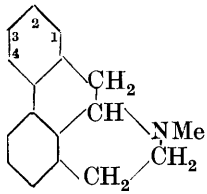
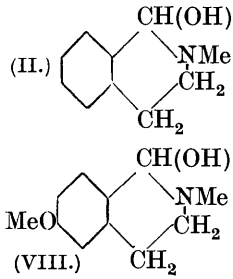
CCXXXVI.—*Anhydro-compounds derived from 2-Nitro-3 : 4-dimethoxyphenylacetonitrile and Certain* pseudo-*Bases.*

By JOHN MASSON GULLAND and CYRIL JOSEPH VIRDEN.

SEVERAL examples are recorded in the literature in which aporphine bases have been synthesised by means of series of reactions which have as their starting point the condensation of *o*-nitrotoluene, or a derivative, with a *pseudo*-base of the *iso*quinoline group. For instance, Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) prepared the simplest member of the series, aporphine (I), using *o*-nitrotoluene and 1-hydroxy-2-methyl-1 : 2-dihydro*iso*quinoline, obtained from *iso*quinoline methiodide. The application of this method to the synthesis of the large group of aporphines, or their ethers, which contain oxygen atoms in positions 3 and 4 requires the condensation of suitable *pseudo*-bases with 2-nitrohomoveratrole (III). This substance, which we have obtained in the

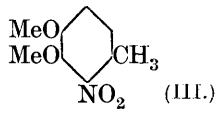


(I.)



(II.)

(VIII.)



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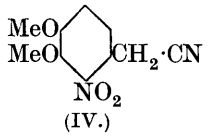
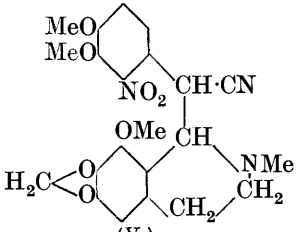


(IV.)

manner described by Oberlin (*Arch. Pharm.*, 1925, **263**, 641) and also by the methylation of 2-nitro-3-hydroxy-*p*-tolyl methyl ether

(Gulland and Robinson, J., 1926, 1977), does not appear to undergo such condensations, and it is evident that the activation by the nitro-group in position 2 is insufficient; this observation is noteworthy when contrasted with the reactivity of 6-nitrohomoveratrole (Robinson and Robinson, J., 1914, **105**, 1456).

It seemed possible that this obstacle might be surmounted by the use of a derivative of 2-nitrohomoveratrole in which the methyl group was activated in such a manner that, first, no interference with the reduction of the nitro-group would occur, and, secondly, the activating group might be removed at a later stage without affecting the remainder of the molecule. Some years ago, therefore, one of the authors directed his attention to the use of 2-nitro-3 : 4-dimethoxyphenylacetonitrile (IV), which was obtained by the interaction of 2-nitro-3 : 4-dimethoxybenzyl chloride with potassium cyanide in aqueous alcohol (Kay and Pictet, J., 1913, **103**, 953). 2-*Nitro*-3 : 4-*dimethoxyphenylacetamide* has been isolated as a by-product of this reaction. The expectation that the methylene group of this nitrile would exhibit the same high reactivity as that of phenylacetonitrile was justified, and *anhydrocotarnine*-2-*nitro*-3 : 4-*dimethoxyphenylacetonitrile* (V), *anhydrolaudaline*-2-*nitro*-3 : 4-*dimethoxyphenylacetonitrile* (VI), and 1-α-*cyano*-2′-*nitro*-3′ : 4′-*dimethoxybenzyl*-6-*methoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (VII) were readily obtained in crystalline condition by warming alcoholic solutions of the nitrile (IV) and cotarnine, laudaline, and 1-*hydroxy*-6-*methoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (VIII) respectively.



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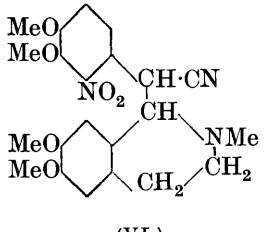
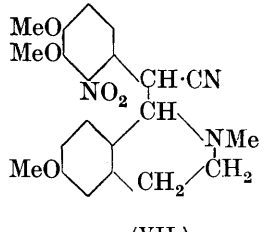


(VI.)



