acetylindoline:

The preparation of N-acetylindoline was essentially the same as that for N-chloroacetylindoline.

An acetone solution of acetyl chloride (0.8 g) and of indoline (1.2 g) were mixed in the cold. The cold solution was poured into a saturated solution of sodium acetate, stirred and the acetone layer was separated. The acetone solution was dried and evaporated and the residue was crystallized from methanol to give 1.5 g (93%) of needles, m. p.

101-102°. The melting point reported by Bennet and Hafez (86) is 105°. Farbenfabriken Bayer (91) reports a melting point of 102-103°.

N-Trichloroacetylindoline (LXXVI):

A solution of indoline (1.5 g) in diethyl ether and a solution of trichloroacetyl chloride (2.3 g) in ether were cooled. The cold solutions were mixed and poured into a saturated solution of sodium acetate and stirred. Crystallization from petroleum ether (30-65°) gave 2.8 g (84%) of N-trichloroacetylindoline, m. p. 72.5-73.5°.

Attempted Cyclization of N-Trichloroacetylindoline:

Method I:

N-Trichloroacetylindoline (0.2 g) was dissolved in carbon disulphide and stirred in the presence of purified aluminum chloride for 4 hours at room temperature. At the end of this time the solvent was evaporated and the residue was crystallized from petroleum ether (30-65°) to give needles, m. p. 72.5-73°. Mixed-melting-point determination with the starting material gave no depression.

Method II:

N-Trichloroacetylindoline (0.2 g) was heated with purified aluminum chloride (0.4 g) at 110° for 10 minutes. After cooling, cracked ice was added and the aqueous solution was extracted with chloroform. The chloroform solution was washed with water, dried and evaporated. The orange residue was slightly soluble in ether and alcohol.

An orange amorphous substance was precipitated from the chloroform solution by the addition of petroleum ether (30-65°). This material did not melt below 310°.

N-Nitrosoindoline:

Concentrated hydrochloric acid (12 ml) and indoline (10 g) were placed in a large beaker along with some crushed ice. The beaker was surrounded by an ice-salt bath. When the temperature of the acid solution had dropped to -5°, a cold solution of sodium nitrite (6 g) in water (25 ml) was added with efficient stirring at such a rate that the temperature did not rise much over 0°. After completion of addition of the sodium nitrite solution, the mixture was stirred at 0° for an additional 30 minutes. The mixture was filtered and washed several times with cold water. The yellowish solid was crystallized from aqueous methanol to yield yellow flakes. Yield, 11.5 g (93%), m. p. 84-84.5°. Ruggli et al. (92) report a m. p. of 82-83°. Plancher and Ravenna (93) report a m. p. of 83-84°.

N-Aminoindoline:

N-Nitrosoindoline (12.0 g) was reduced by adding the ether solution of the nitroso-compound to a solution of lithium aluminum hydride in ether. After completion of addition of the nitrosoindoline, the mixture was refluxed for 30 minutes and then cooled.

The excess lithium aluminum hydride was destroyed and a 10% solution of sodium hydroxide solution (20 ml) was added and the mixture

filtered. The residue was washed with ether and the combined ether solution was dried and evaporated. The resulting oily residue was distilled under reduced pressure and the fraction distilling at 88-91°/ 0.7 mm was collected. Yield, 5 g (46%), n_D^{18} = 1.5950.

Reaction of N-Aminoindoline with Cyclohexanone:

The hydrazine (1.0 g) was added to an alcoholic solution of cyclohexanone (1.0 g). Two drops of concentrated hydrochloric acid were added and the solution warmed for five minutes. Upon cooling, a solid mass was obtained which, after recrystallization from ethanol, afforded a quantitative yield of crystals melting at 155-156°.

The same reaction was carried out without the use of an acid catalyst. A comparable yield of the same compound was obtained after refluxing for 1 hour.

Lions and Ritchie (40) report a melting point of 154° (picrate 141°) for a compound obtained by the reductive treatment of N-nitroso-indoline in the presence of cyclohexanone.

Reaction of N-Nitrosoindoline with Cyclohexanone:

The method given by Lions and Ritchie (41) was followed for this preparation.

Nitrosoindoline (0.2 g) and cyclohexanone (0.2 g) were dissolved in glacial acetic acid and placed in an ice bath. Powdered zinc (1.0 g) was added in small portions while stirring rapidly. After

completion of addition, the ice bath was removed and the mixture stirred for another 30 minutes. The zinc was filtered and allowed to stand overnight.

The solution was heated on a steam cone for 1 hour and water was added. The precipitate was filtered and crystallized from petroleum ether (30-65°) to yield crystals melting at 153-154°.

A mixed-melting-point determination with the product from the N-aminoindoline experiment showed the two compounds to be identical in all respects.

Isobutylphenylhydrazide (LXXVII):

The hydrazide was prepared according to the method of Brunner (59).

An equimolar proportion of redistilled phenylhydrazine (36 g) and isobutyric acid (29.4 g) were heated at 130° for 3 hours and allowed to cool. To the thoroughly cooled mixture, water was added and the solid was well triturated. The resulting slurry was filtered and the reddish mass was air dried. The dried solid was suspended in ether, filtered, washed with ether and crystallized from ethanol to give a compound melting at 140° after drying over sulphuric acid in a vacuum dessicator. Yield, 29.9 g (56%).

