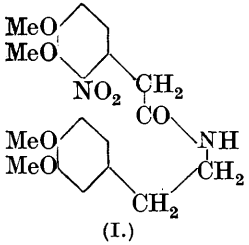
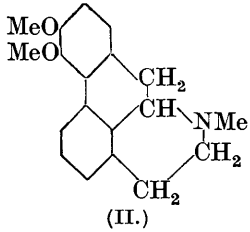
CCXXI.—*Synthetical Experiments on the Aporphine Alkaloids. Part VII. Attempted Syntheses of* apo*Morphine Dimethyl Ether.*

By JOHN MASSON GULLAND, ROBERT DOWNS HAWORTH, CYRIL JOSEPH VIRDEN, and (in part) ROBERT KENNETH CALLOW.

IN Parts I—V of this series (J., 1928, 581, 1132, 1834, 2083; this vol., p. 658), the syntheses of the methyl ethers of certain phenolic aporphine alkaloids were achieved by the interaction of phosphorus pentachloride and suitably substituted amides in cold chloroform solution. Thus, 2′-nitro-3′ : 4′-dimethoxyphenylaceto-β-3 : 4-dimethoxyphenylethylamide (I) yielded corytuberine dimethyl ether (p. 1834). Efforts have now been made to apply this method to the synthesis of *apo*morphine dimethyl ether (II), but we have been unable to obtain this substance by the action of phosphorus pentachloride on 2-nitro-3 : 4-dimethoxyphenylaceto-β-phenylethylamide (III).



(I.)



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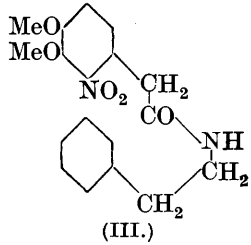
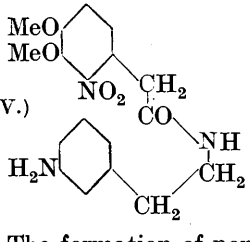


(III.)

This lack of success and a similar failure to synthesise 3 : 4 : 5-trimethoxyaporphine (Part VI, this vol., p. 1444) led to the conclusion that the facile closure of the *iso*quinoline ring requires the presence of a strongly para-directive group in the para-position to that in which ring closure is to take place. It was hoped that this activation might be attained and the difficulty overcome by the use of an acyl derivative of 2′-nitro-3′ : 4′-dimethoxyphenylaceto-β-3-aminophenylethylamide (IV). Considerable difficulties were encountered in the preparation of β-3-aminophenylethylamine, but this base was ultimately obtained by the following series of reactions. The condensation of 3-nitrobenzyl chloride with sodiomalonic ester yielded a mixture of ethyl 3-nitrobenzylmalonate and *ethyl di-(3-nitrobenzyl)malonate*, from which *3-nitrobenzylmalonic acid* was readily isolated by taking advantage of the relative ease with which its ester is hydrolysed by alkali as compared with di-(3-nitrobenzyl)malonic ester. β-3-Nitrophenylpropionic acid, which was obtained by heating the corresponding malonic acid, was converted into β-3-*nitrophenylpropionamide* by the action of ammonia on the acid chloride. This amide, when submitted to the Hofmann reaction, yielded β-3-*nitrophenylethylamine*, which was reduced to β-3-*aminophenylethylamine dihydrochloride* by means of stannous chloride in a mixture of acetic and hydrochloric acids. *2′-Nitro-3′ : 4′-dimethoxyphenylaceto-β-3-(2″-nitro-3″ : 4″-dimethoxyphenylacetamido)phenylethylamide* (V) was readily obtained as a neutral oil by the action of β-3-aminophenylethylamine on 2-nitro-3 : 4-dimethoxyphenylacetyl chloride, but no basic material could be isolated when this diamide was treated with phosphorus pentachloride in chloroform solution. This behaviour is similar to that of 2′-nitro-3′ : 4′-dimethoxyphenylaceto-β-3-(2″-nitro-3″ : 4″-dimethoxyphenylacetamido)-4-methoxyphenylethylamide (Part VI), and it is evident that activation by the 2-nitrohomoveratroylamido-group is insufficient for facile ring closure to a derivative of *iso*quinoline.

(IV.)