(VII.)

Some description is required of the stages in the preparation of the *pseudo*-base (VIII). The starting point in these experiments was β-3-methoxyphenylethylamine, which has been obtained more recently by Helfer (*Helv. Chim. Acta*, 1924, **7**, 945), and also by Chakravarti, Haworth, and Perkin (J., 1927, 2265) from *m*-methoxybenzaldehyde in the manner originally employed by the authors. An attempt to prepare this amine from ω-*nitro*-m-*methoxystyrene* by way of m-*methoxyphenylacetaldoxime* was abandoned on account of the poor yield obtained. The *formyl* derivative of β-3-methoxy-

phenylethylamine yielded 6-*methoxy*-3 : 4-*dihydro*iso*quinoline* when submitted to the action of phosphorus oxychloride, and the *pseudo*-base (VIII) was readily obtained from this by treatment of the *methiodide* with aqueous potash. Reduction of the methiodide yielded 6-*methoxy*-2-*methyltetrahydro*iso*quinoline*, which was characterised by the preparation of the *hydriodide* and *picrate*, and oxidation by permanganate converted the *pseudo*-base into 1-*keto*-6-*methoxy*-2-*methyltetrahydro*iso*quinoline*.

The subsequent treatment of the anhydro-compounds (VI) and (VII)—namely, reduction of the nitro-group, completion of the phenanthrene system, hydrolysis of the cyano-group, and elimination of carbon dioxide—broke down at the first stage, because these substances were readily hydrolysed by dilute acids with re-formation of their generators, a property shared also by the base (V). Moreover, it was found impossible to effect reduction in alkaline media without causing simultaneous fission of the molecule. For example, reduction of the base (VII) by means of ammoniacal ferrous hydroxide yielded 2-*amino*-3 : 4-*dimethoxyphenylacetonitrile*, which was also prepared for comparison from the nitrile (IV) by a similar process.

Recently, in view of the work of Avenarius and Pschorr (see below) a closer study has been made of the action of hydrochloric acid on the anhydro-compound (VII). This substance dissolved in 2*N*-hydrochloric acid at room temperature, forming a solution which remained clear for some time; when the solution was warmed to about 60°, it became cloudy and deposited an oil which soon crystallised, and was identified as the nitrile (IV). The *pseudo*-base (VIII) was isolated from the mother-liquor. A group of experiments was then carried out in which solutions of the base (VII) in concentrated hydrochloric acid, in various strengths of dilute hydrochloric acid, and in aqueous-alcoholic hydrochloric acid respectively, were boiled for periods ranging from two to fifteen minutes. In every case fission of the molecule occurred, and the *pseudo*-base was isolated as the *periodide*, $C_{11}H_{14}ONI_5$, by the addition of sodium iodide to the acid solution. This periodide and the very similar *periodide*, $C_{11}H_{14}ONI_3$, of the same melting point, were prepared for comparison by adding the requisite amount of standardised alcoholic iodine solution to alcoholic solutions of 6-methoxy-3 : 4-dihydro*iso*quinoline methiodide. Finally, the procedure adopted by Avenarius and Pschorr in their experiments—namely, hydrolysis with concentrated hydrochloric acid and subsequent reduction with tin—was followed and resulted in the isolation of a small quantity of a base (probably 6-methoxy-2-methyltetrahydro*iso*quinoline), which could not be diazotised.