3,3-Dimethyloxindole:

The cyclization of the phenylhydrazide was carried out accord-

ing to the method of Brunner (59). An intimate mixture of isobutylphenylhydrazide (15 g) and freshly ignited calcium oxide (45 g) was placed in a round bottom flask and heated in an oil bath for 3 hours at 190-200° with frequent stirring.

The light brown mass was cooled and water (10 ml) and concentrated hydrochloric acid were added until most of the solid had dissolved. The mixture was heated under reflux for 1 hour, cooled and filtered. The crystals were washed repeatedly with water and air dried.

The dried greyish mass was dissolved in ether and filtered. The filtrate was evaporated and the residue was taken up in benzene. On cooling, 8.2 g (61%) of prisms, m. p. 152° were obtained. Brunner (59) reports a melting point of 151°. Kates and Marion (94) have reported a m. p. of 152.5-153°.

3,3-Dimethylindoline (LXXIX):

Reduction of the oxindole was accomplished according to Kates and Marion (94) except that tetrahydrofuran was used as solvent instead of dioxane. The dimethyloxindole (12 g) was dissolved in tetrahydrofuran and added dropwise to a stirred solution of lithium aluminum hydride (5 g) in tetrahydrofuran. After completion of addition, the solution was heated at reflux for 10 minutes. After cooling in a water bath, water was added carefully to the mechanically stirred solution to destroy the excess lithium aluminum hydride.

The solution was filtered and the residue was washed with

tetrahydrofuran. The combined tetrahydrofuran solution was evaporated to dryness and the residue taken up in ether. The ether solution was extracted with 6 N hydrochloric acid. The aqueous hydrochloric acid solution was made alkaline and extracted with ether. The ether solution was dried and evaporated. After several recrystallizations from petroleum ether (30-65°), long needles, m. p. 36°, having a sweet, ester-like odour were obtained. Yield, 10.6 g (97%). Kates and Marion (94) report a yield of 82%, m. p. 34-34.5°.

N-Chloroacetyl-3,3-Dimethylindoline (LXXX):

3,3-Dimethylindoline (10.9 g) and chloroacetyl chloride (8.5 g) were dissolved separately in acetone and allowed to cool. The cold solutions were mixed and poured into a saturated solution (50 ml) of sodium acetate and stirred. The acetone solution was separated and the aqueous sodium acetate solution was extracted several times with acetone and the combined extract was dried and evaporated to one-half volume and cooled. Plates melting at 113° were obtained after recrystallization from acetone. Yield, 14.1 g (85%).

Cyclization of N-Chloroacetyl-3,3-Dimethylindoline:

Chloroacetyl-3,3-dimethylindoline (2.0 g) was treated with purified aluminum chloride (6.0 g) at 220-230° for 10 minutes with constant stirring, after which time no further evolution of gas was observed. The hot liquid was poured into a mortar so as to form a thin film. After cooling, the brittle solid was ground and ice (20 g) was

added while mixing.

The aqueous solution was extracted with chloroform, dried and evaporated. The residue was taken up in a small volume of acetone and allowed to cool when the unchanged starting material crystallized. The acetone was evaporated and the residue was taken up in petroleum ether (30-65°). After numerous crystallizations from petroleum ether (30-65°) a product having a melting point of 78.5-80° was obtained.

A purer product was obtained by filtering the solid substance insoluble in water and recrystallizing from petroleum ether (30-65°). This procedure gave a product melting sharply at 54-55°. However, after repeated recrystallizations from this solvent or upon standing for about one week in the refrigerator, a product of melting point 78.5-80° was obtained. Further recrystallizations did not change the melting point.

The yield seemed to vary with each run, the best yield being 30%. Sublimation and chromatography were tried to get a faster separation of the products but these methods were not successful. Finally, it was decided to remove the unchanged material by dissolving in hot water and fractionally crystallizing the residue from petroleum ether (30-65°). Calc. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48%. Found: C, 77.04; H, 6.80; N, 7.40%.

The ultraviolet spectrum showed a λ_{max} at 253 mμ, log ϵ = 4.00 and 284 mμ, log ϵ = 3.27. The infrared spectrum had an absorption at 1692 cm^{-1} (Nujol) corresponding to a five-membered cyclic amide.

Reduction of the Oxindole:

The oxindole compound (m. p. 78-80°) was reduced with lithium aluminum hydride. The oxindole (1.0 g) was dissolved in redistilled tetrahydrofuran and placed in a dropping funnel. After refluxing the lithium aluminum hydride (1.0 g) in tetrahydrofuran for 10 minutes, the solution containing the oxindole compound was added dropwise with constant stirring. After completion of addition, the reaction mixture was refluxed for a further 10 minutes and cooled. The excess lithium aluminum hydride was decomposed by a slow addition of water to the reaction mixture, with good mechanical stirring. The slurry was filtered and the residue was washed several times with tetrahydrofuran. The combined extract was evaporated to dryness and the residue taken up in ether, The base was extracted with 6N hydrochloric acid. The aqueous acid solution was made alkaline and extracted with ether. The infrared spectrum of the residual base after evaporation of the solvent showed a N-H absorption band. The mixture was therefore acetylated and an acid-base extraction was carried out again. Evaporation of the ether extract of the aqueous alkaline solution yielded a yellow oil which distilled at 61-62°/0.15-0.1 mm. The yield was 0.5 g (54%). The base exhibited a maximum absorption in the ultraviolet at 300 mμ, log ϵ = 5.31 and 251 mμ, log ϵ = 5.80. The infrared spectrum showed no N-H or carbonyl absorption band. It showed a band at 1377 cm^{-1} corresponding to a C-methyl group. The pK_a measured spectroscopically (95) was 4.90. n_D^{20} = 1.5752. Calc. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09%. Found: C, 82.99; H, 8.72; N, 8.00%.

