THE REDUCTIVE CONDENSATION OF 2,5-DISUBSTITUTED PYRROLES

by

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ABSTRACT

The problem initially presented was the structural elucidation of a compound obtained when 2,5-dimethylpyrrole was subjected to conditions of acidic reduction. Previous workers had assigned a molecular formula $C_{12}H_{17}N$ to this product and a partial structure had been put forward based on the indolenine system.

In the course of this work it was found that the compound obtained by these earlier workers was the result of a reductive self-condensation of 2,5-dimethylpyrrole, and its structure was conclusively established as 1,3,4,7-tetramethylisoindoline. The methods used in the structural elucidation of this product included elemental analysis of its derivatives, measurement of its basicity and equivalent weight, infrared and ultraviolet spectroscopic evidence, oxidative degradation, and its proton magnetic resonance spectrum.

Two related isoindolines were prepared by different routes. 2,4,7-trimethylisoindoline was synthesised by methods analogous to those already known, and the ultraviolet spectrum of its methiodide, when compared with that of the methiodide from 1,3,4,7-tetramethylisoindoline, reinforced the structural assignment of the latter. 1,3-diphenyl-4,7-dimethylisoindoline was obtained by the reductive condensation of acetonylacetone with 2,5-diphenylpyrrole (which did not undergo self-condensation).

The favourable result of this reaction suggested that a similar condensation may have occurred to give the 1,3,4,7-tetramethylisoindoline and also admitted the possibility of a general synthesis of substituted isoindolines by this route.

An attempt was made to resolve the mechanism of the 2,5-dimethylpyrrole condensation, for which either a Diels-Alder reaction or a ring-opening process may be postulated. The failure of the dimethylpyrrole to show dienic character, even in the presence of very strong dienophiles, together with positive evidence for ring-opening and ketone-pyrrole condensation argued forcibly for the latter mechanism.

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ACKNOWLEDGMENT

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CHAPTER I

INTRODUCTION

The importance of pyrrole compounds in plant and animal life is well established and their chemistry has attracted a proportionately large share of the attention devoted to heterocyclic compounds. The incorporation of the pyrrole nucleus in the macrocyclic porphyrin systems of such molecules as chlorophyll and hemin testifies to the significant part which it plays in living processes. Other examples of biologically important pyrrole compounds include the enzyme catalase, the bile pigment bilirubin and the mould pigment prodigiosin.

The parent compound, pyrrole, has been known for some time as a constituent of bone-oil and its earliest preparations consisted of distillation of coal tar, bones, and horn. Runge, in 1834, described a method for detecting pyrrole prepared in this way using a pine-splinter moistened with hydrochloric acid (1). The pine-splinter turned bright red in the presence of pyrrole and the name of this class of compounds derives from the Greek equivalent for this colour.

Pyrrole is generally regarded as intermediate in aromaticity between furan and thiophene, although pyrrole itself is unstable in air, turning rapidly yellow and then orange. The presence of alkyl groups on the ring accelerates this deterioration while electron-withdrawing substituents inhibit the

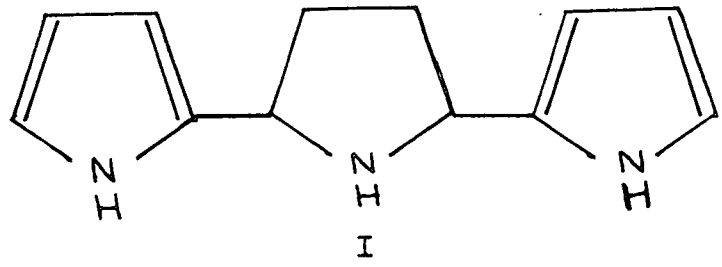

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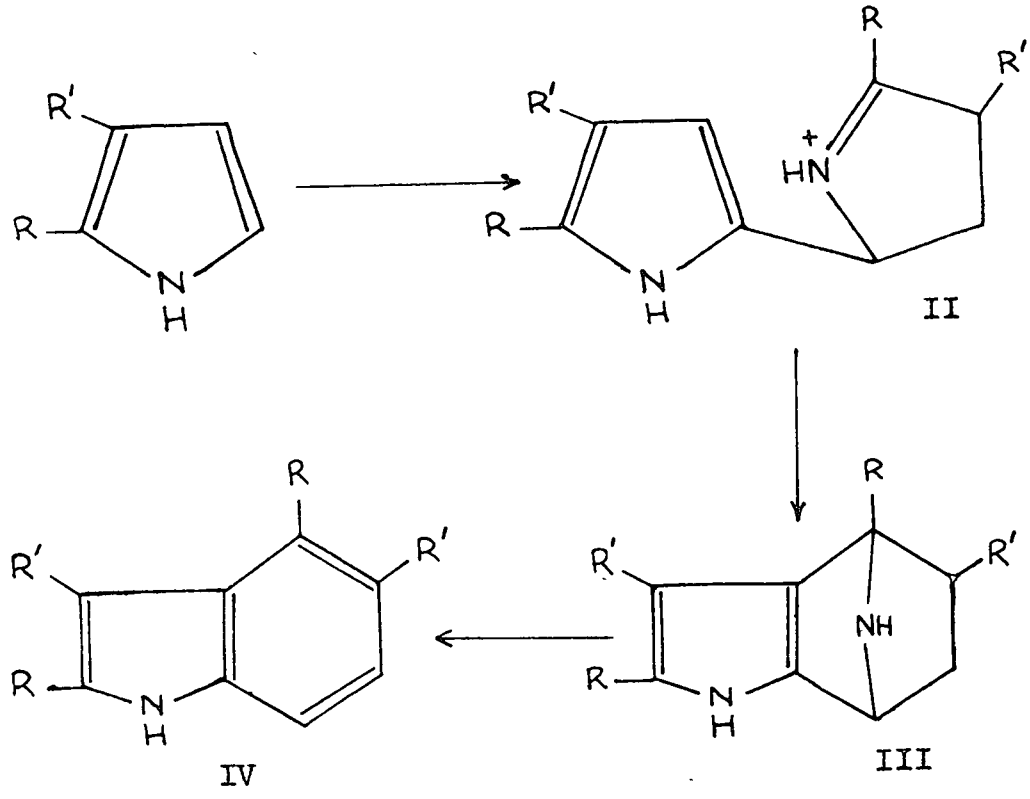
Figure 1. The pyrrole trimer.



II III IV

Figure 2. Reaction sequence in the condensation of 2,3-disubstituted pyrroles.

effect. Among the reactions of pyrrole is one, first reported in 1888, in which pyrrole is treated with acid to give a trimer (2). After several incorrect assignments, the structure of the trimer was eventually established as (I) (3).

Acid treatment of 2-methylpyrrole was found to give a product, $C_{10}H_{11}N$, which Dennstedt concluded to be 2,4-dimethylindole (IV; R = CH_3, R' = H) (4). A similar reaction occurred with 2,3-dimethylpyrrole giving the dipyrrole (II; R = R' = CH_3) and subsequently 2,3,4,5-tetramethylindole (5), although later workers proposed a bis structure for this compound (6). Allen, in 1938, suggested that condensation to form indoles was a general reaction of 2,3-disubstituted pyrroles (7). Allen's scheme consisted of an initial linkage at the free α-positions to give the dipyrrole (II). Ring-closure, giving the bridge-compound (III), followed by elimination of ammonia would result in the 2,3,4,5-substituted indole. In the case of 2-phenylpyrrole it was found that the dipyrrole (II; R = Ph, R' = H) was formed but no further reaction occurred (8).

It was first thought that the condensation of 2,4-dialkylpyrroles followed the pattern of the 2,3-disubstituted pyrroles. Plancher, on treating 2,4-dimethylpyrrole with zinc and acetic acid, obtained a solid for which analysis indicated a molecular formula $C_{12}H_{15}N$ (9). On the basis of an initial $\alpha\alpha'$-linkage giving the dipyrrole (VII), Plancher proposed that ring-closure occurred between the substituted α-position of one pyrrole nucleus and the free β-position of the other ((a) in Figure 3). Upon elimination of ammonia this would give the

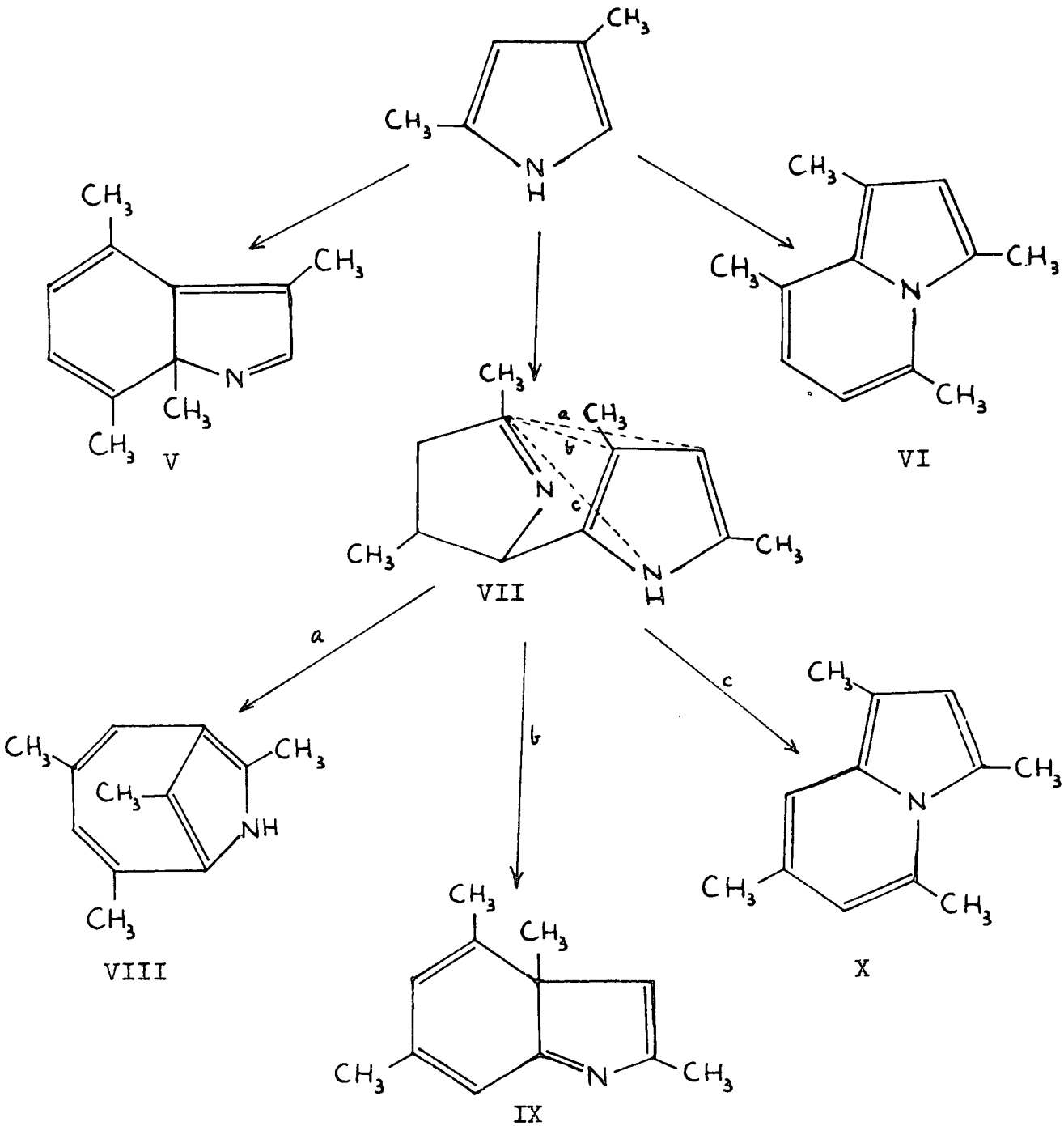


Figure 3. Schemes proposed for the condensation of 2,4-dimethylpyrrole.

bicyclic structure (VIII) (10). This structure was later revised to an indolenine (IX) which, Plancher claimed, better accounted for the basicity of his product and also afforded a closer analogy with a reaction between acetonylacetone and pyrrole which gave 4,7-dimethylindole (11). The indolenine would result from cyclisation of the dipyrrole (VII) by means of the bond (b) in Figure 3. Since the structure of the intermediate dipyrrole was not known (although (VII) would be most likely on steric grounds) the possibility of three other isomers of the indolenine had to be admitted.

The structure of the 2,4-dimethylpyrrole condensation product was left in doubt until 1951, when Saxton took up the problem (12). The product was shown to be a pyrrocoline (X), formed from the dipyrrole by the linkage (c) between the α-position of one nucleus and the nitrogen atom of the second. The positions of the methyl groups in the pyrrocoline established (VII) as the dipyrrole intermediate. Saxton found that reaction of acetonylacetone with 2,4-dimethylpyrrole gave an isomeric pyrrocoline (VI), thus dismissing the indolenine structure (V) proposed by Plancher for this compound (11)

Condensation products have been reported for certain tri- and tetrasubstituted pyrroles (13). Those for kryptopyrrole (2,4-dimethyl-3-ethyl-) and phyllopyrrole (2,4,5-trimethyl-3-ethyl-) have been dubiously assigned bis structures (14), while those from other trisubstituted pyrroles have been formulated as indoles (15).