Recently Avenarius and Pschorr (*Ber.*, 1929, **62**, 321) have described a synthesis of *apo*morphine dimethyl ether (I, with OMe in positions 3 and 4), in which the anhydro-compound obtained from 2-nitro-3 : 4-dimethoxyphenylacetonitrile (IV) and 1-hydroxy-2-methyltetrahydro*iso*quinoline (II) was heated with hydrochloric acid and then reduced with tin. This treatment was claimed, first, to have hydrolysed the cyano-group and eliminated the resulting carboxyl as carbon dioxide, and, secondly, to have reduced the nitro-group, and a description is given of 1-(2′-amino-3′ : 4′-dimethoxybenzyl)-2-methyltetrahydro*iso*quinoline dihydrochloride, and of its conversion into " apomorphine dimethyl ether methiodide," which formed colourless needles, m. p. 195°. It is remarkable that Avenarius and Pschorr state " Diese erwiesen sich als identisch mit dem aus natürlichem Apomorphin-dimethyläther erhaltenen Jodmethylat." *apo*Morphine is lævorotatory, and there can surely be no possibility that its methyl ether methiodide (m. p. 195°, corr.; $[\alpha]_D$ — 42·03°; Pschorr, Jaeckel, and Fecht, *Ber.*, 1902, **35**, 4389) is identical with the synthetical material of Avenarius and Pschorr. Further, there is no fundamental reason why *dl-apo*morphine dimethyl ether methiodide should melt at the same temperature as its lævorotatory isomeride.

In view of the apparent discrepancy between the results of the experiments with the substance (VII) and those recorded by Avenarius and Pschorr, it was decided to attempt to repeat the synthesis of *apo*morphine dimethyl ether as described by these authors. We cannot claim to have duplicated their conditions exactly, since the experimental details of their paper are at times vague, and this lack of detail is especially in evidence in the all-important description of the hydrolysis of the cyano-group by hydrochloric acid.

Avenarius and Pschorr used as starting material either *iso*quinoline methiodide or 1-hydroxy-2-methyltetrahydro*iso*quinoline (II), which they obtained by the isomerisation of formyl-β-phenylethylmethylamine * by means of thionyl chloride. Up to the present, we have been unable to obtain the substance (II) by this method, nor has a careful search of the literature revealed any instance in which the action of thionyl chloride has brought about either (*a*) ring closure of formyl-β-phenylethylamine (or a derivative) to a 3 : 4-dihydro*iso*quinoline base, or (*b*) isomerisation of formyl-β-phenyl-

* The analytical figures recorded for this substance by Avenarius and Pschorr show that it can scarcely have been pure : " $C_{10}H_{13}NO$. Ber. C 67·01, H 7·31; Gef. C 67·42, H 7·38." This theoretical percentage is surely incorrect, since $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0%. It is unfortunate that the boiling point is not stated.

ethylmethylamine (or a derivative) to the corresponding *pseudo*-base. We have therefore restricted ourselves to the use of *iso*-quinoline methiodide. Solutions of the nitrile (IV) and *iso*quinoline methiodide in equimolecular proportion in sodium ethoxide solution (containing two equivalents of sodium) were boiled gently for a short time and then kept at room temperature for periods ranging from 24 to 60 hours. The subsequent treatment of these solutions was diversified as widely as possible. In some cases, they were heated with various quantities of concentrated hydrochloric acid under reflux or in open flasks, reduced with tin, basified, and extracted with ether. In others, a more elaborate process was resorted to, by which the basic constituents, including potentially the condensation product, were separated from considerable fractions of acidic and feebly basic character, and were then heated with concentrated hydrochloric acid, reduced with tin, and extracted with ether after basification. Treatment of the dried ethereal extracts with hydrogen chloride yielded mixtures of crystals and oily material, which were dissolved in dilute sulphuric acid and "diazotised." In every case, only a fraction of the theoretical amount of nitrite solution, if any, was required, assuming that the material under investigation was 1-(2′-amino-3′ : 4′-dimethoxybenzyl)-2-methyltetrahydro*iso*quinoline dihydrochloride. From each of these solutions, following the usual methods of treatment with copper powder, we have isolated as the only crystalline product a methiodide, m. p. 192° (corr.), which has been shown to be 2-methyltetrahydro*iso*-quinoline methiodide, both by analysis, and by comparison with a specimen prepared from 2-methyltetrahydro*iso*quinoline.