The hydrochloride from acetone melted at 148-149.5° and the

picrate recrystallized from methanol had a m. p. 164.5-166°. Calc. for $C_{12}H_{15}N \cdot C_6H_3N_3O_7$: C, 53.73; H, 4.51%. Found: C, 53.97; H, 4.38%.

α-Methylacrolein Diacetate:

α-Methylacrolein diacetate was prepared according to the method of Brant and Conklin (96).

A mixture of acetic anhydride (90 g) and stannous chloride (16 g) was added slowly to α-methylacrolein (56 g) such that the temperature of the reaction mixture did not rise above 10°. After completion of addition, the mixture was allowed to stand at room temperature for 10 hours.

The crude mixture was washed with cold sodium bicarbonate solution and then with water until neutral. The crude diacetate which separated from the aqueous solution was dried and distilled under vacuum. The fraction distilling at 58-60°/0.6 mm was collected. Yield, 32.8 g (24%).

3-Methylquinoline:

3-Methylquinoline was prepared according to the method of Utermohlen Jr. (97).

Nitrobenzene (197 g) was sulphonated by running it into 20% oleum (880 g) at 20-30°. The temperature of the reaction mixture was gradually raised to 60-70° over a period of 3 hours and maintained at this temperature for an additional 6 to 8 hours until a sample was

completely soluble in water.

α-Methylacrolein diacetate (16.4 g) was added dropwise to the following solution held at 125°. Nitrobenzenesulphonic acid (67 g) was poured into water (20 ml) in a three-necked flask with stirring and aniline (16 g) was added. The apparatus was set up so that water and acetic acid could be removed during the addition of the diacetate.

After completion of addition of the diacetate, the temperature of the reaction mixture was raised to 175° and held at this temperature for 3 hours. The mixture was partially cooled and poured into ice (50 g) and made slightly alkaline with 50% sodium hydroxide. The crude mixture was steam distilled and the distillate which formed two layers was separated. The water layer was extracted with ether and combined with the organic phase. The combined extract was dried and the fraction distilling at 255-257° was collected. $n_D^{22} = 1.6112$. Yield, 3.4 g (25%). Utermohlen (97) reports a yield of 49%. The picrate was crystallized from ethanol, m. p. 188°. Utermohlen (97) reports a m. p. of 187.5° for the picrate.

3-Methyl-1,2,3,4-Tetrahydroquinoline:

3-Methylquinoline (2.0 g) was hydrogenated under a hydrogen pressure of 60 psi using 1 teaspoon of "W-6" Raney nickel catalyst according to the method of Adkins and Billica (98).

The catalyst was filtered after 2 hours of shaking and the solvent evaporated. The residue was distilled under reduced pressure

and the fraction distilling at 134-138°/10-15 mm was collected. The total yield was 1.3 g (63%). The picrate, crystallized from ethanol melted at 171.5-173° which corresponds to the picrate of 3-methyl-5,6,7,8-tetrahydroquinoline (99). However, the ultraviolet spectrum of the distillate resembled that of substituted aniline rather than that of a substituted pyridine. No attempt was made to separate the two isomers at this stage.

N-Chloroacetyl-3-Methyl-1,2,3,4-Tetrahydroquinoline:

A cooled solution of the above mixture of tetrahydroquinolines (1.0 g) in acetone and chloroacetyl chloride (0.8 g) in acetone were added and the mixture poured into a saturated solution of sodium acetate. The acetone layer was separated and the acetone evaporated. The residue was taken up in ether, washed with water to remove traces of sodium acetate and the ethereal solution was extracted with 5% hydrochloric acid to remove the unreacted 3-methyl-5,6,7,8-tetrahydroquinoline. The ether solution was washed with water, dried and evaporated to dryness leaving a yellow oil. The oil was distilled under reduced pressure and the fraction distilling at 135-140°/0.03 mm was collected. The yellow oil crystallized on standing. Yield, 7 g (44%).

N-Chloroacetyl-3-methyl-1,2,3,4-tetrahydroquinoline (0.2 g) was hydrolyzed in boiling 2% sodium hydroxide and the aqueous solution was extracted with ether. The ether solution was dried and evaporated to a small volume. To one-half the volume was added a solution of picric acid in ether. The picrate which precipitated immediately or recrystal-

lization from ethanol-ether yielded crystals melting at 156°. Braun et al. (99) report a m. p. of 155° for the picrate.