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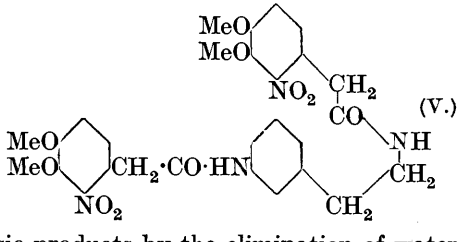
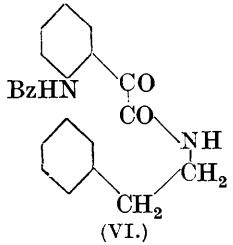


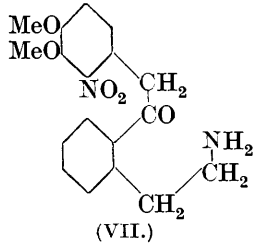
The formation of non-basic products by the elimination of water from the amide (III) (compare Kay and Pictet, J., 1913, **103**, 950) and from similar amides in which nuclear activation is insufficient

(Part VI; Gadamer, Oberlin, and Schoeler, *Arch. Pharm.*, 1925, **263**, 81) is probably to be explained by the activation of the methylene group of the acyl residue by the nitro-group in the *o*-position. Experiments were therefore instituted to achieve the *iso*quinoline synthesis by using an amide in which the methylene group was replaced by a carbonyl group, which could be reduced at a later stage. The preparation of 2-nitro-3 : 4-dimethoxyphenylglyoxylic acid for this purpose by the interaction of 2-nitro-3 : 4-dimethoxybenzoyl chloride and potassium cyanide proved unsatisfactory, and attention was therefore directed for trial experiments to the use of 2-benzamidophenylglyoxylic acid, which may be obtained from isatin by benzoylation in alkaline solution (Schotten, *Ber.*, 1891, **24**, 773). When some preliminary difficulties in the preparation of the acid chloride of this acid had been surmounted, 2-*benzamidophenylglyoxylo*-β-*phenylethylamide* (VI) was submitted to the action of dehydrating agents. Unfortunately, no *iso*quinoline derivative could be isolated, and investigations along these lines were abandoned.

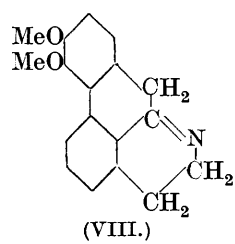
The ease with which a carbonyl and an amino-group lose the elements of water to form a five- or six-membered ring has for long seemed to us to offer a possible means of building the nitrogenous ring of the aporphines on to a pre-formed phenanthrene system. If this were possible, the difficulties presented by the synthesis of the ethers of *apo*morphine and *iso*thebaine might be overcome. The experiments carried out with this object in view have not so far been successful, but they reveal several points of interest. The fundamental idea has been the preparation of a substituted deoxybenzoin (VII) or an allied substance, which would not only undergo the Pschorr reaction, forming a phenanthrene derivative, but would also lose with ease the elements of water, yielding a dihydro*iso*quinoline (VIII).



(VI.)



(VII.)

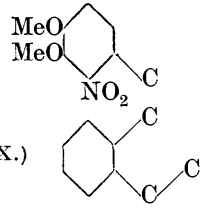


(VIII.)

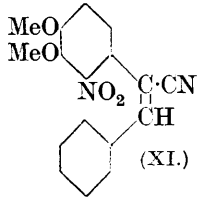
A consideration of the problem in its various aspects made it clear that the reacting molecules in the proposed synthesis must be (IX) and (X) respectively, and that processes such as the Friedel–Crafts reaction could not be employed. In furtherance of this idea,

it seemed that 2-nitro-3 : 4-dimethoxyphenylacetonitrile was the most suitable compound containing activated hydrogen attached to the α-carbon atom, and a number of preliminary experiments were performed under various conditions in order to test the possibility of preparing a derivative of deoxybenzoin by the action of ethyl benzoate or benzoyl chloride on the sodio-derivative of this nitrile. No crystalline product could be isolated; this result may possibly be due to self-condensation of the nitrile, as has been observed in the case of phenylacetonitrile (compare Thorpe and collaborators, J., 1906, **89**, 1913; 1907, **91**, 1287).