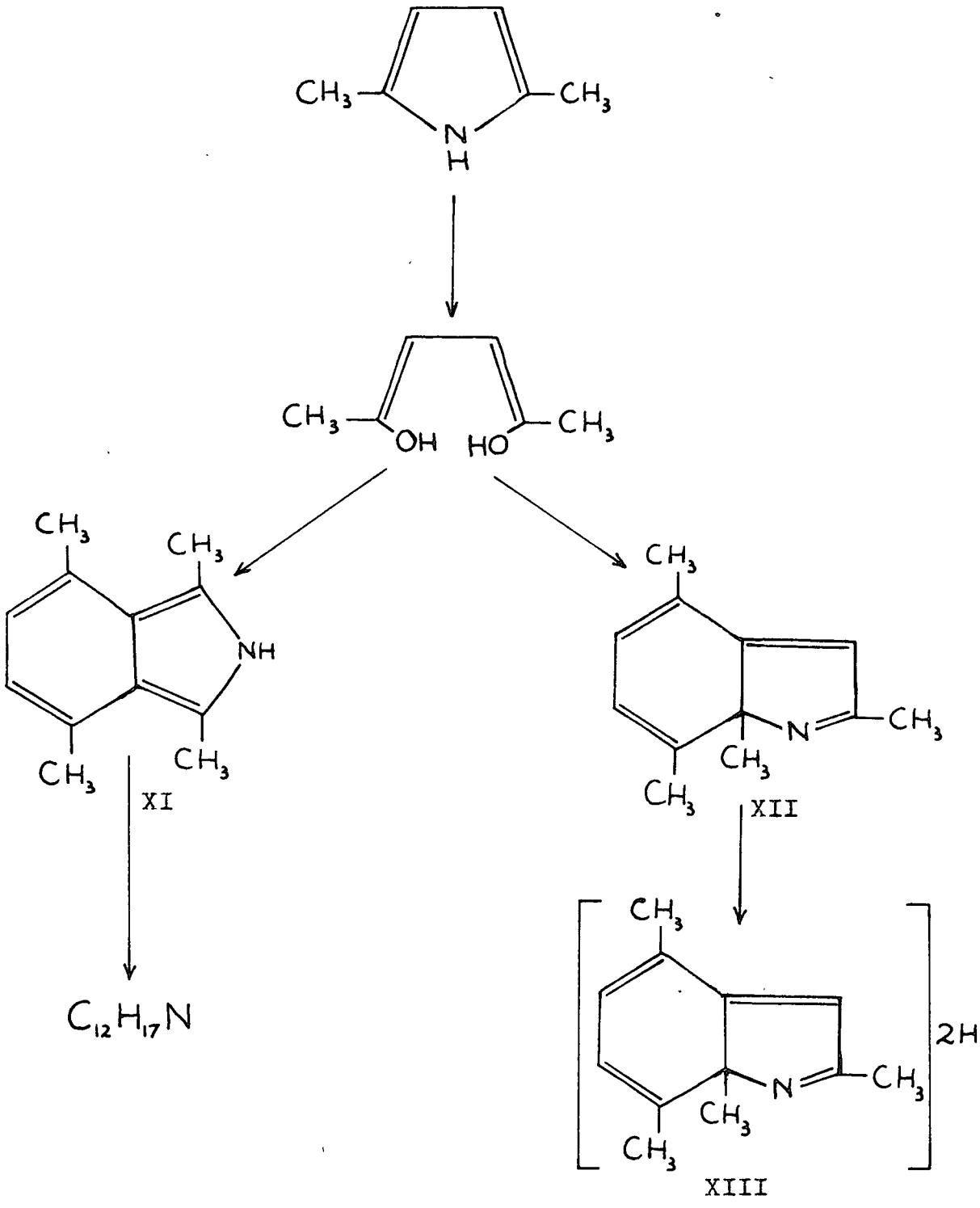


Figure 4. Plancher's schemes for the reductive condensation of 2,5-dimethylpyrrole.

As early as 1897 it was known that 2,5-dimethylpyrrole, on treatment with zinc and acetic acid over a long period, gave a condensation product with a molecular formula $C_{12}H_{17}N$ (16). The product was described as a basic oil which reddened rapidly in air and easily solidified. Plancher first explained this reaction (10) by an initial ring-opening of one molecule of 2,5-dimethylpyrrole, followed by condensation of the resulting acetonylacetone at the two β-positions of a second pyrrole molecule to give the isoindole (XI). On reduction, the isoindole would give the C_{12} base by the saturation of one double bond, although no structure was proposed for the latter compound.

At the same time as he advanced the indolenine structure (IX) for the 2,4-dimethylpyrrole condensation product, Plancher suggested the indolenine (XII) as the condensation product of acetonylacetone and 2,5-dimethylpyrrole (11), thereby rejecting his own previous isoindole assignment. His reaction scheme involved condensation of the acetonylacetone (in the enol form) at the α- and β-positions of the dimethylpyrrole. His reasons for preferring the indolenine (XII) to the isoindole formulation (XI) were the same as those which he put forward in favour of the indolenine (IX) as the 2,4-dimethylpyrrole condensation product - namely, that the indolenine (XII) accounted more satisfactorily for the basicity of his product and that the reaction leading to its formation preserved the analogy with the acetonylacetone-pyrrole condensation. Reduction of one double bond of the indolenine (XII) would give a $C_{12}H_{17}N$ compound and this base was, until now, assigned the partial structure (XIII) (17).

When Saxton, in 1954, showed that Plancher's indolenine structure (V) was incorrect for the condensation product of acetonylacetone and 2,4-dimethylpyrrole (12), the indolenine (XII), formulated as the 2,5-dimethylpyrrole condensation product, became questionable. This was especially so in view of the lack of positive evidence for these indolenines and Plancher's reservations about his structural assignments (11). It seemed, therefore, that a reinvestigation of the 2,5-dimethylpyrrole condensation might prove fruitful. This was undertaken with the immediate objective of condensing 2,5-dimethylpyrrole under conditions of acidic reduction to obtain the $C_{12}H_{17}N$ base. After the structural elucidation of this compound and a study of related reactions it was hoped that a mechanism for the condensation might be suggested.

CHAPTER II

REDUCTIVE CONDENSATION OF 2,5-DIMETHYLPYRROLE

2,5-dimethylpyrrole was prepared by an established method (18) and subjected to conditions of acidic reduction. For this purpose it was found convenient to replace the zinc and acetic acid medium of previous workers (16) by tin and dilute hydrochloric acid. This decreased reaction time from several days to about 24 hours. Basification of the reaction mixture followed by steam-distillation gave a red liquid which was extracted with ether and distilled under reduced pressure. The product was a basic oil, b.p. 76-83°/0.7 mm., with an unpleasant, mouse-like odour. Although colourless on distillation, it reddened rapidly in air and, after prolonged exposure to the atmosphere, formed a powdery, white solid - presumably by reaction with carbon dioxide.

Comparison of these properties of the base with those of certain isoindolines revealed a similarity. For instance, the parent compound isoindoline (19) and 1-methylisoindoline (20) are both reported as oils which redden in air and absorb carbon dioxide to form solid derivatives. The latter has a b.p. of 213°/758 mm. while that of N-methylisoindoline (21) is given as 92-95°/25 mm.

The product of the 2,5-dimethylpyrrole reductive condensation proved, as previously reported (16), to be a $C_{12}H_{17}N$

base and its structure was shown to be 1,3,4,7-tetramethylisoindoline (XIV). An account of the evidence which led to this assignment follows.

I. STRUCTURAL ELUCIDATION OF THE PRODUCT

Preparation and analysis of derivatives. The base readily gave a nitrate and a hydrochloride, analysis of which indicated a molecular formula $C_{12}H_{17}N$ for the base. Titration of the hydrochloride with silver nitrate, using potassium chromate as indicator, gave an equivalent weight of 208 (calc. for $C_{12}H_{18}NCl$, 212). The nitroso derivative and the benzenesulphonamide of the base were also prepared. The former gave a positive result to Liebermann's test and the latter was insoluble in alkali; hence, both were derivatives of a secondary amine. Reaction of the base with carbon dioxide gave an adduct for which the carbamic acid structure (XV) is suggested.

N-Methylation. Methylation of the base was accomplished using the Eschweiler-Clarke procedure. The 1,2,3,4,7-pentamethylisoindoline (XVI) was a basic, viscous oil which turned yellow in air. Its infrared spectrum showed the absence of NH absorption and was characterised by the appearance of a strong band at 2760 $cm.^{-1}$. Wright (22) showed that strong absorption in this region can be attributed to the $N-CH_3$ group of aliphatic amines. The pentamethylisoindoline gave a methiodide (XVII), analysis of which confirmed the C_{12} molecular formula for the base.

Infrared spectrum. The absorption bands of chief significance are shown in Table I.

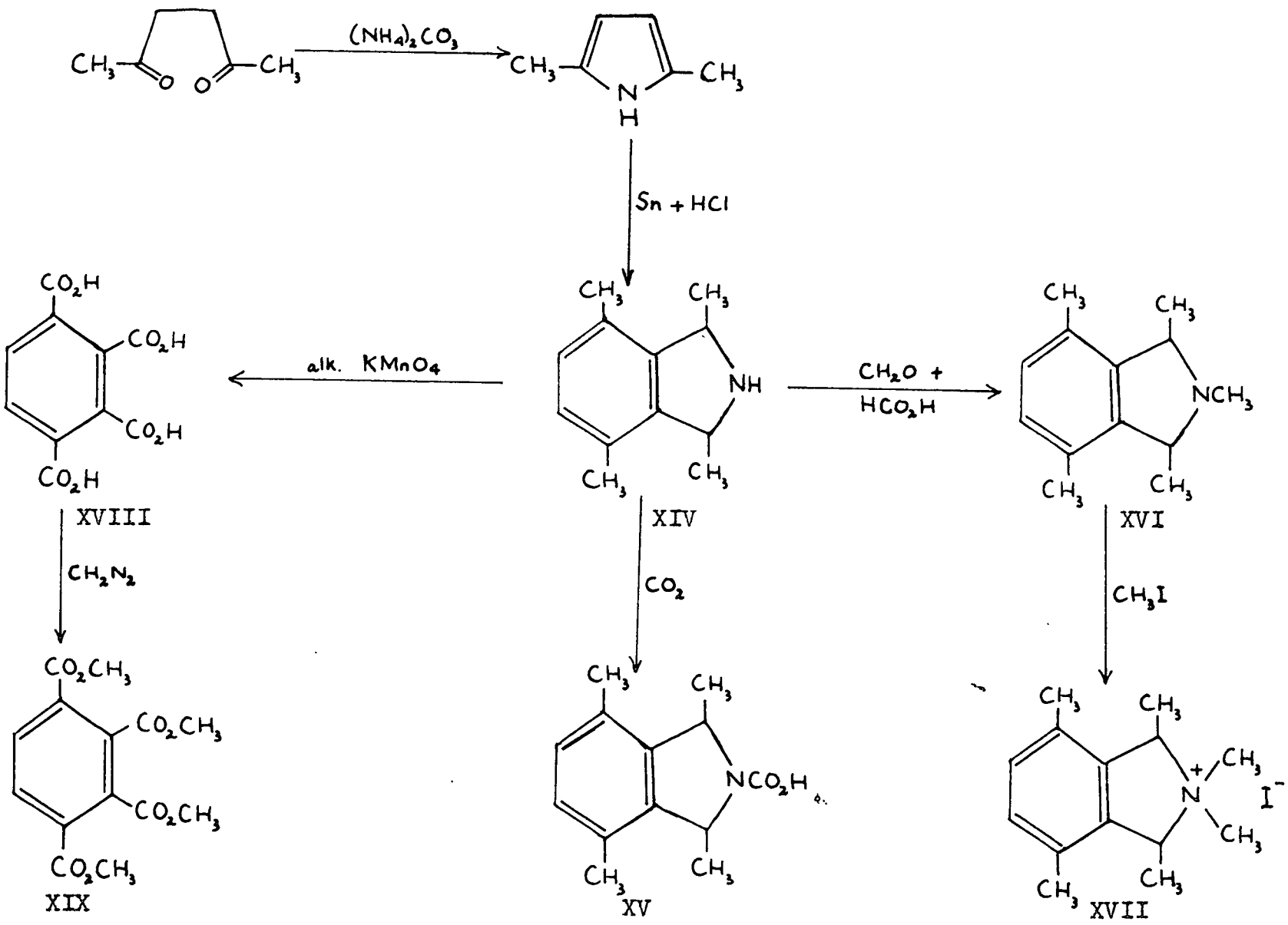


Figure 5. The reductive condensation of 2,5-dimethylpyrrole; derivatives and oxidative degradation of the product.