The other half of the ether solution was evaporated to dryness. The residue was taken up in a small amount of ethanol and two drops of concentrated hydrochloric acid were added and stirred. Upon addition of a small amount of diethyl ether, crystals of hydrochloride were obtained which melted at 206°. The melting point reported by Braun et al. (99) is 207°.

Cyclization of N-Chloroacetyl-3-Methyl-1,2,3,4-Tetrahydroquinoline:

The chloroacetyl derivative of the tetrahydroquinoline (0.2 g) was added to purified aluminum chloride (0.4 g). The mixture was heated gradually to 150° and held at this temperature for 5 minutes and cooled. Crushed ice was added to the cooled solid and the resulting mixture was extracted with carbon tetrachloride. The carbon tetrachloride solution was washed, dried and evaporated. The residue was taken up in petroleum ether (30-65°) and cooled. The fluffy white precipitate was recrystallized from a small amount of ethanol to give needles melting at 133.5-134°. Yield, 0.09 g (54%). Calc. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00%. Found: C, 76.21, 76.91; H, 6.84, 7.03%.

2-Methyl-1,2,3,4-Tetrahydroquinoline:

The redistilled 2-methylquinoline (11.6 g) was dissolved in ethanol (100 ml) and 7 times excess of sodium (50 g) was added as rapidly as possible. The mixture was then heated until all the sodium had dis-

solved.

The solution was cooled to about 50° and water was added. The cooled alkaline solution was extracted with ether and the ether solution was washed with water, dried over magnesium sulphate and evaporated. The residue was distilled under reduced pressure and the fraction distilling at 84-85°/1.1 mm was collected. Yield, 9.72 g (81%). n_D^{23} = 1.5710. Oldham and Jones (100) report a yield of 70%, b. p. 125°/17 mm.

N-Chloroacetyl-2-Methyl-1,2,3,4-Tetrahydroquinoline:

The cold solutions of 2-methyl-1,2,3,4-tetrahydroquinoline (3.0 g) in acetone and chloroacetyl chloride (2.3 g) in acetone were mixed and the mixture poured into a saturated solution of sodium acetate. The mixture was stirred well and the acetone layer was separated and the solvent evaporated. The residue was taken up in ether, washed with dilute hydrochloric acid followed by water, dried and evaporated. The oil was used directly in the next experiment without further purification.

Cyclization of N-Chloroacetyl-2-Methyl-1,2,3,4-Tetrahydroquinoline:

The above oil (0.2 g) was added to purified aluminum chloride (0.4 g) and mixed. The mixture was heated to 200° and held at this temperature for 10 minutes. After cooling, crushed ice was added and the aqueous solution was extracted with carbon tetrachloride. Carbon tetrachloride was evaporated and the residue taken up in petroleum ether (30-65°) and cooled. An oil deposited which on stirring crystallized.

The solid was recrystallized several times from petroleum ether (30-65°) to give crystals, m. p. 56-57.5°. Calc. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00%. Found: C, 77.12; H, 7.03%.

4-Methyl-1,2,3,4-Tetrahydroquinoline:

The redistilled 4-methylquinoline (10 g) was reduced with sodium and ethanol in the same manner as for the reduction of 2-methylquinoline. The ether extract of the alkaline solution was washed, dried and evaporated to leave an oily residue. The oil was distilled under reduced pressure and the fraction distilling at 80-85°/0.6 mm was collected. Braun et al. (99) report a boiling point of 130°/12 mm.

The oil gave a N-H absorption band in the infrared and the ultraviolet spectrum exhibited similar properties to that of aniline.

N-Chloroacetyl-4-Methyl-1,2,3,4-Tetrahydroquinoline:

The 4-methyl-1,2,3,4-tetrahydroquinoline (3.0 g) was chloroacetylated with chloroacetyl chloride (2.5 g) in the same manner as for 2-methyl-1,2,3,4-tetrahydroquinoline. The residue after evaporation of acetone was taken up in ether and extracted with 5% hydrochloric acid. The ethereal solution was washed, dried and evaporated. The residue was not purified further but put into the following reaction.

The infrared spectrum showed the absence of a N-H absorption band and the ultraviolet spectrum was similar to that of other N-chloroacetyl derivatives.

Cyclization of N-Chloroacetyl-4-Methyl-1,2,3,4-Tetrahydroquinoline:

The cyclization was carried out as in the previous Friedel and Crafts reaction. The crude product after the evaporation of carbon tetrachloride was taken up in petroleum ether (30-65°) and cooled to yield fluffy white precipitate melting at 45-50°. After several recrystallizations from this solvent, the melting point rose to 52°. The precipitate was allowed to sit in the refrigerator for several days after which time the crystal structure had changed and the product after one recrystallization melted at 78.5-79.5°. Mixed-melting-point determination with the cyclization product of N-chloroacetyl-3,3-dimethylindoline showed the two compounds to be identical. The infrared spectra of the two compounds were also identical in all respects.

2-Nitroisophthalic Acid (LXXXVIII):

The nitroisophthalic acid was prepared according to the method of Noelting and Gachot (77).

Potassium permanganate (405 g) was added in small portions (2-5 g) to a well stirred, boiling solution of 2,6-dimethylnitrobenzene (50 g) and sodium carbonate (50 g) in water (4 l). After completion of addition of the potassium permanganate, the mixture was refluxed for an additional 12 hours with good mechanical stirring.