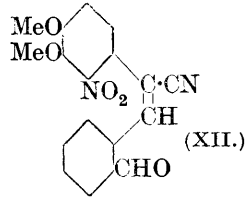
2-Nitro-3 : 4-dimethoxyphenylacetonitrile readily reacted with benzaldehyde in sodium ethoxide solution, yielding *α-cyano-2-nitro-3 : 4-dimethoxystilbene* (XI).* This substance was extremely stable to hydrolysis, and attempts to convert it into a derivative of deoxybenzoin were unsuccessful. Conditions were then devised for the preparation of *α-cyano-2-nitro-3 : 4-dimethoxy-2′-aldehydostilbene* (XII) by the condensation of phthalaldehyde with 2-nitro-3 : 4-dimethoxyphenylacetonitrile, but the aldehyde (XII) yielded no crystalline acid when heated with malonic acid and piperidine in pyridine solution in an attempt to introduce the requisite side chain into the molecule. A warm solution of the aldehyde (XII) and phenylhydrazine in glacial acetic acid deposited the crystalline *phenylhydrazone*.

(IX.) 

(X.)



(XI.)

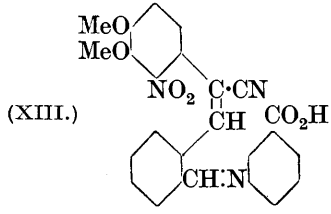


(XII.)

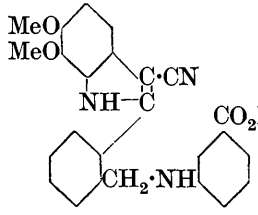
Several unsuccessful attempts were made to reduce the nitro-group in (XII) directly to the amino-group. Finally, after some preliminary experiments in which *piperonylidene-*m*-aminobenzoic acid* and *piperonylidene-*p*-aminobenzoic acid* were prepared, the aldehyde (XII) was converted into *α-cyano-2-nitro-3 : 4-dimethoxy-*

* After the experiments described in this paper had been completed, Pfeiffer, Engelhardt, and Alfuss (*Annalen*, 1928, **467**, 158) showed that the condensation of phenylacetonitrile with certain aldehydes probably leads to the *cis*-nitrile, $\begin{matrix}Ph—C—CN\\ H—C—Ar\end{matrix}$, and not to the *trans*-form. These results may also apply to 2-nitro-3 : 4-dimethoxyphenylacetonitrile, in which case the substances described here would be useless for the synthesis of aporphines. Since no investigations along these lines have been made, we prefer to retain the *trans*-configuration in the formulæ to avoid obscuring the ideas underlying this work.

2′-m-*carboxyphenyliminomethylstilbene* (XIII) by condensation with *m*-aminobenzoic acid in order to render the material soluble in ammonia solution, and this Schiff's base was reduced by means of ferrous sulphate and ammonia to a basic acid, $C_{25}H_{21}O_4N_3$ or $C_{25}H_{23}O_4N_3$, which appeared from its properties to be 2-(2′-m-*carboxyanilinomethylphenyl*)-3-*cyano*-6 : 7-*dimethoxyindole* (XIV) or the corresponding *dihydroindole* derivative. The analytical figures for this substance and its derivatives are in equal agreement with those required by either formula, and we have been unable to arrive at a definite conclusion on this point. The substance did not exhibit the colour reactions characteristic of indoles, and it might therefore be argued that the structure of a dihydroindole was the more probable, but it would be unwise to predict the behaviour of a complex 2 : 3-disubstituted indole of this nature. Whichever structure be correct, it is clear that the substance is unsuitable for the synthesis of *apo*morphine dimethyl ether. It was readily soluble in cold sodium carbonate solution and in hydrochloric acid, but the latter solution immediately deposited the sparingly soluble *hydrochloride*. This salt was unaffected by boiling concentrated hydrochloric acid, thus affording a clear proof that the double bond of the Schiff's base had been reduced. The solution in concentrated sulphuric acid was emerald, and a characteristic colour change to blue occurred when a trace of sodium nitrite was added. The colour was completely discharged on dilution, and extraction of the diluted solution with ether yielded a nitroso-compound in the form of a colourless oil which gave Liebermann's nitroso-reaction. Diazotisation did not take place. Decomposition of the hydrochloride with sodium acetate regenerated the basic acid (XIV) in the forms of a *tri*- and a *hexa-hydrate*, which were partly dehydrated when heated, and were converted into the anhydrous compound by crystallisation from glacial acetic acid. Further details are described in the experimental section.