TABLE I

CHIEF FEATURES OF THE INFRARED SPECTRUM
OF 1,3,4,7-TETRAMETHYLISOINDOLINE

3310 cm.$^{-1}$	(m)	-	NH stretch
1865	(w)	-	overtone of 931 cm.$^{-1}$
1603	(w)	-	overtone of 806 cm.$^{-1}$
1496	(s)	-	aromatic C=C
931	(m)	-	aromatic H (out-of-plane def.)
806	(s)	-	" "

The single, sharp NH absorption suggested that a secondary amine group was present. Strong bands at 1496 cm.$^{-1}$ and 806 cm.$^{-1}$, together with a series of peaks of medium to weak intensity in the 900-1225 cm.$^{-1}$ region, supported an aromatic structure, and the absence of strong absorption in the 700-750 cm.$^{-1}$ range suggested a structure with two adjacent hydrogen atoms on the benzene ring (23). A comparison was drawn between aromatic absorption in the infrared spectra of the base and 1,2,3,4-tetramethylbenzene (24), the latter showing fundamental aromatic bands at 804 cm.$^{-1}$ and 936 cm.$^{-1}$, and weak overtone bands corresponding to these at 1603 cm.$^{-1}$ and 1865 cm.$^{-1}$ respectively. The similarity between the aromatic absorptions of these two compounds was endorsed by the fact that tetraalkyl benzenes with other substitution patterns show no absorption in the 1870 cm.$^{-1}$ region (24). Infrared evidence, therefore, suggested that a 1,2,3,4-tetrasubstituted benzene nucleus was involved in the structure of the base.

Ultraviolet spectrum. The ultraviolet spectra of the base and its nitrate and hydrochloride derivatives confirmed the presence of a benzene nucleus, all showing the fine structure characteristic of the benzenoid chromophore. The spectrum of the methiodide (XVII) (obtained from the base by Eschweiler methylation and subsequent treatment with methyl iodide) also showed the benzenoid pattern of absorption and, moreover, closely resembled the spectrum of 2,4,7-trimethylisoindoline methiodide (XXIV) (see Figure 6, p. 18), the synthesis of which is described in the following chapter. A comparison was made with the ultraviolet spectrum of 4,7-dimethylindane (25) and a similarity noted. The positions of absorption maxima, with extinction coefficients in parentheses, are recorded below:

TABLE II

THE ULTRAVIOLET SPECTRA OF 1,3,4,7-TETRAMETHYLISOINDOLINE AND RELATED COMPOUNDS

1,3,4,7-Tetramethyl-isoindoline (XIV)	265.5 mμ*	271 mμ	274 mμ
Hydrochloride of (XIV)	265 (377)	270.5 (322)	274 (307)
Nitrate of (XIV)	265.5 (330)	270.5 (290)	274.5 (280)
1,2,3,4,7-Pentamethyliso-indoline methiodide (XVII)	266.5 (340)	271 (282)	275.5 (313)
2,4,7-Trimethyliso-indoline methiodide (XXIV)	265.5 (300)	270.5 (251)	274.5 (272)
4,7-Dimethylindane	264 (290)	271 (200)†	

*extinction coefficients not determined owing to absorption of carbon dioxide.

†shoulder.

All spectra were determined with ethanol as solvent except in the case of 4,7-dimethylindane (in isooctane).

The close resemblance between the spectra of the tetramethylisoindoline and its salts suggested that nitrogen was not attached directly to the benzene ring (a result in conformity with the basicity of the isoindoline), since protonation of the former produced no evident effect on the electronic absorption of the latter. The evidence from the ultraviolet spectra of these compounds therefore supported the formulation (XIV) as the structure of the base.

Electrometric titration. The base in 20% aqueous ethanol was titrated against standardised hydrochloric acid using a Beckmann pH meter. The titration curve gave a pK_a value for the base of 8.9, and an equivalent weight of 178 (calc. for $C_{12}H_{17}N$, 175). The fairly strongly basic nature of this compound is consistent with it being an aliphatic amine, and a comparison with known pK_a values showed that its dissociation constant was of the correct order of magnitude for an isoindoline such as (XIV).

TABLE III

pK_a VALUES OF 1,3,4,7-TETRAMETHYLISOINDOLINE AND RELATED COMPOUNDS

N-methylisoindoline (in 80% methyl cellosolve)	7.7	(26)
1,3,4,7-Tetramethylisoindoline (XIV) (in 20% aqueous ethanol)	8.9	
Benzylamine (in water)	9.3	(27)
α-Methylbenzylamine (in water)	9.5	(28)

Oxidative degradation. Further evidence for a 1,2,3,4-tetrasubstitution pattern around a benzene nucleus was afforded

by oxidation of the base. Treatment with alkaline permanganate gave a 32% yield of benzene-1,2,3,4-tetracarboxylic acid (XVIII). Esterification of this acid with diazomethane converted it to the tetramethyl ester (XIX), which was identified by a mixed melting point and infrared comparison with an authentic sample (prepared by oxidation of 1,2,3,4-tetramethylbenzene).

Proton magnetic resonance spectrum. Confirmation of the structure of the base was provided by its proton magnetic resonance spectrum (neat, at 40 mc. $sec.^{-1}$, using dichloromethane as external standard). Chemical shifts (given in τ values), spin-spin splitting, and area ratios supported the tetramethylisoindoline formulation (XIV) as the structure of the reductive condensation product of 2,5-dimethylpyrrole.

TABLE IV

THE PROTON MAGNETIC RESONANCE SPECTRUM OF 1,3,4,7-TETRAMETHYLISOINDOLINE

Field (τ)	Splitting	Area	Assignment
3.4	sing.	1.0	armomatic H
6.0	quad.(J=7cps.)	1.0	H at 1 & 3 split by CH_3 at those positions
8.2	sing.	2.9	CH_3 at 4 & 7
8.9	doub.(J=7cps.)	2.8	CH_3 at 1 & 3 split by H at those positions

Comparison with a comprehensive list of chemical shifts given by Tiers (29) showed that the above values were consistently high by about 0.5 τ units. This is not surprising in view of the fact that Tiers' values are reported for dilute solution, for it

has been shown that chemical shifts are generally greater for the pure liquid than for its dilute solution, often by considerable amounts (30). In addition to any effects due to changes in bulk diamagnetic susceptibility, each molecule of the pure liquid is in a quite strongly basic environment and this might be expected to make a further contribution to the diamagnetic shielding.

The ratio of areas of the signals is in good agreement with the statistical weight of each type of hydrogen, and the magnitude of the splitting constant (J) is consistent with coupling between protons located on adjacent carbons of a saturated system.

II. STEREOCHEMISTRY OF THE PRODUCT

The evidence already presented established the reductive condensation product of 2,5-dimethylpyrrole as 1,3,4,7-tetramethylisoindoline (XIV). Examination of this structure revealed the possibility of cis-trans isomerism with respect to the methyl groups at positions 1 and 3. The cis form has a plane of symmetry and is therefore in the meso configuration, while the trans form should be resolvable. Attempts to isolate such isomers by fractional distillation and vapour phase chromatography, as well as an attempted resolution of the base, have so far proved unsuccessful.

CHAPTER III

RELATED ISOINDOLINES

I. 2,4,7-TRIMETHYLISOINDOLINE

Having established the structure of the 1,3,4,7-tetramethylisoindoline (XIV) (see Figure 5, p. 11), the possibility of synthesising this or a closely related compound by an alternative route was considered. In this way supplementary evidence for the structure of the base would be obtained. The route chosen is shown in Figure 6 and was designed to lead to the 1,2,3,4,7-pentamethylisoindoline (XVI). Although this was not achieved (a result which may be explained in terms of the considerable steric interference involved in the 1,2,3,4,7-pentasubstituted system), it did prove possible to prepare 2,4,7-trimethylisoindoline (XXIII). The resemblance between the ultraviolet spectra of the methiodide (XXIV) of this compound and the methiodide (XVII) of the pentamethylisoindoline (see Figure 5, p. 11) provided further support for (XIV) as the structure of the 2,5-dimethylpyrrole reductive condensation product.

The synthetic scheme started with the conversion of acetonylacetone to 2,5-dimethylfuran, which then underwent a smooth Diels-Alder reaction with maleic anhydride to give the adduct (XX). This compound may exist in either an exo or endo

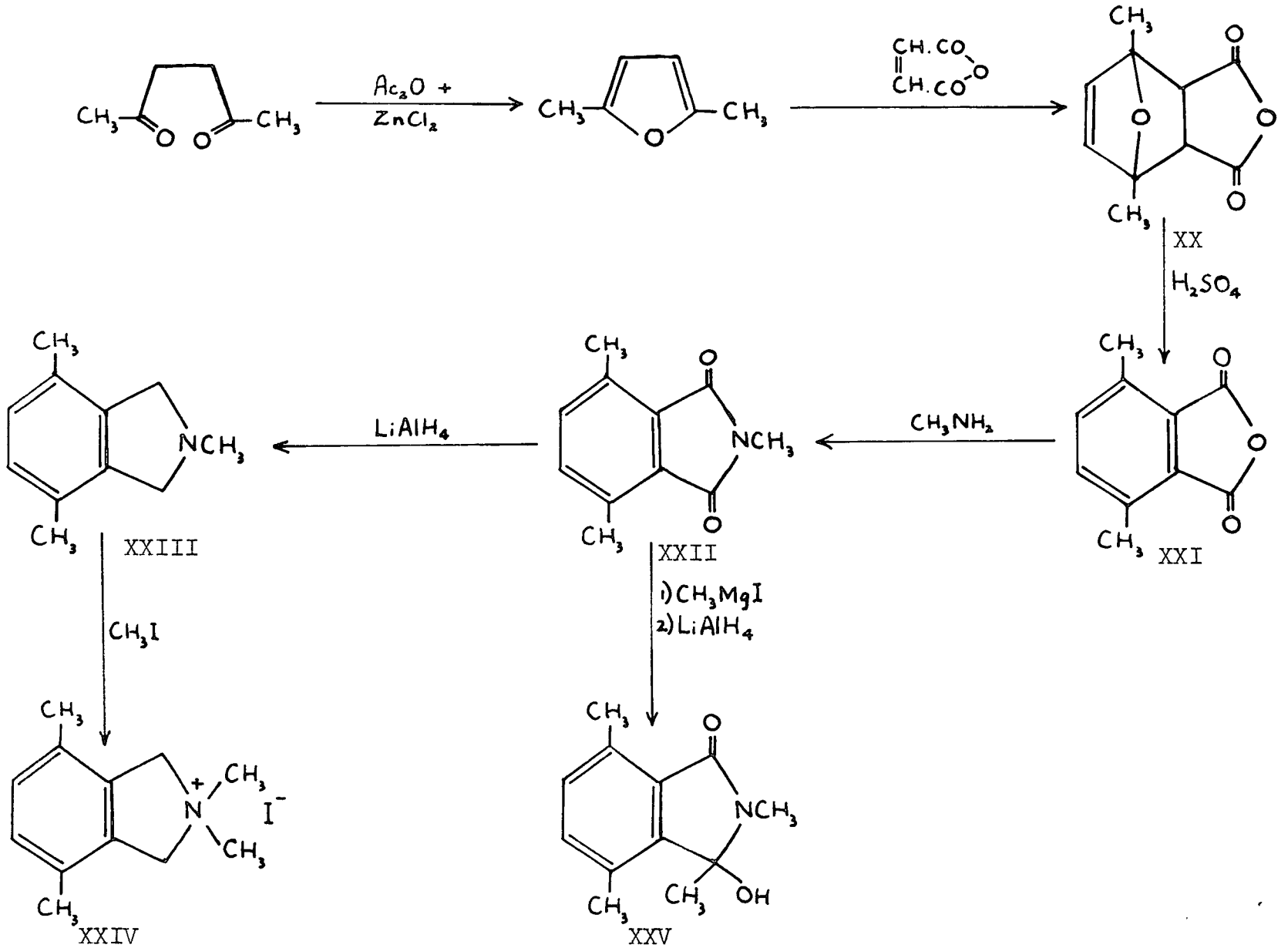


Figure 6. The synthesis of 2,4,7-trimethylisoindoline

configuration and, while early opinions (31) favoured exclusively endo products from Diels-Alder reactions, it has been shown that addition of maleic anhydride to furan in ether gives an adduct with the exo configuration (32). Treatment of the Diels-Alder adduct with concentrated sulphuric acid at -8° gave 3,6-dimethylphthalic anhydride (XXI). On warming the dimethylphthalic anhydride with methylamine, N-methyl-3,6-dimethylphthalimide (XXII) resulted, and this compound served as an intermediate on which several attempts at the synthesis of 1,2,3,4,7-pentamethylisoindoline were based.