At the end of this time, the slightly pink colour of the potassium permanganate was destroyed by the addition of sodium bisulphite and the mixture was filtered hot. The residue was washed several times with

hot water and the filtrates were combined. The clear, colourless solution was cooled and made acidic with concentrated hydrochloric acid. The crystals which precipitated were filtered and washed with cold water. The organic acid was crystallized from methanol to yield 38.1 g (55%), m. p. 320-322° (decomp.). Another 6 g was recovered from the mother liquor. Noelting and Gachot (77) report a m. p. of 310-312°. Huisinga (78) reports a melting point of 300°.

The dimethyl ester of the acid, prepared by the addition of the ether solution of the acid to an ethereal solution of diazomethane, crystallized as needles, m. p. 144°. Noelting and Gachot (77) report a melting point of 135°.

2-Nitroisophthalyl Chloride (LXXXIX):

The acid chloride was prepared using thionyl chloride which was purified according to the method given by Vogel (79c). Purified thionyl chloride (35 ml) was added to 2-nitroisophthalic acid (20 g) and the whole was refluxed overnight with a drop of pyridine. A clear green solution resulted and, upon cooling, yielded a solid mass which was filtered and washed with cold carbon tetrachloride. These manipulations yielded white crystals melting at 128-130° which were pure enough for the subsequent reaction. Yield, 21.1 g (90%). Calc. for $C_8H_3Cl_2NO_4$: Cl, 28.63%. Found: Cl, 28.28%.

1,3-Bisdiazoacetyl-2-Nitrobenzene (CX):

A solution of the above acid chloride (20 g) in tetrahydrofuran

was added dropwise to a well stirred solution of diazomethane in ether kept at 0° in an ice-salt bath. One molar excess of the diazomethane was used. The mixture was allowed to stand overnight and the precipitate was filtered and recrystallized from chloroform:benzene (1:1) to yield needles melting at 105° (decomp.). However, the bulk of the bisdiazoketone was not recrystallized but put directly into the next reaction. The yield of the crude diazoketone was 19 g (91%). Calc. for $C_{10}H_5N_5O_4$: N, 27.02%. Found: N, 23.17%.

Wolff Rearrangement of Bisdiazoketone:

Method I:

The bisdiazoketone (2.6 g) was dissolved in dioxane (150 ml) and added dropwise with stirring to a water suspension (100 ml) containing freshly precipitated silver oxide (1.0 g), sodium thiosulphate (1.0 g) and anhydrous sodium carbonate (1.5 g) at 70° (80a). The stirring was continued for 1 hour after completion of addition and the temperature was gradually raised to the boiling point. The reaction mixture was cooled and acidified with dilute nitric acid. The acid solution was extracted with ethyl acetate and the solvent evaporated after drying. The red residue was taken up in ethanol and after several recrystallizations from ethanol, a compound having a melting point of 215° was isolated in very low yield (15%). The neutralization equivalent of this acid was found to be 116.5.

Methylation of the dicarboxylic acid with diazomethane yielded needles from ethanol, melting at 144.5-145°.

Method II:

The bisdiazoketone (1.0 g) was dissolved in 99.9% methanol (35 ml) and heated to 65°. A slurry of silver oxide (0.3 g) in methanol (10 ml) was added with stirring over an interval of 30 minutes (80). Nitrogen was evolved and the solution became dark brown due to the precipitation of metallic silver. After no further evolution of nitrogen was noticed, Norite was added and the mixture was heated at reflux for 1 hour and filtered hot. Upon cooling, needle-like plates were obtained which upon recrystallization from methanol, melted at 144-145°. Yield, 0.4 g (51%).

Mixed-melting-point determination with the esterified acid obtained in the Wolff rearrangement, Method I, did not lower the melting point.

Method III:

The bisdiazoketone (1.0 g) was dissolved in warm absolute methanol (60 ml). A solution of silver benzoate (1.0 g) in triethylamine (9.0 g) was prepared and filtered to remove any suspension (82). The benzoate solution was added in small portions to the well stirred solution of the bisdiazoketone at 60°. The reaction mixture turned dark brown and the evolution of nitrogen soon commenced. As soon as the evolution of the gas slackened, a new portion of the silver benzoate solution was added. This was continued until no further evolution of the gas was noticed and then heated for a further 1 hour at reflux with Norite and filtered hot. The solvent was evaporated and the residue

was taken up in ether. An acid-base extraction of the ether solution yielded a compound having a m. p. of 89-90° in a yield of 0.2 g (26%) from ethanol.

Method IV:

The benzyl alcohol used in this experiment was purified by shaking with saturated solution of sodium bisulphite for 1 hour and allowing it to stand overnight (81). It was then shaken with 45% potassium hydroxide and dried over potassium carbonate and distilled at 92-94°/12 mm.

The diazoketone (1.0 g) was dissolved in the purified benzyl alcohol (5 ml) and the solution was rapidly heated to the reaction temperature by immersing it in an oil bath preheated to 170-190°. After 1 minute, a slow evolution of gas was noticed. After 10 minutes of heating, the mixture was cooled and the nitro-compound was hydrolyzed with hydrochloric acid (10 ml) and acetic acid (10 ml) for 20 hours. The solution was evaporated to a small volume and extracted with 10% sodium hydroxide and the aqueous alkaline solution was acidified and extracted with ether. This yielded a small amount (10%) of an acid melting at 210-212°.