(XIII.)



(XIV.)

EXPERIMENTAL.

3-*Nitrobenzylmalonic Acid and Ethyl Di*-(3-*nitrobenzyl*)*malonate*.—*m*-Nitrobenzyl chloride (17 g.; 1 mol.) in alcohol (150 c.c.) was

added to a solution of sodiomalonic ester, prepared from ethyl malonate (32 g.; 2 mols.), sodium (4·6 g.; 2 mols.) and alcohol (100 c.c.). The mixture was boiled under reflux for 2 hours, most of the alcohol removed by distillation, and the residue acidified with dilute hydrochloric acid, and extracted with chloroform. The extract was dried, and freed from solvent, and the resulting semi-solid mass, consisting of 3-nitrobenzylmalonic ester and di-(3-nitrobenzyl)malonic ester, was shaken with warm 30% potassium hydroxide solution (50 c.c.) until the violent reaction had ceased. After dilution with water, the solid *ethyl di-(3-nitrobenzyl)malonate* was collected (A); it crystallised from alcohol in colourless prisms (10 g.), m. p. 112° (Found: C, 58·4; H, 5·1. $C_{21}H_{22}O_8N_2$ requires C, 58·6; H, 5·1%). The filtrate from (A) was acidified with concentrated hydrochloric acid and extracted repeatedly with ether. The solvent was removed from the dried extract; the residual *3-nitrobenzylmalonic acid* crystallised from hot water in colourless prisms (10 g.), m. p. 171° (decomp.) (Found: C, 49·9; H, 3·9. $C_{10}H_9O_6N$ requires C, 50·2; H, 3·8%).

β-3-Nitrophenylpropionic acid was prepared by heating 3-nitrobenzylmalonic acid at 180° until the evolution of carbon dioxide had ceased. It crystallised from hot water in needles, m. p. 117—118° (compare Gabriel and Steudemann, *Ber.*, 1882, **15**, 846) (Found: equiv., 194. Calc., 195).

β-3-*Nitrophenylpropionamide.* — β-3-Nitrophenylpropionic acid (10 g.) and thionyl chloride (10 c.c.) were heated under reflux for 2 hours. The excess of thionyl chloride was removed by distillation, and the residue was stirred into cold concentrated ammonia solution (*d* 0·880; 150 c.c.). The *amide* crystallised from benzene in colourless plates (8 g.), m. p. 99° (Found: N, 14·5. $C_9H_{10}O_3N_2$ requires N, 14·4%).

β-3-*Nitrophenylethylamine.* — Powdered β-3-nitrophenylpropionamide (3·3 g.) was shaken until dissolved in a solution of sodium hypochlorite prepared from sodium hydroxide (33 c.c. of 10%) and chlorine (from potassium permanganate, 1 g., and concentrated hydrochloric acid). The solution was heated at 60—70° for 1 hour, mixed with sodium hydroxide (10 g.), and extracted with benzene. The dried extract was saturated with hydrogen chloride, and the *hydrochloride* (2·5 g.) collected; it crystallised from alcohol in pale yellow prisms, m. p. 207—209° (Found: Cl, 17·7. $C_8H_{10}O_2N_2$,HCl requires Cl, 17·5%).

β-3-*Aminophenylethylamine.*—A solution of stannous chloride (30 g.) in concentrated hydrochloric acid (60 c.c.) was added to a warm solution of β-3-nitrophenylethylamine hydrochloride (10 g.) in glacial acetic acid (15 c.c.). The white precipitate which separated at first dissolved when the mixture was heated on the water-

bath for 2 hours. Water was then added, the solution evaporated to dryness, the residue dissolved in hot water, and the tin precipitated as sulphide and removed by filtration. The filtrate was evaporated to dryness, and the residue crystallised from alcohol, from which β-3-*aminophenylethylamine dihydrochloride* (6·5 g.) separated in colourless needles, m. p. 310° (decomp.) (Found : Cl, 34·3. $C_8H_{12}N_2,2HCl$ requires Cl, 34·0%).