By analogy with a known synthesis of a 1-substituted isoindoline (33), the trimethylphthalimide was treated first with lithium methyl and then, without isolation of an intermediate, reacted with lithium aluminium hydride. Evidently no reaction occurred with the lithium methyl since the product, a basic oil which turned yellow on standing, proved to be the result of direct reduction of (XXII). This product was identified as 2,4,7-trimethylisoindoline (XXIII) by elemental analyses of the hydrochloride and methiodide derivatives. The close correspondence between the ultraviolet spectrum of this methiodide (XXIV) and the methiodide (XVII) has been previously noted (see Table II, p. 13).

The infrared spectrum of (XXIII) as a thin film showed a strong band at 2770 $cm.^{-1}$, attributed to $N\text{-}CH_3$ (22), and strong absorption at 805 $cm.^{-1}$. Both bands were absent in the phthalimide and the latter appears to be characteristic of the 1,2,3,4-tetraalkylsubstituted benzene system.

A Grignard reaction on the trimethylphthalimide (XXII), followed by an attempted lithium aluminium hydride hydrogenolysis, produced a compound which is probably the N-methyl-3,4,7-trimethyl-3-hydroxyphthalimidine (XXV). The evidence in favour of this structure comprises a satisfactory elemental analysis and an infrared spectrum which showed a broad absorption at 3390 $cm.^{-1}$, corresponding to OH, and a strong carbonyl band characteristic of a γ-lactam at 1678 $cm.^{-1}$. The phthalimidine was apparently formed by reaction of the phthalimide with one mole of methyl magnesium iodide (despite the presence of a considerable excess), the second carbonyl function remaining unattacked. A reaction of this type is not without precedence, for Grignard reactions with N-substituted succinimides has been used as a general synthetic route to 1,5,5-trisubstituted 2-pyrrolidones. Lukeš, for example, reports a general reaction between N-methylsuccinimide and alkyl magnesium bromides to give 1-methyl-5,5'-alkylhydroxypyrrolidones (34), and Walton has used a similar reaction between N-substituted succinimides and Grignard reagents to obtain pyrrolidones (35).

The failure of the phthalimide (XXII) to react with two moles of Grignard reagent is probably due to steric factors. In the case of the phthalimide the methyl radical approaching the carbonyl function of the phthalimidine (XXV) is obstructed by the methyl group at the 7-position (co-planar with the ring system) as well as by the neighbouring methyl group at nitrogen and a 1,3-interaction across the five-membered ring. If hydrogenolysis of (XXV) could be achieved, further reaction with

Grignard reagent would become more feasible. Attempts at such hydrogenolysis have so far proved unsuccessful, however.

II. 1,3-DIPHENYL-4,7-DIMETHYLISOINDOLINE

When the structure of 1,3,4,7-tetramethylisoindoline (XIV) (see Figure 5, p. 11) had been confirmed it was decided to investigate the application of the reductive condensation reaction to other 2,5-disubstituted pyrroles. If successful, this would give rise to isoindolines with the same substitution pattern as (XIV) but with variations in the substituent groups. To this end, 2,5-diphenylpyrrole was prepared from trans-dibenzoylethylene by hydrogenation and autoclave reaction with ammonia. It was obtained as greenish-yellow flakes and, unlike the 2,5-dialkylpyrroles, was stable in air.

An attempt to condense the diphenylpyrrole with itself, using the tin and hydrochloric acid conditions, failed, suggesting that either excessive steric interaction in an intermediate or the conjugating effect of two phenyl rings prevented a reaction analogous to that of the 2,5-dimethylpyrrole. Earlier workers (8) noticed a similar lack of reactivity in 2-phenylpyrrole compared with the 2-alkylpyrroles, the phenylpyrrole failing to give an indole although it did form a dipyrrole by coupling at the free α-position (see p. 3).

When a mixture of acetonylacetone and 2,5-diphenyl-pyrrole was subjected to the same acidic, reducing conditions a deep wine-red colour resulted initially. On prolonged refluxing this faded to a pale yellow as reduction of the highly-coloured

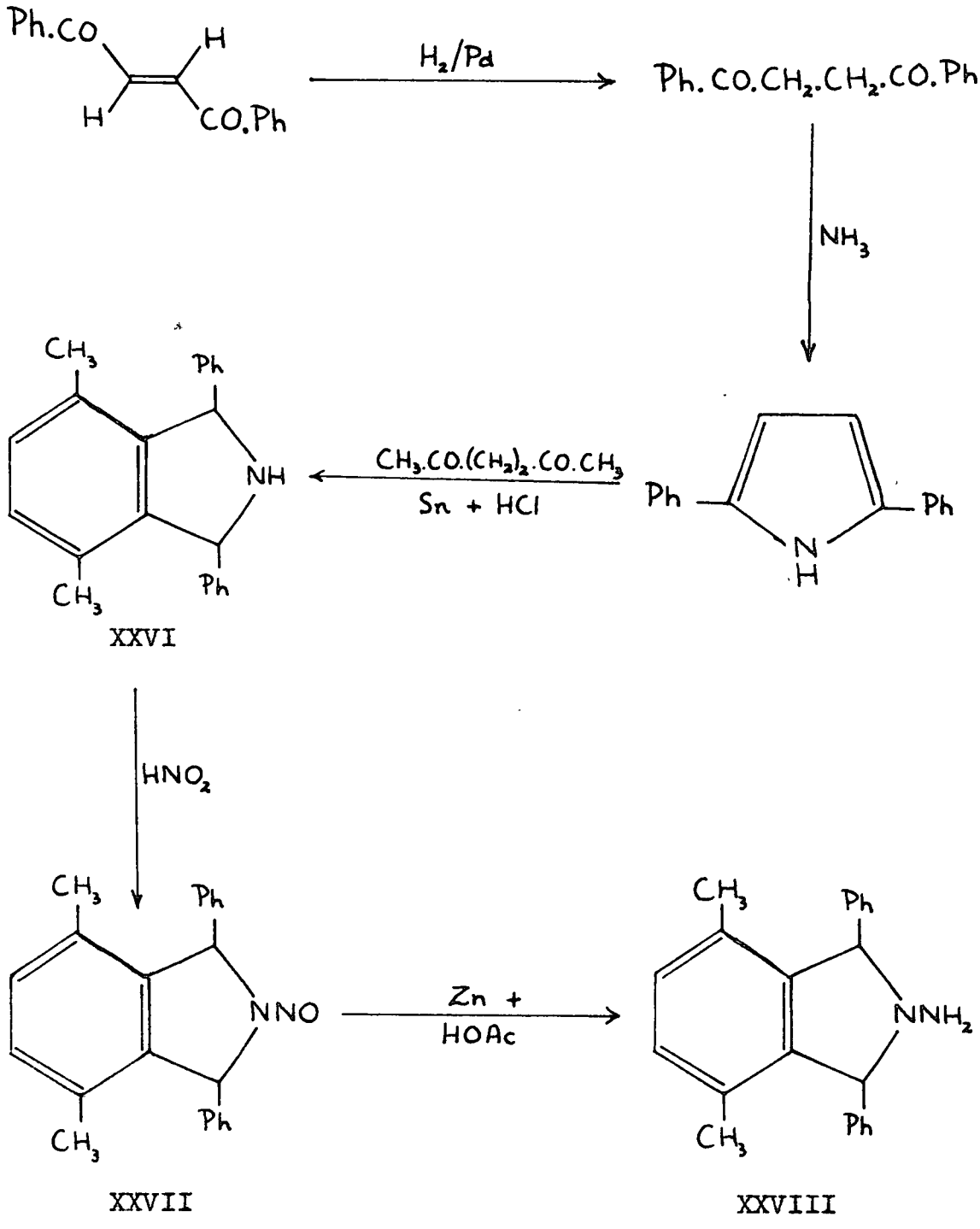


Figure 7. The synthesis of 1,3-diphenyl-4,7-dimethyl-isoindoline and derivatives.

intermediate took place. After basification of the reaction mixture and extraction with benzene, a pale yellow crystalline solid was obtained. This product was identified as 1,3-diphenyl-4,7-dimethylisoindoline (XXVI), supporting evidence being obtained from elemental analysis of this compound and derivatives and from its infrared and ultraviolet spectra.

Derivatives. Treatment of the diphenyldimethyl-isoindoline (XXVI) with sodium nitrite solution gave the nitroso derivative (XXVII). A positive Liebermann's test established that this was the derivative of a secondary amine (36). Reduction of the nitroso amine with zinc and acetic acid produced the N-amino derivative (XXVIII) in which the primary amino group was detected by the appearance of NH absorption at 3378 $cm.^{-1}$ (w) and 3311 $cm.^{-1}$ (m) in the infrared spectrum. Analysis of these two derivatives confirmed the $C_{22}H_{21}N$ molecular formula for the parent compound which was indicated by analysis of the isoindoline itself.

The isoindoline (XXVI) showed a marked decrease in basicity as compared with 1,3,4,7-tetramethylisoindoline (a fact which may be attributed to the replacement of the 1- and 3-methyl groups by electron-withdrawing phenyl groups), but it did form a salt with hydrogen chloride. This derivative, when titrated against silver nitrate (using potassium chromate as indicator), gave an equivalent weight of 336 (calc. for $C_{22}H_{22}NCl$, 336).

Infrared spectrum. The infrared spectrum of the isoindoline (XXVI) showed an expected increase in complexity in the fundamental aromatic region compared to the spectrum of 1,3,4,7-tetramethylisoindoline (see p. 10). Strong absorption at 698 cm.$^{-1}$ with a slightly weaker band at 753 cm.$^{-1}$ indicated the presence of monosubstituted benzene rings (37). The band which previously characterised the 1,2,3,4-tetrasubstituted benzene system (at 800 cm.$^{-1}$) had moved to 817 cm.$^{-1}$ with somewhat diminished intensity. The NH absorption occurred at 3344 cm.$^{-1}$ with the simgle, sharp band characteristic of secondary amines (38).

Ultraviolet spectrum. The ultraviolet spectra of the isoindoline (XXVI) and its hydrochloride (both in ethanol) showed the fine structure of the benzenoid chromophore with the enhanced extinction coefficient expected for three unconjugated benzene rings. A comparison was made with the ultraviolet spectrum of o-dibenzylbenzene (39) and the similarity noted. Positions of absorption maxima, with extinction coefficients in parentheses, are shown in Table V.

TABLE V

THE ULTRAVIOLET SPECTRA OF 1,3-DIPHENYL-4,7-DIMETHYL-ISOINDOLINE AND RELATED COMPOUNDS

The Isoindoline (XXVI)	Hydrochloride of (XXVI)	o-Dibenzyl-benzene
253 mμ (744)	253 mμ (478)	
258 (817)	258 (665)	257 mμ (813)
265 (744)	265 (712)	263 (832)
	269 (622)	269 (692)

The ultraviolet spectrum of the acetonylacetone-diphenylpyrrole reductive condensation product eliminated the possibility of an isoindole formulation, which seemed the most likely alternative to (XXVI). The reported spectrum of 2-methyl-1,3-diphenylisoindole in dioxan (40) showed λmax. 380 (ϵ 20,000) and 280 mμ (ϵ 18,000) with a shoulder at 270 mμ (ϵ 14,000).

As in the case of 1,3,4,7-tetramethylisoindoline, it was realised that cis-trans isomerism could occur at the 1,3-positions of the isoindoline (XXVI). However, chromatography of the 1,3-diphenyl-4,7-dimethylisoindole on florisil, as well as fractional crystallisation of it and its derivatives, failed to reveal any evidence of isomeric products. In view of the steric interference which would be expected if the phenyl groups in (XXVI) were cis to each other, it was concluded that the more stable trans isomer was probably formed, perhaps with the exclusion of the cis isomer.

It seems likely that the reaction between acetonylacetone and 2,5-diphenylpyrrole is a special case of a more general reaction between 1,4-diketones and 2,5-disubstituted pyrroles, especially since there is some evidence that self-condensation of these pyrroles occurs by a ring-opening process (see following chapter). If this is so, then this route affords a novel and convenient synthesis of substituted isoindolines. The simplest and most useful application of this reaction is the case where the 2,5-disubstituted pyrrole is resistant to self-condensation (as, for example, with 2,5-diphenylpyrrole), since, in these circumstances, only one product may be expected.

CHAPTER IV

THE MECHANISM OF THE 2,5-DIMETHYLPYRROLE CONDENSATION

In considering a mechanism for the self-condensation of 2,5-dimethylpyrrole two possibilities have been favoured. The first of these is a Diels-Alder type of addition of a protonated pyrrole molecule to a neutral molecule, according to the scheme shown in Figure 8 (over). The second possible mechanism was that proposed originally by Plancher (10) (see p. 5) but later abandoned by him. This involves ring-opening of a molecule of 2,5-dimethylpyrrole to form acetonylacetone, followed by condensation of the diketone at the β-positions of another pyrrole molecule. The resulting isoindole intermediate then undergoes reduction to the tetramethylisoindoline. This scheme is shown in Figure 10, p. 32. These two mechanisms will now be reviewed in detail.