In an effort to improve this yield, a mixture of benzyl alcohol (5 ml) and dimethylaniline (5 ml) was used as solvent but no appreciable improvement was obtained.

Method V:

In a method slightly modified from that of Newman and Beal (82),

the slurry of silver benzoate in methanol was added in small portions to a well stirred solution of bisdiazoketone (24 g) in absolute methanol (200 ml). When no further evolution of nitrogen gas was observed upon addition of silver benzoate, Norite was added and refluxed for another 30 minutes.

The hot solution was filtered and the alcoholic solution was allowed to cool. The crystals were filtered and the mother liquor was evaporated to yield further quantities of the diester. Yield, 14 g (54%), m. p. 144-145°. Calc. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90%. Found: C, 53.92; H, 4.84%.

"W-6" Raney Nickel:

This especially active Raney nickel was prepared according to the method of Adkins and Billica (84). Sodium hydroxide (160 g) and water (600 ml) were placed in a three litre beaker equipped with a thermometer and a stirrer (non-sparking). With the solution maintained at 50-52°, Raney nickel-aluminum alloy (125 g) was added in small portions. After completion of addition of the alloy the mixture was digested at 50° for 15 minutes. It was then washed three times by decantation with distilled water and transferred immediately to the washing tube.

With the system under a slight hydrogen pressure, the catalyst was washed with distilled water (approximately 15 l). The water was decanted and washed three times with 95% ethanol with stirring (not shaking). Finally, it was washed three times with absolute ethanol and

stored under absolute ethanol in the refrigerator.

Reduction of the Methyl Ester of 2-Nitrophenyl-1,3-Diacetic Acid:

Method I:

The reduction of the nitro group was attempted by the method of Fletcher and Namking (83), slightly modified for our purpose. The nitro-ester (1.0 g) was dissolved in ethanol (100 ml) by heating on a steam bath. When the nitro-compound was completely in solution, 98% hydrazine (1 ml) was carefully added and stirred. Fresh Raney nickel was added immediately in small portions, and although a violent evolution of nitrogen was expected, only a small amount of gas was given off. After several more portions of Raney nickel had been added, the solution was heated at reflux but no appreciable amount of nitrogen was evolved. At reflux temperature, palladium on charcoal was next added but still the evolution of the gas was only slight. Finally, rhodium on carbon was added which increased the rate of evolution somewhat.

The reaction mixture was heated at reflux overnight after which time the vapours were no longer basic. The solution was filtered, evaporated and the residue was taken up in ether. The ether extract upon evaporation of the solvent yielded a red tar which was soluble in ethanol. Despite much effort, no crystallizable compound was obtained.

Method II:

Several conditions of reduction of the nitro-compound were attempted using Adams' catalyst. In every case, the nitro-compound (1.0 g)

was dissolved in glacial acetic acid and put under a hydrogen pressure of 50 psi.

TABLE II

Trial	Time of Reaction	Temperature
1	30 min.	R. T.
2	30	60°
3	60	60
4	90	60

The catalyst was filtered and the filtrate was evaporated to dryness. The residue was then crystallized from ethanol. The best yield (32%) was obtained under conditions of Trial No. 4. Under these conditions, approximately 50% of the starting material (0.45 g) was isolated unchanged. The remainder was recrystallized several times from ethanol but the melting point was not sharp (145-153°). The infrared spectrum showed a single carbonyl absorption at 1692 cm^{-1} (60) and the ultraviolet spectrum was reminiscent of the oxindole spectrum.

When the compound melting at 149-153° was taken up in alkali and acidified, a compound melting at 225° separated in fine needles. The ultraviolet and the infrared spectra of the new compound were similar to that of the starting material. This compound was identical in all respects with the hydrogenation product of 2-nitrophenyl-1,3-diacetic acid.

Method III:

The specially prepared "W-6" Raney nickel (1 teaspoon) and acetic acid (1 ml) were added to a suspension of the above nitro-ester (8.6 g) in methanol. The mixture was put under a hydrogen pressure of 50 psi and shaken overnight.

The alcoholic solution was treated with Norite and filtered. The solvent was evaporated to one-half volume and cooled. The crystals were filtered and recrystallized from tetrahydrofuran to yield the oxindole-ester which melted at 153-154°. Yield, 5.0 g (76%). Calc. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40%. Found: C, 64.86; H, 5.51%.

Similar treatment with "W-6" Raney nickel of 2-nitrophenyl-1,3-diacetic acid yielded needles, m. p. 225°, identical with the product obtained from the hydrolysis of the corresponding methyl ester.