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3-(2″-*nitro*-3″ : 4″-*dimethoxyphenylacetamido*)*phenylethylamide* (V).—A benzene solution of β-3-aminophenylethylamine, obtained by decomposing the hydrochloride (2 g.) with sodium hydroxide, extracting the solution with benzene, and drying the extract, was added to a cooled solution of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (prepared from the acid, 5 g.) in benzene (40 c.c.). A slight excess of 10% sodium hydroxide solution was then added, and the benzene layer was separated, washed first with sodium hydroxide solution and then with dilute hydrochloric acid, dried, and freed from solvent. The neutral gummy residue (5 g.) dissolved readily in all the usual organic solvents except light petroleum, and all attempts to crystallise it have been unsuccessful (Found : N, 9·2. $C_{28}H_{30}O_{10}N_4$ requires N, 9·6%). No basic material could be isolated after this diamide and phosphorus pentachloride had been allowed to react in chloroform solution for 12 days at room temperature.

[With R. K. CALLOW.] 2-*Benzamidophenylglyoxylo*-β-*phenylethylamide* (VI).—2-Benzamidophenylglyoxylic acid was prepared from sodium isatinate by benzoylation in presence of the least possible excess of alkali. The clear yellow solution obtained by dissolving isatin (15 g.) in warm sodium hydroxide solution (100 c.c. of 2*N*) was cooled, and shaken with an excess of benzoyl chloride. As the solution became acid, it deposited the product as a sticky solid, which was collected, and crystallised from dilute acetic acid; it then melted at 193—195°. When an ethereal solution of this acid was added to an ethereal solution of β-phenylethylamine, β-*phenylethylamine* 2-*benzamidophenylglyoxylate* separated; it formed colourless needles, m. p. 177—179° (decomp.), when crystallised from water (Found : N, 7·4. $C_{23}H_{22}O_4N_2$ requires N, 7·2%).

Fruitless attempts were made to prepare the amide from the salt just described by treating an ethereal suspension with phosphorus pentachloride or phosphoric oxide. Eventually, however it was obtained by dissolving dried, powdered 2-benzamidophenylglyoxylic acid (2·5 g.) in thionyl chloride (20 g.), removing the excess of thionyl chloride and the gaseous products by repeated evaporation of the mixture with dry benzene under reduced pressure,

and adding the resulting benzene solution to a cooled solution of β-phenylethylamine (3 g.) in benzene. The solution of the amide thus obtained was washed with sodium carbonate, hydrochloric acid, and water, dried, and freed from solvent. Two crystallisations from alcohol yielded the *amide* as pale yellow needles, m. p. 136·5—138° (Found: C, 74·6; H, 5·5. $C_{23}H_{20}O_3N_2$ requires C, 74·2; H, 5·4%). This substance was recovered unchanged after being submitted to the action of phosphorus pentachloride in chloroform for 1 month.

α-*Cyano*-2-*nitro*-3 : 4-*dimethoxystilbene* (XI).—A *N*-solution of sodium ethoxide in absolute alcohol (4—6 drops) was added gradually to a solution of 2-nitro-3 : 4-dimethoxyphenylacetonitrile (1 g.) and benzaldehyde (0·5 g.) in a small quantity of absolute alcohol (heated to 40—50°) until a faint permanent red colour was produced. Piperidine (2 drops) was used occasionally in place of sodium ethoxide without affecting the yield. The mixture was maintained at 55° for 1 hour and cooled; α-*cyano*-2-*nitro*-3 : 4-*dimethoxystilbene* (0·78 g.) then separated and was collected next day. It crystallised from alcohol in faintly yellow needles, m. p. 125·5°, which dissolved readily in ether and acetone (Found: C, 65·6; H, 4·5. $C_{12}H_{14}O_4N_2$ requires C, 65·8; H, 4·6%). This substance was recovered unchanged from an anhydrous ethereal solution which had been saturated with hydrogen bromide and preserved for some days.