I. DIELS-ALDER MECHANISM

Evidence from nuclear magnetic resonance spectra has indicated that, in acidic solution, alkyl pyrroles are protonated predominantly at the α-position (41). The resulting pyrrolenine (XXIX) is analogous to a protonated, $\alpha\beta$-unsaturated Schiff's base and, as such, might be expected to have some degree of dienophilic character. Addition of this species to a molecule of 2,5-dimethylpyrrole behaving as a diene in the Diels-Alder

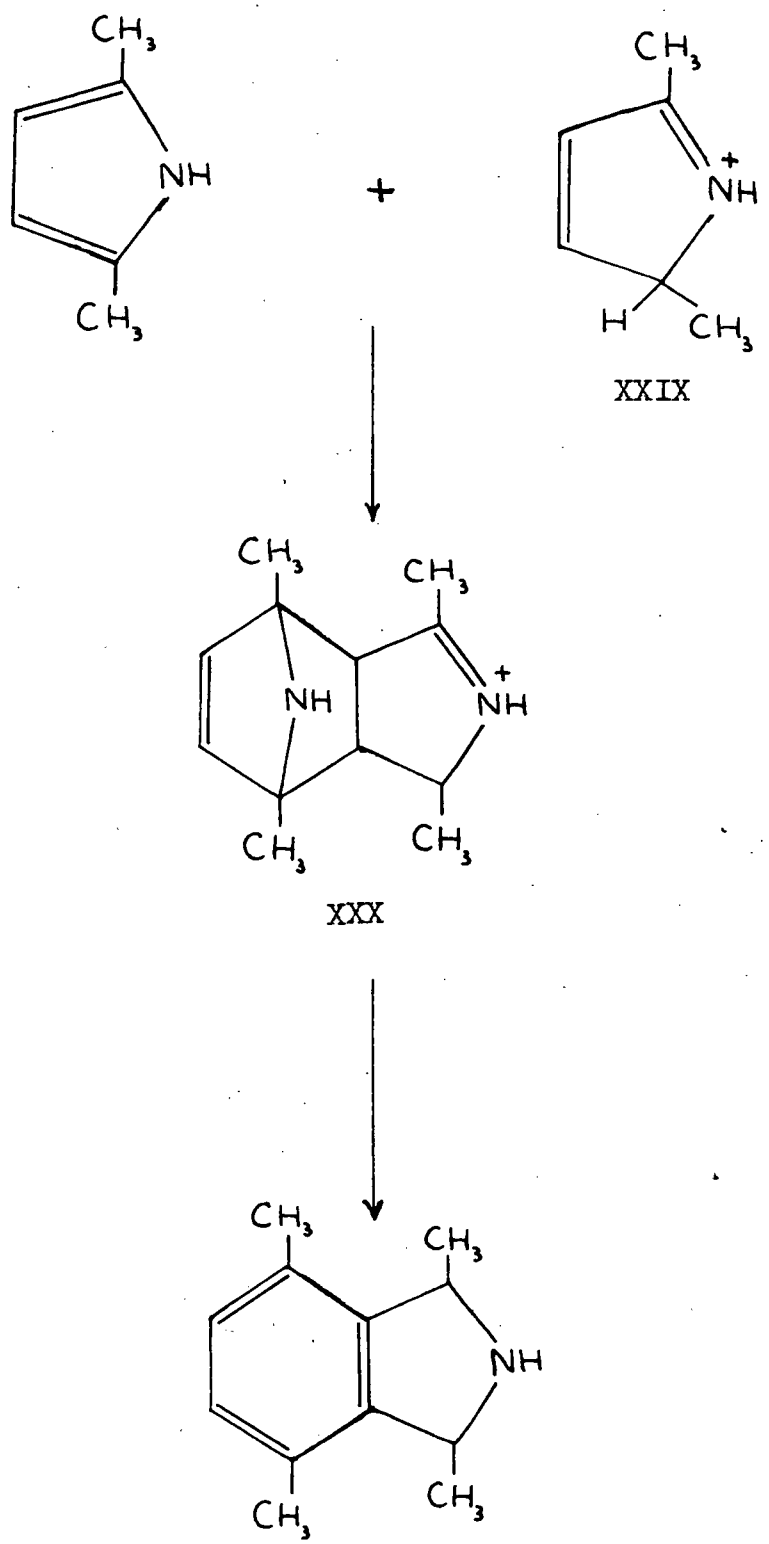
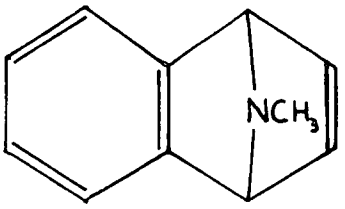


Figure 8. A proposed Diels-Alder mechanism for the reductive condensation of 2,5-dimethylpyrrole.

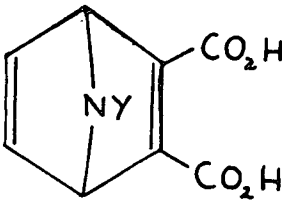
fashion could lead to the adduct (XXX) which, on reduction, basification, and elimination of ammonia, might give the isoindoline. The intermediate (XXX), as in the case of the adduct of 2,5-dimethylfuran and maleic anhydride ((XX) in Figure 6, p. 18), may have the exo or endo configuration. In the case of the dimethylpyrrole condensation, ammonia was detected on making the reaction mixture alkaline and elimination had probably occurred in the acidic medium just as the adduct (XX) had readily eliminated water under acidic conditions.

Unlike the furans and thiophenes which are endowed with a considerable measure of dienic character, pyrroles are not generally active as dienes in the Diels-Alder reaction. The usual result of bringing a pyrrole and dienophile into contact is addition of the latter to the α-position of the pyrrole nucleus (42,43,44). The few isolated instances of authentic Diels-Alder addition to pyrroles which are known have been reported comparatively recently and include the addition of dehydrobenzene to N-methylpyrrole giving (XXXI) (45), and the reaction between N-benzylpyrrole and acetylenedicarboxylic acid to give (XXXII) (46). A third example is the reaction between N-carbomethoxypyrrole and the dimethyl ester of acetylenedicarboxylic acid (47). This gives 1,3,4-tricarbomethoxypyrrole and acetylene by decomposition of the suggested intermediate (XXXIII), which was not isolated.

These cases of pyrroles undergoing a Diels-Alder reaction appear to owe their existence to an unusual condition of decreased aromaticity and increased dienic character of the

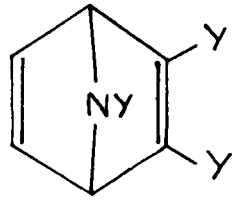


XXXI



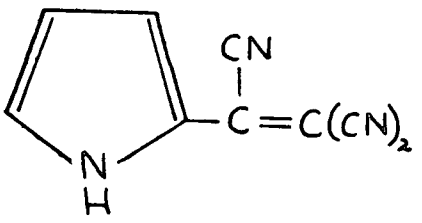
Y = .CH_2Ph

XXXII

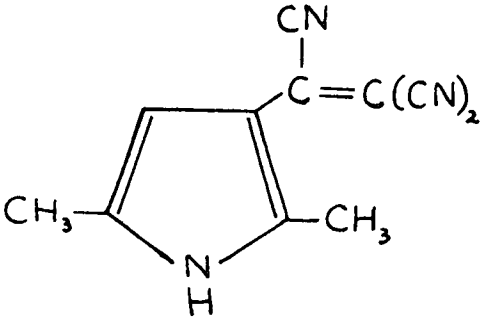


Y = .CO_2CH_3

XXXIII



XXXIV



XXXV

Figure 9. Products of the reaction of certain pyrroles with dienophiles.

pyrrole nucleus in the compounds involved. With N-carbomethoxypyrrole this has been explained (47) by the electron-withdrawing effect of the ester group, which thus inhibits conjugation of the nitrogen electron pair with the π-electrons of the rest of the system. A decrease in aromaticity of the pyrrole nucleus has also been postulated as responsible for the N-benzylpyrrole addition (46). No comparable effects appear to operate to enhance the dienic character of 2,5-dimethylpyrrole and a Diels-Alder reaction involving this compound would, therefore, be somewhat unexpected.

A further objection to a Diels-Alder mechanism for the 2,5-dimethylpyrrole condensation concerns the nature of the solvent. The aqueous conditions of the isoindoline preparation are not those in which Diels-Alder syntheses are normally carried out - an inert hydrocarbon or ethereal solvent being most commonly preferred.

The ability of 2,5-dimethylpyrrole to undergo a Diels-Alder reaction was tested with two of the most reactive dienophiles known. Maleic anhydride gave only a dark red, polymeric substance (cf. 48), while tetracyanoethylene reacted to give a compound which was not an adduct. This latter compound, the only product observed in the reaction, was considered to be 2,5-dimethyl-3-tricyanovinylpyrrole (XXXV) on the basis of its analysis, its infrared spectrum (which showed NH absorption), and the analogy with the reaction of pyrrole and tetracyanoethylene which gives (XXXIV) (49).

Since tetracyanoethylene, which would be expected to be a stronger dienophile than the protonated pyrrolenine (XXIX),

failed to elicit any dienic character from 2,5-dimethylpyrrole, an addition reaction of the type shown in Figure 8 must be regarded as unlikely. In fact, the product (XXXV), which is the result of electrophilic substitution by tetracyanoethylene, testifies to the aromatic rather than dienic nature of the pyrrole. The evidence, therefore, argues against a Diels-Alder mechanism for the condensation process.

II. RING-OPENING MECHANISM

Pyrroles exhibit a certain facility with regard to ring-opening by aqueous alkali, a reaction which is accelerated by alkyl groups but retarded by phenyl, acyl, and carboxyl groups (50). Plancher (10), as early as 1905, realised the possibility of this being the initial step in the condensation reaction of 2,5-dimethylpyrrole (see p. 5). Although ring-opening by acid, as in the furan series, is not generally possible with pyrroles, it has been shown that with Brady's reagent 2,5-dimethylpyrrole suffers cleavage to give a product which is fixed as the 2,4-dinitrophenylhydrazone derivative (48).

This result was verified and extended by comparing the reaction of 2,5-dimethylpyrrole, 2,5-diphenylpyrrole, and acetonylacetone with 2,4-dinitrophenylhydrazine. It was found that acetonylacetone and 2,5-dimethylpyrrole gave derivatives immediately; these were identical (by mixed melting point and a comparison of infrared spectra) and, by analysis, were shown to be the bis-2,4-dinitrophenylhydrazone of acetonylacetone (cf. (48)). 2,5-Diphenylpyrrole gave no derivative even after several weeks