We do not maintain that *apo*morphine dimethyl ether cannot be synthesised by this procedure, but wish rather to state that if 2-nitro-3 : 4-dimethoxyphenylacetonitrile does react with *iso*-quinoline methiodide under the influence of sodium ethoxide to form an anhydro-compound, then in our hands fission of this anhydro-compound occurred under widely divergent conditions of hydrolysis, and that this result is supported by similar experiments with analogous substances.

EXPERIMENTAL.

ω-Nitro-3-methoxystyrene.—(i) A cold solution of sodium (2·3 g.) in absolute alcohol (50 c.c.) was added in the course of 1 hour to a solution of *m*-methoxybenzaldehyde (12·4 g.) and nitromethane (6·1 g.), which was cooled in ice. After the mixture had remained in ice until a test portion deposited no oil when diluted with water, the sodium salt of the *aci*-form of 3-methoxy-α-hydroxy-β-nitroethylbenzene (compare Bouveault and Wahl, *Compt. rend.*, 1902,

135, 41) was precipitated with ether, collected, and dehydrated by heating with fused zinc chloride (10 g.) and acetic acid (50 c.c.) for 3 hours. When this solution was mixed with water, *ω-nitro-3-methoxystyrene* separated in crystalline condition; it was recrystallised from alcohol or benzene–ligroin, from both of which it separated in shining yellow leaflets, m. p. 91—92° (Found: C, 60·3; H, 5·4. $C_9H_9O_3N$ requires C, 60·3; H, 5·1%). It dissolved readily in chloroform, acetone, and hot benzene, but was insoluble in ligroin.

(ii) The conditions used successfully in other cases by Knoevenagel and Walter (*Ber.*, 1904, **37**, 4502) resulted in the formation of a very sparingly soluble substance, and the following conditions were therefore employed. A mixture of *m*-methoxybenzaldehyde (10·8 g.), nitromethane (5·2 g.), methylamine hydrochloride (0·4 g.), and anhydrous sodium carbonate (0·2 g.) in absolute alcohol (10 c.c.) was kept at room temperature for 48 hours. Almost pure ω-nitro-3-methoxystyrene separated in glistening plates, which were collected and washed with alcohol. The filtrate was kept at room temperature, and after 24 hours the crystals were collected, and successive crops were removed from the filtrate at intervals of 12 hours. After a total yield of 12 g. had been isolated, a mixture of two substances began to separate from the solution. One of these was very sparingly soluble in the usual solvents and appeared to be the insoluble substance mentioned above, whilst the other could be crystallised from ethyl alcohol. A separation was therefore readily effected, and after several crystallisations from alcohol, the more soluble substance was obtained in pale yellow, non-lustrous clusters of needles, which melted at 91—92° and at the same temperature when mixed with the glistening plates. Investigation of the two forms showed that they were dimorphic.

3-Methoxyphenylacetaldoxime.—A mixture of ω-nitro-3-methoxystyrene (4 g.), zinc dust (15 g.), acetic acid (10 g.), and water (200 c.c.) was warmed on the water-bath until the styrene had dissolved. The liquid was filtered, and on cooling, the filtrate deposited a brown oil, which soon became partly crystalline. It was dissolved in ether, and the oxime separated from coloured oily impurities by repeated extraction of the ethereal solution with small quantities of sodium hydroxide solution. Acidification of the alkaline extract with acetic acid yielded the *oxime* as a colourless oil which soon solidified, and crystallised from ligroin (b. p. 60—80°) in colourless needles (0·4 g.; 11% of theory), m. p. 91° (Found: C, 65·6; H, 6·7. $C_9H_{11}O_2N$ requires C, 65·5; H, 6·7%). It readily dissolved in the usual solvents.