α-*Cyano*-2-*nitro*-3 : 4-*dimethoxy*-2′-*aldehydostilbene* (XII). — *N*-Sodium ethoxide solution (0·5 c.c.) was added to 2-nitro-3 : 4-dimethoxyphenylacetonitrile (10 g.) and *o*-phthalaldehyde (5·6 g.) dissolved in a small quantity of absolute alcohol at 45°, the vigour of the reaction being checked by cooling in tap-water. The product separated as an oil which rapidly solidified. The yield was 80% of that theoretically possible, and was considerably decreased by the use of piperidine in place of sodium ethoxide. When recrystallised from alcohol, α-*cyano*-2-*nitro*-3 : 4-*dimethoxy*-2′-*aldehydostilbene* formed long colourless needles, m. p. 153°, which were sparingly soluble in the usual solvents (Found: C, 63·8; H, 4·3. $C_{18}H_{14}O_5N_2$ requires C, 63·9; H, 4·1%). This substance was recovered unchanged from a suspension in concentrated hydrochloric acid which had been boiled for 24 hours. It was destroyed by reduction with zinc dust in hot dilute hydrochloric or acetic acid, but was not reduced by treatment with stannous chloride or tin in a cold mixture of glacial acetic and hydrochloric acids, nor by the action of ferrous hydroxide in aqueous-alcoholic ammonia.

A dark green amorphous precipitate was obtained by pouring into hydrochloric acid a mixture of the aldehyde (XII) (0·5 g.),

malonic acid (0·75 g.), and piperidine (3 drops) which had been heated with pyridine at 100° for 2 hours. This precipitate was collected and extracted with sodium carbonate solution, and the extract was acidified with hydrochloric acid. The resulting pale brown, amorphous solid dissolved readily in alcohol, acetone, acetic acid, and chloroform, was sparingly soluble in benzene, and insoluble in water and ligroin, and yielded no crystalline material.

The *phenylhydrazone* separated from a solution of the aldehyde (XII) and phenylhydrazine in warm glacial acetic acid, and crystallised from alcohol in golden-yellow leaflets, m. p. 179—180° (Found : N, 13·1. $C_{24}H_{20}O_4N_4$ requires N, 13·1%).

Piperonylidene-m-*aminobenzoic Acid.*—This and the following experiment were performed in order to investigate the conditions for preparation, and the properties, of Schiff's bases of this type.

An intimate mixture of piperonal and *m*-aminobenzoic acid was heated at 160° for 30 minutes. The product crystallised from alcohol in cream-coloured needles, m. p. 244—245°, which were sparingly soluble in cold alcohol (Found : C, 66·8; H, 4·2. $C_{15}H_{11}O_4N$ requires C, 66·9; H, 4·1%). It was rapidly hydrolysed by warm dilute mineral acids, and was not reduced by ferrous hydroxide in cold ammoniacal solution in an atmosphere of hydrogen.

Piperonylidene-p-*aminobenzoic acid*, which did not crystallise well, was prepared in a similar manner to that just described. It formed brown nodules of needles, m. p. 243°, when crystallised from alcohol (Found : N, 5·3. $C_{15}H_{11}O_4N$ requires N, 5·3%).

α-*Cyano*-2-*nitro*-3 : 4-*dimethoxy*-2′-m-*carboxyphenyliminomethylstilbene* (XIII).—An intimate mixture of equimolecular proportions of *m*-aminobenzoic acid and α-cyano-2-nitro-3 : 4-dimethoxy-2′-aldehydostilbene (XII) was heated slowly in an oil-bath. At 135°, the mass shrank together and became darker in colour, and the temperature was maintained at this point for 30 minutes. The resulting Schiff's base crystallised from alcohol in yellow needles, m. p. 237° (decomp.) (Found : N, 9·2. $C_{25}H_{19}O_6N_3$ requires N, 9·2%). It was readily hydrolysed by warm dilute mineral acids, and dissolved in cold dilute ammonia solution, from which it was precipitated in an amorphous condition by acetic acid. An ammoniacal solution decomposed when heated at 100° for a short time, changing in colour from bright yellow to green, and finally to black. An uncrystallisable material was obtained by acidification of this solution.