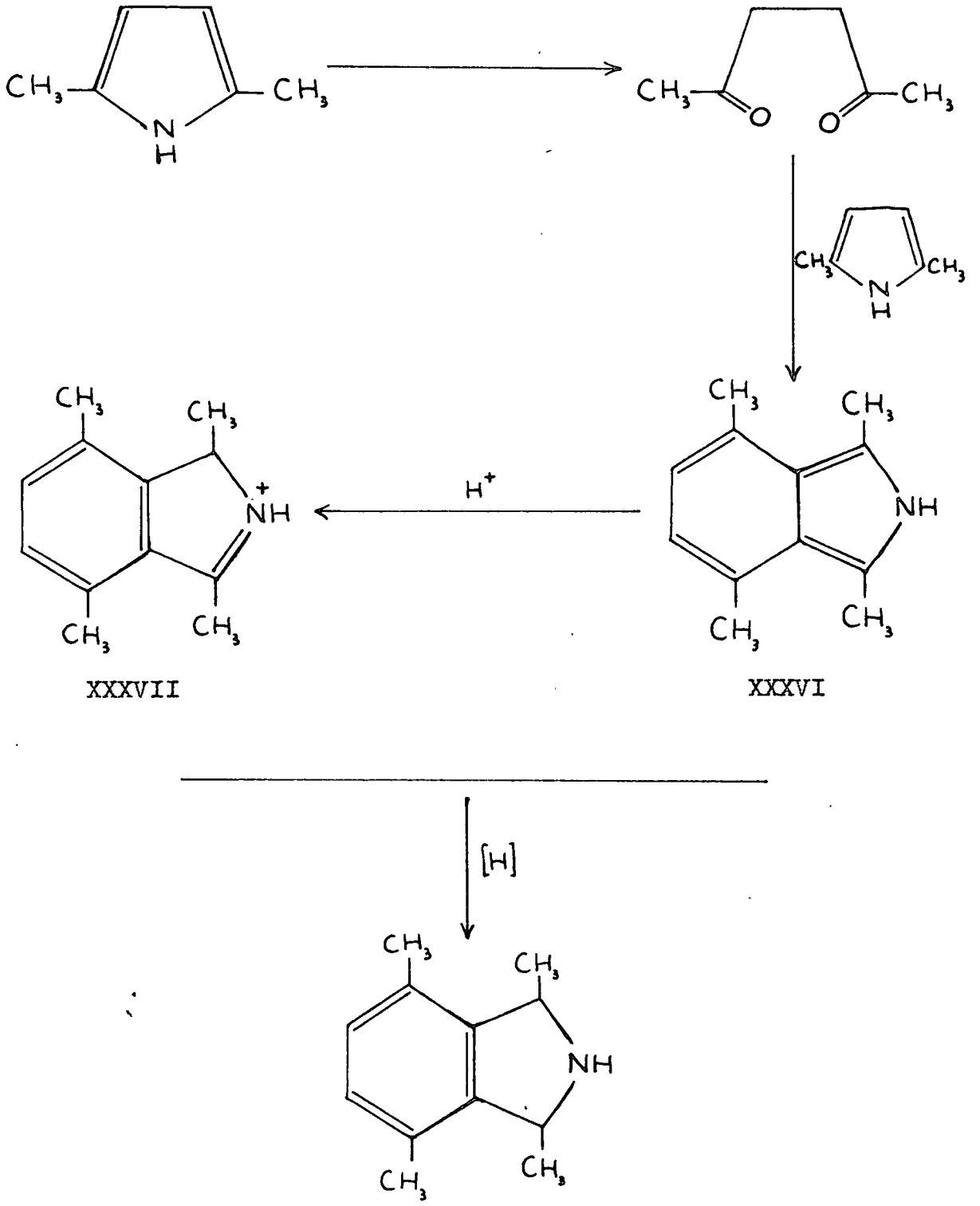


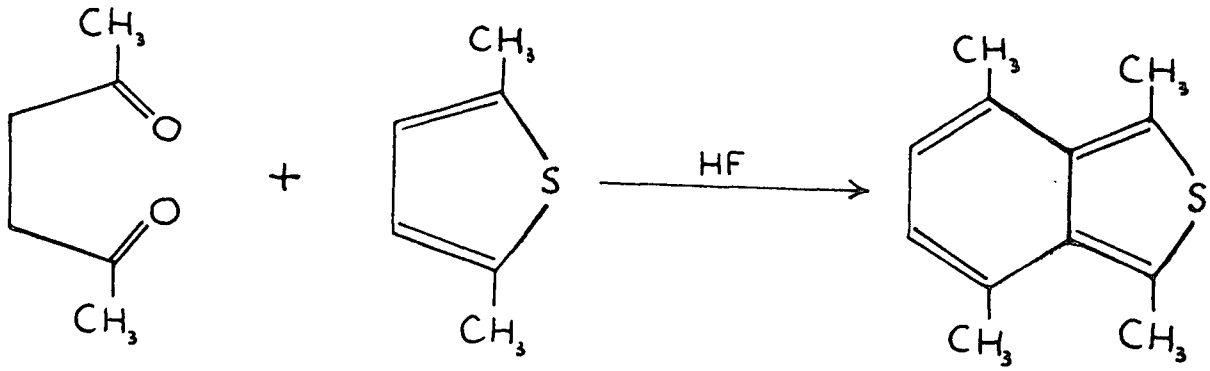
Figure 10. A proposed ring-opening mechanism for the reductive condensation of 2,5-dimethylpyrrole.

and it appeared that ring-opening was completely inhibited in this case. Thus, a parallel between ring-opening and condensation is evident with these two 2,5-disubstituted pyrroles since the dimethylpyrrole gave an isoindoline while the diphenylpyrrole was recovered unchanged from the reaction mixture.

Following ring-opening of a pyrrole molecule to give acetonylacetone (or its equivalent), the second stage of the condensation process is presumed to involve reaction of the two carbonyl functions with the β-positions of a second pyrrole molecule to give the isoindole (XXXVI). It is significant that a reaction exactly analogous to this occurred in the condensation of acetonylacetone with 2,5-diphenylpyrrole, an account of which has been given in the previous chapter. This reaction entailed condensation of the diketone with the two β-positions of the diphenylpyrrole, probably to form an isoindole intermediate, which was then reduced in the reaction medium to 1,3-diphenyl-4,7-dimethylisoindoline (XXVI) (see figure 7, p. 22).

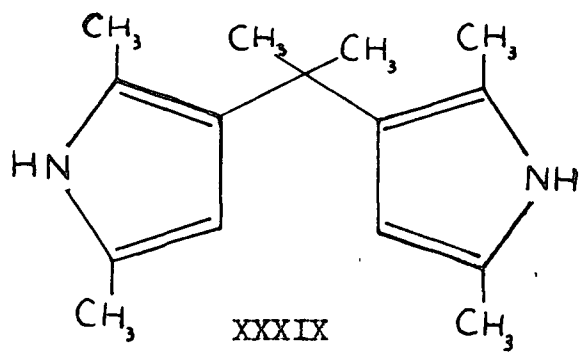
A similar condensation has been shown to occur in the thiophene series (51), in which acetonylacetone and 2,5-dimethylthiophene are treated with hydrofluoric acid to give 1,3,4,7-tetramethylisothionaphthene (XXXVIII). This product is evidently considerably more stable than the corresponding isoindole, for attempts to isolate the latter from an ethereal solution of 2,5-dimethylpyrrole treated with hydrogen chloride have so far resulted in only highly-coloured, polymeric products, the nature of which remains obscure.

A further piece of evidence in support of the ketone-pyrrole condensation was afforded by a reaction between acetone



XXXVIII

Figure 11. Condensation of acetonylacetone with 2,5-dimethylthiophene



XXXIX

Figure 12. Condensation product of acetone and 2,5-dimethylpyrrole.

and 2,5-dimethylpyrrole. This reaction, which was carried out in the presence of hydrochloric acid, yielded a pink compound for which analysis indicated a molecular formula $C_{15}H_{22}N_2$ (cf. (48)). The product gave a positive Ehrlich reaction (suggesting an unsubstituted position on a pyrrole nucleus), and the infrared spectrum showed NH absorption at 3413 $cm.^{-1}$ with the enhanced intensity characteristic of the pyrrole system. The ultraviolet spectrum was also similar to that of 2,5-dimethylpyrrole and this evidence led to the proposed structure (XXXIX) for this compound. A reaction between acetone and 2-methylindole has also been recently reported (52).

The isoindole (XXXVI) thus seems to be a reasonable, if hypothetical, intermediate in the reductive condensation of 2,5-dimethylpyrrole. The actual reduction of the isoindole may take place directly from (XXXVI) (by saturation of one double bond and rearrangement or by addition of hydrogen across the ends of the conjugated system at the 1- and 3-positions) or, possibly, via the aromatic imine intermediate (XXXVII). This second course would result from protonation of the isoindole at the 1-position (which would be expected to occur readily since it leads to aromatisation), followed by reduction of the imine double bond. The formation of the aromatic imine would depend on whether protonation or direct reduction of the isoindole took place the more rapidly.

As yet, the nature of the reduction process has not been ascertained since it has proved impossible to obtain conclusive results from products isolated by treatment of

2,5-dimethylpyrrole and the acetonylacetone-diphenylpyrrole mixture with acid alone. However, the evidence available is considered to support a ring-opening rather than a Diels-Alder mechanism for the initial condensation process of 2,5-dimethylpyrrole.

CHAPTER V

EXPERIMENTAL

Melting points were determined on a heated block and are uncorrected. Unless otherwise stated, infrared spectra were determined as liquid films or nujol mulls between salt plates on a Perkin-Elmer Infracord spectrophotometer. In general, only bands of medium to strong intensity have been reported. Ultraviolet spectra were determined using a Cary 14 recording spectrophotometer.

2,5-Dimethylpyrrole

2,5-Dimethylpyrrole was prepared from acetonylacetone and ammonium carbonate by the method of Young and Allen (18). It was obtained as a colourless, slightly viscous liquid, b.p. 72-75° (22 mm.), n_D^{25} 1.502 (although this increased on standing), in 35% yield. The pyrrole slowly turned red in air. Its infrared spectrum (of the pure liquid) showed absorption at 3425 (NH), 2933 (CH_3), 1590, 1511 (both C=C), 1035, 927, and 768 $cm.^{-1}$ (ring hydrogen).

The proton magnetic resonance spectrum of 2,5-dimethylpyrrole (determined neat at 40 $mc.\ sec.^{-1}$, using hexamethyldisiloxane as external standard) displayed resonances at fields (on the τ scale) of 3.3 (broad and low due to NH), 4.6 (ring hydrogens), and 8.3 (methyl hydrogens). The signal at 4.6 on

the τ scale was split into an almost symmetrical doublet (J, 2.1 cps.) and has been attributed to coupling between hydrogens at the 1- and 3-positions (54). (A splitting of the same magnitude and ascribed to the same cause has also been observed in the spectrum of 2,3,5-trimethylpyrrole (41)).

1,3,4,7-Tetramethylisoindoline (XIV) and Derivatives

25 g. of 2,5-dimethylpyrrole was added in small lots to a mixture of 125 g. of tin and 500 ml. of 6N hydrochloric acid boiling under reflux. Refluxing was continued for 22 hours. Excess of 40% caustic soda solution was added to the cooled reaction mixture, which was then steam-distilled. A colourless oil appeared with the distillate which, after addition of 20 g. of solid sodium hydroxide, was continuously extracted with ether for 10 hours. The extract was dried over anhydrous sodium sulphate and the ether distilled off. The residue was distilled in nitrogen under reduced pressure, and the isoindoline was obtained as an initially colourless oil, b.p. 76-83° (0.7 mm.), n_D^{25} 1.5271, in yields varying from 6.50 g. (28%) to 11.4 g. (50%). The major loss occurred at the steam-distillation stage for it was found that yields were improved by making the reaction mixture more strongly basic prior to distillation. Even under these conditions the isoindoline steam-distilled reluctantly, a relatively large volume of distillate being required to carry over all the product.

Hydrochloride. When anhydrous hydrogen chloride was passed through an ethereal solution of the base a white precipitate resulted immediately. Recrystallisation of the

product from a dichloromethane-hexane mixture gave the isoindoline hydrochloride as colourless prisms, m.p. 267-8° (dec.) (Found: C, 68.3; H, 8.75; N, 6.8; Cl, 16.4%; M (by titration with silver nitrate), 208). $C_{12}H_{18}NCl$ requires C, 68.1; H, 8.6; N, 6.6; Cl, 16.8%; M, 212. The infrared spectrum of the hydrochloride showed absorption bands at 2674, 2488, 2421, 2037 (all NH_2^+), 1585, 1499 (both C=C), 1416, 1353, 1168, 1067, 1035, 896, and 809 $cm.^{-1}$.

Nitrate. With dilute nitric acid the isoindoline gave a copious white precipitate which was recrystallised from ethanol. The nitrate was obtained as colourless blades, m.p. 176-8° (Found: C, 60.8; H, 7.4; N, 11.9%. $C_{12}H_{18}N_2O_3$ requires C, 60.5; H, 7.6; N, 11.8%). The infrared spectrum showed absorption at 2703, 2500 (both NH_2^+), 1605, 1493 (both C=C), 1292, 1266, 1031, 841, and 821 $cm.^{-1}$.

Nitrosamine. Addition of a freshly prepared solution of sodium nitrite in dilute hydrochloric acid to the base precipitated the nitroso derivative. The nitrosamine was recrystallised from ethanol as colourless prisms, m.p. 94°, and, on addition of phenol and concentrated sulphuric acid, gave the greenish-blue colour (changing to red on dilution) which is characteristic of nitroso derivatives of secondary amines (Liebermann's Test). Bands occurred in the infrared spectrum of the nitrosamine at 1495, 1412, 1299, 1250, 1166, 1099, 1073, 1053, 1032, 978, 870, 817, and 737 $cm.^{-1}$ The broad band of high intensity at 1299 $cm.^{-1}$ appears to be characteristic of dialkylnitrosamines in the dimeric state, for which the N=O frequency is reported to fall at about 1310 $cm.^{-1}$ (54).

Benzenesulphonamide. This derivative was prepared by the Schotten-Baumann method. After recrystallisation from ethanol

it was obtained as colourless blades, m.p. 127-8° (Found: C, 68.5; H, 6.5; N, 4.35%. $C_{18}H_{21}NO_2S$ requires C, 68.5; H, 6.7; N, 4.4%). The infrared spectrum of the benzenesulphonyl derivative showed absorption at 1490, 1339 ($-SO_2-$), 1279, 1164 ($-SO_2-$), 1125, 1094, 1081, 1065, 816, 761, 748 (C_6H_5), 716, and 698 cm.$^{-1}$ (C_6H_5). Absorption in the regions of 1340 cm.$^{-1}$ and 1165 cm.$^{-1}$ has been shown to be characteristic of sulphonamides (55).