Reduction of the Methyl Ester of Oxindole-7-Acetic Acid:

Method I:

The oxindole-ester (3.8 g) was dissolved in dioxane-ether and added dropwise to a refluxing solution of ether containing lithium aluminum hydride (1.0 g). After completion of addition, the mixture was refluxed for a further 1 hour and cooled. The excess lithium aluminum hydride was decomposed by a careful addition of water. The resulting mixture was filtered and the residue was washed several times with hot dioxane. The filtrate was evaporated to dryness and the residue was taken up in ether. An acid-base separation of the ether solution yielded

a base having a m. p. of 96-97° in a yield of 0.2 g from benzene. It showed a N-H and O-H absorption peaks in the infrared and an absence of the carbonyl band. The ultraviolet spectrum was similar to that of aniline. However, the majority of the product was a reddish, non-basic compound having a melting point of 148-149°. This compound, which exhibited a typical oxindole spectrum was 7-(2'-hydroxyethyl) oxindole. Calc. for $C_{10}H_{13}NO$: C, 67.78; H, 6.28%. Found: C, 67.42; H, 6.17%.

Several other solvent systems such as dimethoxyethane and tetrahydrofuran were used but the yield of the base was negligible. The following procedure was finally adopted as the best method for the reduction of the oxindole-ester.

Method II:

A solution of lithium aluminum hydride in tetrahydrofuran was prepared by refluxing the metal hydride in redistilled tetrahydrofuran. The filtration of the resulting solution proved to be very difficult, consequently the solution was allowed to settle and the clear supernatant liquid was decanted into the reaction vessel.

The reaction vessel was equipped with a dropping funnel, magnetic stirrer and a condenser. A solution of the oxindole (10 g) in freshly distilled tetrahydrofuran was placed in the dropping funnel and the solution was slowly added to a refluxing solution containing a large excess of lithium aluminum hydride. After completion of addition of the oxindole-ester, the mixture was allowed to reflux for another 30 minutes and then cooled. The magnetic stirrer was replaced by a good

mechanical stirrer and the flask was cooled in an ice-salt bath. Water was added cautiously to the reaction mixture to decompose the excess lithium aluminum hydride. The resulting slurry was filtered and the residue was washed well with tetrahydrofuran. The combined filtrate was evaporated to dryness and the residue was taken up in diethyl ether. Diethyl ether dissolved most of the residue and an acid-base separation carried out on the ether soluble portion yielded a neutral and a basic substance. Various tests such as the Ehrlich test, infrared and ultraviolet spectral analysis indicated that the ether insoluble compound was an oxindole alcohol, 7-(2'-hydroxyethyl) oxindole, m. p. 148-149°, while the neutral fraction was 7-(2'-hydroxyethyl) indole. The basic substance was the fully reduced 7-(2'-hydroxyethyl) indoline but the yield of this substance was very low, the majority of the product being the oxindole alcohol. Although many modifications of this reaction were carried out, the yield of the basic alcohol could not be obtained after the first trial.

The above mixture was then treated with sodium in boiling isopropyl alcohol to reduce the oxindole to the indole. After completion of addition of the sodium, the mixture was refluxed for another 1 hour to completely dissolve the sodium and then cooled to 60° and water was added. The cooled solution was extracted with ether and the solvent evaporated.

The infrared and ultraviolet spectra of the crude product taken up in ether indicated that the majority of the product was 7-(2'-hydroxyethyl) indole. This indole derivative was further reduced with

zinc amalgam and hydrochloric acid as previously described for the reduction of indole. The diethyl ether extract of the mixture was washed and evaporated to dryness. After many recrystallizations from petroleum ether (30-65°):diethyl ether (1:1) the final product melted at 63-64°, b. p. 70°/0.2 mm. The overal yield from the oxindole-ester to the 7-(2'-hydroxyethyl) indoline was 26%. The ultraviolet spectrum resembled that of aniline with λ_{max} at 292 mμ, log ε = 3.32 and 242 mμ, log ε = 3.77. Calc. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03%. Found: C, 73.29; H, 8.13%.

The picrate prepared in the usual manner from diethyl ether melted at 154-155°. Calc. for $C_{10}H_{13}NO \cdot C_6H_3N_3O_7$: N, 14.28%. Found: N, 14.43%.

7-(2'-Bromoethyl) Indoline Hydrobromide (LXXXVI):

The 7-(2'-hydroxyethyl) indoline (6.3 g) was added to a cold solution of 48% hydrobromic acid (30 ml) and the mixture was heated under reflux for 12 hours.

The excess hydrobromic acid was distilled under reduced pressure and the residue was taken up in hot methanol. Upon cooling, crystals were obtained which when recrystallized once from acetone yielded a hydrobromide of m. p. 188-190°. Yield, 7.5 g (64%). It can be sublimed at 180°/0.2 mm. Calc. for $C_{10}H_{12}NBr \cdot HBr$: Br, 52.57%. Found: Br, 52.76%.

Cyclization of 7-(2'-Bromoethyl) Indoline Hydrobromide:

Method I:

The hydrobromide (2.0 g) was treated with dilute sodium hydroxide and extracted with ether. The ether solution was carefully dried and added slowly to a well stirred ether solution of sodium triphenylmethyl solution heated at reflux. After completion of addition of the bromide, the reaction was refluxed for another 30 minutes. The cooled ether solution was extracted with dilute hydrochloric acid, washed with ether and made basic with dilute sodium hydroxide. The ether extract of the basic solution was dried and evaporated to dryness. A small amount of residue which was obtained was sublimed at 100°/0.02 mm. This gave an impure compound melting at 80-85°. Ultraviolet spectrum of this compound was identical with that of triphenylmethane, (m. p. 92°).