2-(2′-m-*Carboxyanilinomethylphenyl*)-3-*cyano*-6 : 7-*dimethoxyindole* (XIV) *or the Dihydro-derivative.*—A solution of the substance (XIII) (0·8 g.) in air-free, ice-cold, dilute aqueous ammonia

(20 c.c.) was added to a solution of ferrous sulphate (4·4 g.) in ice-cold, air-free water (20 c.c.), which was stirred mechanically in a flask fitted with a mercury-sealed stirrer and swept out by a stream of hydrogen. The initial green precipitate slowly darkened in colour, and ultimately became black. Stirring was continued for 6 hours, and the mixture was kept in the atmosphere of hydrogen till next day. The precipitated ferroso-ferric oxide was too finely divided to be collected on a filter, and charcoal was therefore added, and the solution acidified with acetic acid. The mixture thus obtained was collected, washed with water, and extracted with acetone in a Soxhlet apparatus for several hours. After the acetone had been removed by distillation, the crystalline residue of the *substance* (XIV) was recrystallised from alcohol, forming colourless needles, m. p. 225° (Found: by macroanalysis, C, 69·4; H, 5·0: by microanalysis, C, 70·0; H, 5·0; N, 9·8. $C_{25}H_{21}O_4N_3$ requires C, 70·3; H, 4·9; N, 9·8. $C_{25}H_{23}O_4N_3$ requires C, 69·9; H, 5·4; N, 9·8%). This substance dissolved slowly in cold sodium hydroxide, sodium carbonate, or ammonia solution.

When the product of the reduction was dissolved in hot dilute hydrochloric acid, and the solution was cooled, the *hydrochloride* separated in yellow needles, m. p. 307° (decomp.) (Found: C, 62·7; H, 4·9; Cl, 7·2. $C_{25}H_{21}O_4N_3,HCl,H_2O$ requires C, 62·3; H, 5·0; Cl, 7·4. $C_{25}H_{23}O_4N_3,HCl,H_2O$ requires C, 62·2; H, 5·4; Cl, 7·6%). It was sparingly soluble in cold water, but dissolved on boiling. If the resulting solution, which was yellow and faintly cloudy, was allowed to cool without the vessel being scratched with a rod, the liquid set to a jelly. If, on the other hand, the vessel was scratched, a solid separated which was faintly yellow and melted over a wide range from 200° upwards. This was probably a mixture of the hydrochloride and the base, which had been formed by hydrolysis.

When the hydrochloride was warmed gently with aqueous sodium acetate solution, a colourless crystalline substance, m. p. 320°, was deposited. It was sparingly soluble in the usual solvents, and was crystallised by dissolving it in much hot 95% alcohol and concentrating the filtered solution; it then formed colourless needles, m. p. 322° [Found in different specimens: (i) loss at 100°, 7·9. $C_{25}H_{21}O_4N_3,3H_2O$ losing $2H_2O$ requires H_2O, 7·5%. $C_{25}H_{23}O_4N_3,3H_2O$ losing $2H_2O$ requires H_2O, 7·4%. Found in material dried at 100°: by macroanalysis, C, 67·2; H, 5·4; N, 9·2. $C_{25}H_{21}O_4N_3,H_2O$ requires C, 67·4; H, 5·2; N, 9·4%. $C_{25}H_{23}O_4N_3,H_2O$ requires C, 67·2; H, 5·6; N, 9·4%. (ii) Loss at 110° under reduced pressure in presence of phosphoric oxide, 6·9. Loss of $2H_2O$ from $C_{25}H_{21}O_4N_3,6H_2O$ or $C_{25}H_{23}O_4N_3,6H_2O$

requires H_2O, 6·7%. Found in material dried thus : by micro-analysis, C, 60·2; H, 5·6; N, 8·5. $C_{25}H_{21}O_4N_3,4H_2O$ requires C, 60·1; H, 5·8; N, 8·4%. $C_{25}H_{23}O_4N_3,4H_2O$ requires C, 60·0; H, 6·2; N, 8·4%]. These analyses, when considered in conjunction with the properties described below, indicated that these specimens were a tri- and a hexa-hydrate respectively of the substance (XIV). These hydrates dissolved in sodium hydroxide, sodium carbonate, and ammonia solution, regenerated the hydrochloride when dissolved in dilute hydrochloric acid, and were converted into the reduction product, m. p. 225°, when crystallised from glacial acetic acid.

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