Carbon dioxide adduct (XV). A white precipitate slowly separated when carbon dioxide was passed through an ethereal solution of the isoindoline. The product was washed several times with ether but could not be recrystallised without decomposition. On heating the adduct, decomposition occurred (at 85-90°) with regeneration of the isoindoline (Found: C, 71.0; H, 7.8; N, 6.2%. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%). Analysis thus eliminated the possibility of this compound being the carbonate or bicarbonate derivative of the isoindoline. The infrared spectrum, which had bands at 2604, 2481, 1639 (C=O), 1553, 1490, 1372, 1036, 814, and 777 cm.$^{-1}$, revealed a significant absence of absorption associated with the carbonate ion at 1450-1410 cm.$^{-1}$ and 880-860 cm.$^{-1}$ (56).

Picrate. 2 drops of the tetramethylisoindoline were dissolved in 4-5 drops of ether and a solution of picric acid (in moist ether) added until the solution was just acidic. The picrate, which precipitated with some difficulty, was collected and recrystallised from ethanol to give yellow plates, m.p. 187-9°.

2,4-Dinitrophenyl derivative. Approximately equimolecular quantities of the base and 2,4-dinitrochlorobenzene

were dissolved in a little alcohol and a small excess of anhydrous potassium carbonate added. The mixture was heated on a steam-bath for a few minutes and poured into water. The brownish-yellow product which separated was washed with sodium carbonate solution and with dilute hydrochloric acid and, after recrystallisation from acetone, gave golden yellow prisms, m.p. 235-6°.

1,2,3,4,7-Pentamethylisoindoline (XVI)

Eschweiler methylation of the tetramethylisoindoline (XIV) was carried out following the procedure of Icke, Wisegarver, and Alles (57). On adding 2 g. of the isoindoline (XIV) to a mixture of 2.1 g. 90% formic acid and 1.3 g. 37% formaldehyde, a vigorous exothermic reaction occurred with evolution of carbon dioxide. When the reaction was complete (after heating for 9½ hours at 90-100°), dilute hydrochloric acid was added and any remaining formic acid was removed under reduced pressure over steam. The solution, on cooling, formed a glue which was taken up in a little water and 3 ml. of 40% caustic soda added. The upper, dark brown layer was separated and the lower aqueous layer extracted with benzene. This extract was dried over potassium carbonate and the benzene was removed using a rotary evaporator (distillation was prevented by excessive frothing). For distillation of the residue under reduced pressure a bath temperature of 180° was necessary to distil the pentamethyl-isoindoline at 56° (0.2 mm.) (considerable frothing again occurred). The isoindoline (XVI) was a pale yellow, basic oil; a yield of 0.48 g. (22%) was obtained. The infrared spectrum of (XVI), recorded as a liquid film on a Perkin-Elmer Model 21

double-beam instrument, showed absorption at 2950, 2863, 2760 ($N-CH_3$), 1622, 1498, 1339, 1325, 1290, 1260, 1225, 1170, 1127, 1064, 941, 806, and 783 $cm.^{-1}$.

Methiodide (XVII). Methyl iodide was added dropwise to the freshly distilled pentamethylisoindoline (XVI) until the mixture became warm and solidified. A few drops of excess methyl iodide were added and the brown solid material was taken up in hot ethanol. Several recrystallisations from ethanol gave colourless needles, m.p. 264-6° (dec.) (Found: C, 51.0; H, 6.5%. $C_{14}H_{22}NI$ requires C, 50.8; H, 6.65%). The methiodide slowly decomposed in air. Infrared absorption occurred at 1497, 1406, 1196, 1076, 1044, 924, 822, and 808 $cm.^{-1}$.

Benzene-1,2,3,4-tetracarboxylic acid (XVIII)

A mixture of 0.98 g. of 1,3,4,7-tetramethylisoindoline, 15 g. of potassium permanganate, and 3.8 g. of potassium carbonate in 100 ml. of water was allowed to stand at room temperature for 3 days. The mixture was then refluxed for 4 hours and made weakly acidic with 6N hydrochloric acid. Sulphur dioxide was passed through the solution to first precipitate and then redissolve the manganese dioxide formed. The solution was acidified to pH 4 with hydrochloric acid and continuously extracted with ether for 8 hours. This removed by-products but very little of the tetracarboxylic acid. The solution was further acidified to a strength of 6N with concentrated hydrochloric acid, upon which some inorganic material was precipitated. This was filtered off and the filtrate continuously extracted with ether for 86 hours. After drying over sodium sulphate, the

ethereal extract was evaporated down to give crude benzene-tetracarboxylic acid. Recrystallisation from dilute hydrochloric acid gave 0.45 g. (32%) of (XVIII) as colourless prisms, m.p. 236-41° (lit. 236-8° (58), 236.5-8° (59)). The infrared spectrum of the acid showed absorption at 2688 (broad, OH), 1701 (C=O), 1272, and 763 $cm.^{-1}$

It was found that a large excess of permanganate was needed for complete oxidation of the isoindoline, as a smaller excess gave only partial oxidation to 3,6-dimethylphthalic anhydride. The anhydride was among the products extracted at pH 4 and was identified by comparison with the synthetic compound (XXI) (see Figure 6, p. 18).

Tetramethyl ester (XIX). Diazomethane was prepared (61), and a solution of 0.038 g. of the tetracarboxylic acid in ether was added. On cooling, 0.032 g. (70%) of the tetramethyl ester (XIX) crystallised. Recrystallisation from ether gave colourless needles, m.p. 129-32° (lit. 131-3° (58), 129-30° (60)). Mixed m.p. with an authentic sample of 1,2,3,4-tetracarbomethoxybenzene gave 130-2°. The infrared spectrum of (XIX) showed absorption at 1724, 1305, 1266, 1248, 1192, 1167, 1143, 1110, 1000, 983, 943, 868, 816, 807, 756, and 730 $cm.^{-1}$, and was identical with the spectrum of the authentic sample of the tetramethyl ester.

2,4,6-Trimethylphthalimide (XXII)

2,5-Dimethylfuran was prepared from acetonylacetone by the method of Gaertner and Tonkyn (62), and was obtained in 37% yield as a colourless liquid, b.p. 86-88° (lit. 92.5-94° (62)).

17 g. of the 2,5-dimethylfuran was dissolved in 100 ml. of anhydrous ether and 18 g. of maleic anhydride added. The resulting yellow solution was shaken at room temperature for 24 hours and refrigerated, on which colourless crystals of the Diels-Alder adduct (XX) separated (63). The product was recrystallised from ether to give 17 g. (49%) of (XX), m.p. 74-5° (lit. 78° (61)). The infrared spectrum of (XX) showed absorption at 1855, 1779 (both C=O of anhydride), 1582 (C=C), 1318, 1238, 1209, 1098, 978, 926, 863, 834, and 745 $cm.^{-1}$ (the carbonyl bands are discussed below).

Dehydration of the Diels-Alder addition product (XX) was accomplished by the method of Newman and Lord (64). After recrystallisation of the product from benzene, a 26% yield of 3,6-dimethylphthalic anhydride (XXI) was obtained as colourless prisms, m.p. 144-6° (lit. 144-6° (64)). The infrared spectrum showed absorption at 1838, 1757 (both C=O of anhydride), 1495, 1241, 1192, 1161, 901, and 890 $cm.^{-1}$. The double carbonyl absorption has been pointed out as characteristic of anhydrides; moreover, the positions of these bands in the Diels-Alder adduct (XX) and the dimethylphthalic anhydride (XXI) correspond closely with the positions of the carbonyl absorptions in succinic and phthalic anhydride respectively, there being a shift to lower frequency for both carbonyl bands going from the aliphatic to the aromatic system (65). The constant separation of the two carbonyl bands of anhydrides, despite overall shifts in frequency, has also been noted (65) and is borne out in this case.

3,6-Dimethylphthalic anhydride was converted to N-methyl-3,6-dimethylphthalimide (XXII) by a reaction similar to that described for phthalic anhydride itself (66). 4.6 g. of dimethylphthalic anhydride (XXI) was dissolved in 40 ml. of 20% methylamine in water and the solution warmed to 50°. A slurry separated which was filtered off and collected. The filtrate was refluxed until the slurry again became too heavy to allow smooth boiling. The cycle of filtering and refluxing was repeated four times, after which no further solid separated. The material, which had been filtered and collected, was heated at 130° for 2 hours and dried in vacuo to give a quantitative yield of the phthalimide (XXII). The product sublimed above 150° and, purified in this way, gave a white sublimate, m.p. 176-7° (Found: C, 70.1; H, 5.6; N, 7.5%. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%). The infrared spectrum showed absorption at 1748, 1704 (both C=O of imide), 1264, 1163, 1010, 893, 820, and 755 $cm.^{-1}$ As with the anhydrides (XX) and (XXI) previously noted, the carbonyl absorption of the phthalimide (XXII) was doubled, but was now at lower frequency. The positions of these bands are in agreement with the values reported for compounds containing the N-substituted imide grouping (67).

2,4,7-Trimethylisoindoline (XXIII) and Derivatives

Methyl lithium was prepared by the method of Gillman, Zollner and Selby (68). To 50 ml. of this freshly prepared solution was added 0.25 g. of N-methyl-3,6-dimethylphthalimide (XXII) in 8 ml. of anhydrous ether. After standing overnight the

mixture was refluxed on a steam bath for 2 hours. The precipitated lithium hydroxide was filtered off and the dried ethereal solution was refluxed with 0.5 g. of lithium aluminium hydride for 10 hours. After decomposition of the excess lithium aluminium hydride with moist ether the solvent was evaporated, leaving 0.11 g. (48%) of crude 2,4,7-trimethylisoindoline (XXIII). This product was obtained as an initially colourless, basic oil, which turned yellow on standing, and was the result of direct reduction of the imide (XXII) (see pp. 18-19). The infrared spectrum of (XXIII) as a liquid film showed absorption at 2770, 1855 and 1681 (both weak), 1590, 1495, 1372, 1316, 1297, 1253, 1220, 1189, 1153, 1116, 1040, 1000, 935, 868, 805, and 726 $cm.^{-1}$

Methiodide. The crude trimethylisoindoline (XXIII) reacted exothermically with methyl iodide and the brown solid formed was taken up in and crystallised from ethanol. Recrystallisation from ethanol gave 2,4,7-trimethylisoindoline methiodide (XXIV) as colourless plates, m.p. 231-2° (Found: C, 47.3; H, 6.0; I, 41.5; N, 4.4%. $C_{12}H_{18}IN$ requires C, 47.5; H, 6.0; I, 41.9; N, 4.6%). Infrared absorption occurred at 1502, 1337, 1316, 1264, 1166, 1038, 988, 923, 897, and 844 $cm.^{-1}$ (see Table II, p. 13 for the ultraviolet spectrum of this product).

Hydrochloride. When anhydrous hydrogen chloride was passed through an ethereal solution of the trimethylisoindoline, solid material separated immediately. The product was collected and recrystallised from acetone to give 2,4,7-trimethylisoindoline hydrochloride as colourless, slightly hygroscopic needles, m.p. 213-6° (Found: Cl, 17.9; N, 7.1%. $C_{11}H_{16}ClN$ requires Cl, 17.9;

N, 7.1%). A qualitative ultraviolet spectrum of the hydrochloride (in methanol) showed values of $\lambda_{max.}$ at 266, 271, and 275 mμ (cf. Table II, p. 13).

Picrate. On adding a solution of the trimethylisoindoline in ether to a solution of picric acid in moist ether a yellow precipitate slowly formed. This picrate derivative was recrystallised from ethanol as yellow plates, m.p. 182-4°. Its infrared spectrum showed absorption at 2695 (broad), 1621, 1558, (NO_2), 1357 (NO_2), 1304, 1256, 1155, 1070, 819, 791, 747, and 706 $cm.^{-1}$

N-methyl-3,4,7-trimethyl-3-hydroxyphthalimidine (XXV)

Methyl magnesium iodide was prepared from 3 g. of magnesium turnings in 25 ml. of anhydrous ether and 7.5 g. of methyl iodide in 30 ml. of anhydrous ether. 1.0 g. of N-methyl-3,6-dimethylphthalimide (XXII) in 60 ml. of anhydrous ether was added dropwise, with stirring, to the Grignard reagent, during which the solution turned yellow and solid was deposited on the walls of the flask. This solid material was removed, treated with water, and extracted with ether. The ether extract was thoroughly dried over anhydrous sodium sulphate and then refluxed for 10 hours with 2 g. of lithium aluminium hydride. Decomposition of the excess lithium aluminium hydride with moist ether, followed by evaporation of the solvent gave a yellow, crystalline product. This crude material was recrystallised twice from a dichloromethane:hexane mixture (1:10) to give 0.74 g. (56%) of a product presumed to be N-methyl-3,4,7-trimethyl-3-hydroxyphthalimidine (XXV). This compound was obtained as

colourless needles, m.p. 159-62° (Found: C, 70.0; H, 7.2; N, 6.8%. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%). The infrared spectrum of the phthalimidine showed absorption at 3390 (OH), 1678 (C=O), 1590, 1499, 1258, 1242, 1172, 1152, 1116, 1083, 1055, 1009, 962, 862, 847, 821, 802, 769, and 715 $cm.^{-1}$ The phthalimidine (in ethanol) exhibited absorption in its ultraviolet spectrum with $\lambda_{max.}$ 231 (ϵ 8,100), 246, (ϵ 5,570), 282 (ϵ 2,700), and 292 mμ (ϵ 2,250).