Formyl-β-3-methoxyphenylethylamine.—*m*-Methoxycinnamic acid was prepared in the manner which has since been described by

Chakravarti, Haworth, and Perkin (*loc. cit.*), and was converted into β-3-methoxyphenylethylamine as described by Helfer (*loc. cit.*). The amine (20 g.) and anhydrous formic acid (20 g.) were heated at 175° for 6 hours; the product was poured into water and extracted with benzene. The extract, when dried and distilled, yielded the *formyl* derivative as an oil, b. p. 216°/17 mm. (Found: N, 7·9. $C_{10}H_{13}O_2N$ requires N, 7·8%).

6-*Methoxy*-3 : 4-*dihydro*isoquinoline *Methiodide*.—The vigorous reaction which occurred when formyl-β-3-methoxyphenylethylamine (30 g.) was added to phosphorus oxychloride (50 c.c.) was moderated by cooling in ice, and the mixture was then heated on the water-bath for 30 minutes, cooled, and mixed with ligroin. The basic product of the reaction, which remained as a salt in the lower layer, was washed with ligroin by decantation and dissolved in dilute hydrochloric acid. Concentrated potassium hydroxide solution precipitated 6-methoxy-3 : 4-dihydro*iso*quinoline as an oil, which was extracted with benzene, dried with solid potash, freed from solvent, and distilled; b. p. 155°/16 mm. When methyl iodide was added to a dry benzene solution of the base, the *methiodide* rapidly separated; it was recrystallised from alcohol, forming bright yellow needles, m. p. 199° (decomp.), which readily dissolved in hot water (Found: I, 41·8. $C_{11}H_{14}ONI$ requires I, 41·9%).

The Periodides of 6-*Methoxy*-3 : 4-*dihydro*isoquinoline *Methiodide*.—The volumes of standard alcoholic iodine solution required for one and for two molecular quantities were added to alcoholic solutions of the methiodide. The dark oils which separated solidified after several hours, and were crystallised from alcohol, from which both *periodides* separated in chocolate-brown needles, m. p. 82° (decomp.) (Found: I, 64·0 and 77·0 respectively. $C_{11}H_{14}ONI_3$ requires I, 68·4%. $C_{11}H_{14}ONI_5$ requires I, 78·3%). These substances did not crystallise readily from alcohol, since they melted under the solvent at a low temperature, and always separated very slowly.

1-*Hydroxy*-6-*methoxy*-2-*methyltetrahydro*isoquinoline (VIII).—3 : 4-Dihydro*iso*quinoline methiodide (5 g.) was dissolved in warm water (50 c.c.), and the solution was cooled so that no separation of material occurred. The addition of concentrated potassium hydroxide (15 c.c. of 50%) precipitated the pseudo-*base* as an oil, which rapidly crystallised when seeded with a crystal obtained previously by rubbing a small portion with ether. This product was collected on asbestos, washed with a little water, and dried in a vacuum over solid potash. When crystallised from benzene, the *pseudo*-base formed colourless prisms, m. p. 102°, which decomposed rather readily when dissolved in hot solvents (Found: N, 7·2. $C_{11}H_{15}O_2N$ requires N, 7·2%).

6-*Methoxy*-2-*methyltetrahydro*iso*quinoline*.—A solution of 6-methoxy-3 : 4-dihydro*iso*quinoline methiodide (4 g.) in concentrated hydrochloric acid (50 c.c.) was heated on the water-bath and reduced by the gradual addition of an excess of granulated zinc. The solution was filtered and made alkaline, and the base liberated was extracted with ether. The extract, when dried and distilled, left 6-methoxy-2-methyltetrahydro*iso*quinoline as a colourless oil which did not crystallise. It was converted into the *hydriodide* by adding sodium iodide to a solution in dilute hydrochloric acid. When crystallised from water, this salt formed colourless needles, m. p. 173—174°, which were sparingly soluble in ethyl alcohol (Found in material dried at 100° : C, 43·5; H, 5·5. $C_{11}H_{15}ON$,HI requires C, 43·3; H, 5·2%).

The picrate separated as an oil when prepared in alcoholic solution, but soon solidified, and formed yellow rosettes, m. p. 130—131°, when recrystallised from methyl alcohol.