The residue which was glossy yellow gave an ultraviolet spectrum almost identical with that of the sublimate thus indicating that this too was impure triphenylmethane.

Method II:

The hydrobromide (0.2 g) was dissolved in distilled water (100 ml) and added dropwise to a boiling solution of 5% sodium hydroxide. The addition required a total of 4 hours. After addition of the bromide, the aqueous solution was steam distilled and 10 ml fractions were collected.

The first five fractions contained various amounts of a product which absorbed in the ultraviolet at 317 mμ (water). Fractions 7 and 8 contained a mixture of compounds and fractions 9 and 10 contained a substance which absorbed at 289 mμ (water) which was the same substance

as was in the reaction pot. The first five fractions were combined and extracted with ether and the ether evaporated after drying. The small amount of residue which had an odour reminiscent of an amine was distilled at 60-65°/0.05 mm (air bath temperature). It had a λ_{max} at 318 mμ (ethanol) which was lost on addition of a drop of hydrochloric acid. The infrared spectrum showed an O-H or an N-H absorption. The yield was extremely poor and the oil was rapidly decomposed, as evidenced by the darkening of the colour on standing and the failure of this dark brown oil to redistil.

The fraction having an absorption at 289 mμ was identified as the 7-(2'-hydroxyethyl) indoline. This compound must have formed by the hydrolysis of the bromide.

Method III:

The hydrobromide (0.2 g) was dissolved in cold dilute sodium hydroxide and extracted with toluene. The toluene solution was dried carefully over magnesium sulphate and then over sodium hydride in the cold. The dried toluene solution was made up to a total volume of 100 ml with dry toluene and added dropwise over a period of 4 hours to a refluxing solution of toluene (500 ml) containing excess sodium hydride (1.0 g).

After completion of addition of the bromide, the reaction mixture was cooled and water was carefully added to destroy the excess sodium hydride. The cooled toluene solution was extracted with 10% hydrochloric acid and the acid solution was made basic and steam distilled.

The first 50 ml fraction seemed to contain two compounds. The aqueous solution was extracted with ether, dried and evaporated. The residue which distilled at 60-70°/0.05 mm (air bath temperature) solidified upon cooling and melted at 22.5-23°. This base, having an odour of an amine showed no O-H or N-H absorption in the infrared. The ultraviolet spectrum resembled that of 7-(2'-hydroxyethyl) indoline except that the λ_{max} was shifted slightly to the longer wavelength to 296 mμ, log ϵ = 3.30 (ethanol). In acid, a yellow solution was obtained having a λ_{max} at 470 mμ. It gave a positive test with the Erhlich reagent, indicative of active hydrogens. The compound was quite sensitive to air oxidation and rapidly decomposed. It appeared to be homogeneous by gas chromatography. E. W. 152, pKa 4.9. Calc. for $C_{10}H_{11}N$: C, 82.71; H, 7.64%. M. W. 145. Found: C, 78.66, 84.40; H, 7.05, 7.98%.

The picrate was prepared from an ether solution. It melted at 184-186°. Calc. for $C_{16}H_{14}N_4O_7$: C, 51.34; H, 3.75%. Found: C, 50.83; H, 3.50%.

CLAIMS TO ORIGINAL RESEARCH

1. The synthesis of N-acetyl-α,β'-diindolyl.
2. The synthesis of N-chloroacetyl-3,3-dimethylindoline (LXXX).
3. The synthesis of N-trichloroacetylindoline (LXXVI).
4. The finding of a novel ring enlargement in the cyclization of N-chloroacetyl-3,3-dimethylindoline.
5. The synthesis of 4-methyl-3,4-dihydrolilolone (LXXXIII).
6. The synthesis of 4-methyl-3,4-dihydroliloline (LXXXII).
7. The synthesis of N-chloroacetyl-4-methyl-1,2,3,4-tetrahydroquinoline.
8. The synthesis of N-chloroacetyl-3-methyl-1,2,3,4-tetrahydroquinoline.
9. The synthesis of N-chloroacetyl-2-methyl-1,2,3,4-tetrahydroquinoline.
10. The synthesis of 3-methyl-3,4-dihydrolilolone (LXXXIV).
11. The synthesis of 2-methyl-3,4-dihydrolilolone (LXXXV).
12. The synthesis of 2-nitroisophthalyl chloride (LXXXIX).
13. The synthesis of 1,3-bisdiazoacetyl-2-nitrobenzene (XC).
14. The synthesis of the methyl ester of nitrobenzene-2,6-diacetic acid (XCII).
15. The synthesis of nitrobenzene-2,6-diacetic acid.
16. The synthesis of methyl oxindole-7-acetate (XCIII).
17. The synthesis of oxindole-7-acetic acid (XCIV).
18. The synthesis of 7-(2'-hydroxyethyl) oxindole (XCV).
19. The synthesis of 7-(2'-hydroxyethyl) indoline (XCII).

20. The synthesis of 7-(2'-bromoethyl) indoline (LXXXVI).

21. The synthesis of a compound, probably cyclopent[cd]indoline (LXX).

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