1,3-Diphenyl-4,7-dimethylisoindoline (XXVI) and Derivatives

Following the method described by Kreutzberger and Kalter (69) for the preparation of 2,5-diphenylpyrrole, trans-1,2-dibenzoylethylene was first hydrogenated to dibenzoylethane. The reaction was carried out in a Magne-Dash autoclave at room temperature, using palladised charcoal as catalyst. The symmetrical dibenzoylethane was obtained as colourless prisms, m.p. 145-8° (lit. 147-8° (69)), in 61% yield.

The dibenzoylethane was treated with ammonia-saturated ethanol in a Magne-Dash autoclave (69) to obtain 2,5-diphenylpyrrole. The pyrrole, after recrystallisation from aqueous ethanol, was obtained as pale yellow plates, m.p. 143-5° (lit. 143-4° (69)), in 96% yield. The infrared spectrum showed absorption at 3584 (NH), 1957, 1869 (both weak aromatic overtones), 1608, 1582, 1520, 1282, 1156, 1104, 1078, 1055, 942, 907, 784, 760, 754, and 691 $cm.^{-1}$ The increased intensity of the normally weak C=C absorption at 1582 $cm.^{-1}$ is consistent with the enhanced conjugation effect in 2,5-diphenylpyrrole (70). The unusual splitting of the monosubstituted benzene absorption

into two components at 760 and 754 cm.$^{-1}$ is noteworthy (cf. (71)). The ultraviolet spectrum of 2,5-diphenylpyrrole (in ethanol) had $\lambda_{max.}$ 230 (ϵ 10,900) and 329 mμ (ϵ 30,100).

A mixture of 10 g. of 2,5-diphenylpyrrole, 6 g. of acetonylacetone and 150 ml. of absolute ethanol was added in small lots to 65 g. of tin, 250 ml. of 6N hydrochloric acid, and 125 ml. of absolute ethanol boiling under reflux. The pyrrole mixture turned a deep red colour when it came into contact with the acidic medium but this gradually faded to a pale yellow as reduction took place. Refluxing was continued for 40 hours, after which ethanol was distilled from the reaction mixture until a heavy slurry formed. The mixture was made strongly basic with 40% sodium hydroxide and solid material precipitated at the interface between an upper, dark red layer and the lower aqueous layer. The solid material and aqueous layer were drawn off and extracted with 50 ml. of benzene. The benzene layer took up the solid, organic material forming a yellow solution, while the remaining inorganic material dissolved in the aqueous layer on dilution. The aqueous layer was further extracted with benzene three times. Evaporation of the benzene extract gave a yellow, crystalline product which was recrystallised from ethanol to yield 8.8 g. (64%) of 1,3-diphenyl-4,7-dimethylisoindoline (XXVI), obtained as off-white needles, m.p. 172-4° (Found: C, 88.0; H, 6.9; N, 4.85%; M 295. $C_{22}H_{21}N$ requires C, 88.2; H, 7.1; N, 4.7%; M 299). The infrared spectrum of (XXVI) showed absorption at 3344 (NH), 1595, 1493, 1414, 1304, 1267, 1185, 1066, 1027, 893, 849, 817, 784, 753, and 698 cm.$^{-1}$ (see Table V for the ultraviolet spectrum).

Nitrosamine (XXVII). A modification of the usual procedure was necessary for the preparation of this derivative on account of the large quantity of ethanol used to dissolve the isoindoline, the nitrosamine being (relatively) soluble in ethanol. 2.1 g. of the isoindoline was dissolved in 120 ml. of absolute ethanol and the solution was cooled in ice. 1.5 ml. of concentrated hydrochloric acid was added, followed immediately by an ice-cooled solution of 1.5 g. of sodium nitrite in 3 ml. of water. The mixture was allowed to stand in ice for 15 minutes, during which some sodium nitrite was precipitated. This was filtered off and the nitrosamine was precipitated by addition of water. The derivative was collected and recrystallised from an ethanol:benzene (3:1) mixture to give 2.05 g. (89%) of 1,3-diphenyl-4,7-dimethylisoindoline nitrosamine, obtained as pale yellow blades, m.p. 183-5° (Found: C, 80.7; H, 6.0; N, 8.5%. $C_{22}H_{20}N_2O$ requires C, 80.5; H, 6.1; N, 8.5%). The infrared spectrum of the nitrosamine showed absorption at 1590, 1488, 1414, 1292, 1236, 1206, 1176, 1076, 1030, 855, 831, 821, 769, 746, 733, 712, and 698 $cm.^{-1}$. As with the 1,3,4,7-tetramethylisoindoline nitrosamine, the presence of the N=O group in (XXVII) was distinguished by the appearance of the very strong band at 1292 $cm.^{-1}$ (54).

N-Amino derivative (XXVIII). 15 g. of glacial acetic acid was added slowly to a stirred mixture of 2.7 g. of the nitrosamine (XXVII) and 15 g. of zinc dust in 30 ml. of water (72). The mixture was stirred in ice for 3 hours and then at room temperature for 3 days. Finally, the reaction mixture was heated

on a steam bath for 1 hour and filtered hot. The residue, which contained the product, was digested with warm benzene and filtered again to remove traces of zinc. Evaporation of the benzene gave a yellow solid which, on recrystallisation from an ethanol:benzene mixture (9:1), produced 0.9 g. (35%) of 2-amino-1,3-diphenyl-4,7-dimethylisoindoline (XXVIII) (which is also a derivative of hydrazine). This compound was obtained as off-white prisms, m.p. 177-9° (Found: C, 83.6; H, 7.1; N, 8.9%. $C_{22}H_{22}N_2$ requires C, 84.0; H, 7.05; N, 8.9%). Its infrared spectrum showed absorption at 3378, 3311 (both NH_2), 3178 (weak), 1597, 1495, 1340, 1309, 1261, 1238, 1115, 1079, 1031, 975, 935, 895, 841, 828, 815, 804, 789, 750, 741, and 698 $cm.^{-1}$. The fact that the frequencies of the symmetric mode (3311 $cm.^{-1}$) and the antisymmetric mode (3378 $cm.^{-1}$) of the amino group obey the empirical relation connecting these two quantities (73) is strong evidence for the presence of a free NH_2 group in (XXVIII).

Hydrochloride. As anhydrous hydrogen chloride was passed through an ethereal solution of 1,3-diphenyl-4,7-dimethyl-isoindoline a white precipitate slowly formed. This was recrystallised from a benzene:chloroform (10:1) mixture to give colourless prisms which decomposed above 210° (Found: Cl, 10.8; N, 4.5%; M (by titration with silver nitrate), 336. $C_{22}H_{22}ClN$ requires Cl, 10.55; N, 4.2%; M, 336). The hydrochloride showed infrared absorption at 2625, 2488, 2183 (all NH_2^+), 1558, 1495, 1277, 1192, 1029, 923, 840, 767, 752, 737, 727, and 697 $cm.^{-1}$

Benzenesulphonamide. The isoindoline (XXVI) was dissolved in a small quantity of pyridine and benzenesulphonyl

chloride was added. The solution turned green and, on standing, solid precipitated. Recrystallisation from ethanol gave a colourless product, m.p. 177-9°, which showed infrared absorption at 1493, 1333 ($-SO_2-$), 1311, 1160 ($-SO_2-$), 1088, 988, 839, 756, 736, and 695 $cm.^{-1}$ (cf. (55)).

2,5-Dimethyl-3-tricyanovinylpyrrole (XXXV)

0.75 g. of freshly distilled 2,5-dimethylpyrrole in 5 ml. of dry tetrahydrofuran was added to 1 g. of tetracyanoethylene in 10 ml. of tetrahydrofuran. The solution turned deep blue initially and then underwent a striking series of colour changes from deep green to pale green and finally to orange. The tetrahydrofuran was evaporated leaving an orange-coloured product which was recrystallised from a 1% solution of ethanol in benzene. 1.2 g. (77%) of 2,5-dimethyl-3-tricyanovinylpyrrole (XXXV) was obtained as brick-red needles, m.p. 192-4° (Found: C, 67.1; H, 4.1; N, 28.6%. $C_{11}H_8N_4$ requires C, 67.3; H, 4.1; N, 28.55%).

The infrared spectrum of (XXXV) showed absorption at 3236 (NH), 2217 (C≡N), 1590, 1515, 1393, 1267, 1134, 1028, 995, 970, 807, 769, 724, and 700 $cm.^{-1}$. The band at 3236 $cm.^{-1}$ had the enhanced intensity characteristic of the pyrrole NH absorption (74) and established that substitution by tetracyanoethylene had not occurred at the nitrogen atom of the pyrrole nucleus. The strong C≡N absorption fell at the lower end of the range quoted for $\alpha\beta$-unsaturated nitriles (75).

The visible and ultraviolet spectrum of the tetracyanoethylene derivative had absorption maxima at 251.5 (ϵ 4,610),

362 (ϵ 13,600), and 433 mμ (ϵ 16,400) (cf. 49).

Acetonylacetone bis-2,4-dinitrophenylhydrazone

0.5 g. of solid 2,4-dinitrophenylhydrazine was dissolved in 25 ml. of warm ethanol, and 0.25 g. quantities of acetonylacetone and 2,5-dimethylpyrrole added to separate portions of the solution. The mixtures were heated to boiling and 1 ml. of 10% sulphuric acid was added to each. A yellow precipitate formed immediately in both cases and, after standing a few minutes, these were collected and recrystallised from pyridine. The acetonylacetone derivative was obtained as yellow prisms, m.p. 269-72° (dec.) and the 2,5-dimethylpyrrole gave a similar, yellow, crystalline product, m.p. 272-3° (dec.) (lit. for "mono" derivative, 262° (48)). Mixed m.p. gave 270-3° (dec.), establishing the identity of these two compounds (Found: C, 45.6; H, 3.95; N, 23.75%. $C_{18}H_{18}N_8O_8$ requires C, 45.6; H, 3.8; N, 23.6%). These two derivatives were, therefore, the bis-2,4-dinitrophenylhydrazone of acetonylacetone (cf. (48)). Their infrared spectra (which confirmed their identity) showed absorption at 3322 (NH), 1608, 1585, 1529, 1508, 1416, 1359, 1330, 1300, 1259, 1134, 1075, 911, 839, 741, and 724 cm.$^{-1}$

Similar treatment of 2,5-diphenylpyrrole with 2,4-dinitrophenylhydrazine reagent gave no derivative, even after standing for several weeks, from which it was concluded that no ring-opening to the diketone occured in this case.

2,2-Bis-[3-(2,5-dimethylpyrrolyl)] propane (XXXIX)

2.5 g. of freshly distilled 2,5-dimethylpyrrole was treated with acetone and hydrochloric acid according to the method described by Allen and Young (48). An orange-coloured product resulted which, after three recrystallisations from 60% aqueous ethanol, yielded 1.9 g. (63%) of a compound, for which the structure (XXXIX) appears most likely. The compound was obtained as pink needles, m.p. 177-8° (dec.) (lit. 174° (48)) (Found: C, 78.7; H, 9.6; N, 12.1%; M, 245. $C_{15}H_{22}N_2$ requires C, 78.2; H, 9.6; N, 12.2%; M, 230). Allen and Young, on the basis of a nitrogen analysis and molecular weight determination, assigned a molecular formula $C_{18}H_{26}N_2$ to this condensation product of acetone with 2,5-dimethylpyrrole but did not propose a structure (48).

The $C_{15}H_{22}N_2$ product obtained in this case decomposed slowly, deterioration being accompanied by reddening of colour and regeneration of 2,5-dimethylpyrrole, the odour of which soon became detectable. The freshly prepared compound gave a positive Ehrlich reaction, suggesting an unsubstituted β-position on a pyrrole nucleus, and its infrared spectrum showed absorption at 3425 (NH), 1582, 1497, 1391, 1199, 1166, 1073, 793, 708, and 692 $cm.^{-1}$. The NH absorption at the same position and with the enhanced intensity which characterised the spectrum of 2,5-dimethylpyrrole, supported a structure for the condensation product in which this nucleus was retained.

The ultraviolet spectrum of (XXXIX) below 270 mμ, in common with that of 2,5-dimethylpyrrole (76), showed absorption

increasing to an extinction coefficient of 9,900 at 220 mμ (with no maximum in this region). Towards longer wavelength the spectrum had $\lambda_{max.}$ at 307 mμ (ϵ 80). A structure such as (XXXIX), therefore, seems to be in accord with the evidence available so far.

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