1-*Keto*-6-*methoxy*-2-*methyltetrahydro*iso*quinoline*.—6-Methoxy-3 : 4-dihydro*iso*quinoline methiodide (6 g.), dissolved in water (300 c.c.), was converted into the corresponding methochloride by the usual method. Dilute sodium hydroxide (60 c.c. of 2*N*) and potassium permanganate (1·1 g. in 30 c.c. of water) were then added, and after 1 hour, the solution was filtered, neutralised with dilute sulphuric acid, and concentrated on the water-bath. The oil which separated was dissolved in ether and dried with potassium carbonate. When distilled, this extract yielded 1-*keto*-6-*methoxy*-2-*methyltetrahydro*iso*quinoline* as an oil which rapidly crystallised, and separated from a mixture of ligroin (b. p. 40—60°) and benzene in colourless rhombic plates, m. p. 50° (Found : C, 68·8; H, 6·7. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8%).

Anhydrocotarnine-2-*nitro*-3 : 4-*dimethoxyphenylacetonitrile* (V).—A solution of cotarnine (1 g.) and 2-nitro-3 : 4-dimethoxyphenylacetonitrile (1 g.) in alcohol (10 c.c.) was warmed for a few moments on the water-bath until crystals formed in the liquid. When cold, the anhydro-compound was collected and recrystallised from ethyl alcohol, forming cream-coloured needles, m. p. 153° (decomp.), having gradually become red from 120° (Found : C, 60·0; H, 5·4. $C_{22}H_{23}O_7N_3$ requires C, 59·9; H, 5·2%). This and the two following compounds were readily hydrolysed by warm dilute acids.

Anhydrolaudaline-2-*nitro*-3 : 4-*dimethoxyphenylacetonitrile* (VI).—A solution of laudaline (Pyman, J., 1909, **95**, 1266; compare Robinson and Shinoda, J., 1926, 1989) (0·2 g.) and 2-nitro-3 : 4-dimethoxyphenylacetonitrile (0·2 g.) in alcohol (6 c.c.) was warmed for a few minutes and kept over-night. The anhydro-derivative then separated when the vessel was scratched with a glass rod, and crystallised

from alcohol in clusters of faintly yellow needles, m. p. 125—127° (Found : C, 62·0; H, 6·1. $C_{22}H_{25}O_6N_3$ requires C, 61·8; H, 5·9%).

1-α-*Cyano*-2′-*nitro*-3′ : 4′-*dimethoxybenzyl*-6-*methoxy*-2-*methyltetrahydroisoquinoline* (VII) was prepared from 2-nitro-3 : 4-dimethoxyphenylacetonitrile (4·8 g.) and 1-hydroxy-6-methoxy-2-methyltetrahydro*iso*quinoline (4·2 g.) in a manner similar to that used above. It crystallised from alcohol in clusters of yellow needles (6 g.), m. p. 95—96° (Found : C, 63·8; H, 5·8. $C_{21}H_{23}O_5N_3$ requires C, 63·5; H, 5·8%). The nitrile (IV) was isolated after an attempt to reduce this base with hot alcoholic ammonium sulphide.

Solutions of the base (VII) (0·5 g.) in each of the following solvents (5 c.c.) were made : (*a*) concentrated hydrochloric acid; (*b*) equal volumes of concentrated hydrochloric acid and water; (*c*) two volumes of concentrated hydrochloric acid and one of water; (*d*) two volumes of concentrated hydrochloric acid and one of alcohol. When these solutions were boiled for periods ranging from 2 to 15 minutes, their colour darkened, and the aqueous solutions deposited tarry material. The solutions were cooled to 0°, diluted with ice, decanted from tar, and mixed with sodium iodide. The initial dark brown, oily precipitate solidified on standing, and when crystallised from alcohol, the periodide of 6-methoxy-3 : 4-dihydro*iso*quinoline methiodide separated in chocolate-brown needles, m. p. 82° (Found : I, 78·3. Calc. for $C_{11}H_{14}ONI_5$: I, 78·3%). This substance was identical with the corresponding periodide described on p. 1797.

In an attempt to combine in one reaction both hydrolysis and reduction, a solution of the base (VII) (1 g.) in concentrated hydrochloric acid (5 c.c.) and alcohol (3·5 c.c.) was boiled under reflux for 30 minutes, and then reduced by heating for 30 minutes with an excess of tin and more concentrated hydrochloric acid (7 c.c.). After the pale yellow solution had been filtered and made alkaline with sodium hydroxide solution, ether extracted a small amount of basic oil, which did not diazotise.

2-Amino-3 : 4-dimethoxyphenylacetonitrile was obtained from the reduction of the anhydro-base (VII), and from 2-nitro-3 : 4-dimethoxyphenylacetonitrile.

(i) The base (VII) (2·1 g.) in hot alcohol (60 c.c.) was added to a reducing mixture previously prepared by the addition of concentrated aqueous ammonia (20 c.c.) and hot alcohol (80 c.c.) to a solution of ferrous sulphate (12·5 g.) in hot water (100 c.c.) containing a trace of sulphuric acid. This mixture was then heated on a water-bath for 30 minutes, filtered, and the filtrate was mixed with about 400 c.c. of alcohol in order to precipitate ammonium sulphate. This was removed by filtration, and the filtrate evaporated on the water-bath under reduced pressure. The residual gum soon crystallised,

and formed honey-coloured, boat-shaped plates, m. p. 107°, when recrystallised from water (Found : C, 62·5; H, 5·9; N, 14·5. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·2; N, 14·6%). This substance was shown by a mixed melting point determination to be identical with the specimen of 2-amino-3 : 4-dimethoxyphenylacetonitrile described below.

(ii) A solution of 2-nitro-3 : 4-dimethoxyphenylacetonitrile (1 g.) in hot alcohol (25 c.c.) was added to a reducing mixture of ferrous sulphate (11·2 g.) in water (100 c.c.) and concentrated aqueous ammonia (20 c.c.). This mixture was heated on the water-bath for 30 minutes, and the liquid was filtered through a very thin layer of charcoal, and evaporated on the water-bath until crystals separated on the surface. 2-*Amino*-3 : 4-*dimethoxyphenylacetonitrile* separated completely on cooling, and was recrystallised from water, forming colourless needles, m. p. 108°. It dissolved in cold dilute hydrochloric acid, and, when diazotised, coupled with β-naphthol in alkaline solution. In attempting to hydrolyse the cyano-group of this compound, a solution in concentrated hydrochloric acid was boiled for 3 hours, poured into water, and rendered alkaline with ammonia. The solution at once became coloured, and rapidly passed through the series of green, purple, blue, and black; no homogeneous material could be isolated.

The acetyl derivative, prepared by warming the base with acetic anhydride, adding water, and collecting the product, crystallised from water in minute colourless needles, m. p. 184°, which were insoluble in dilute acids.

Formyl-β-phenylethylmethylamine.—Potassium (6·25 g.) was powdered by stirring it mechanically under toluene (400 c.c.) in a flask fitted with a mercury-sealed stirrer, swept out by a current of hydrogen, and heated in an oil-bath. A solution of formyl-β-phenylethylamine (23 g.) in toluene (50 c.c.) was then added, and stirring was continued for 4 hours until all the potassium had reacted, the temperature being maintained at 85°. The mixture was allowed to cool, and after methyl iodide (40 g.) had been added, stirring was continued at room temperature for 18 hours, and then, after the addition of more methyl iodide (20 g.), the mixture was warmed gently for 4 hours, and kept over-night. When potassium iodide had been removed by filtration, the solvent was evaporated, and the residual *formyl-β-phenylethylmethylamine* (21 g.) distilled as a colourless oil, b. p. 183·5°/30 mm. (Found : C, 73·3; H, 8·3. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0%). In an attempt to convert this substance into the *pseudo*-base (II), a solution of the formyl derivative (21 g.) and thionyl chloride (26 c.c.) in toluene (100 c.c.) was heated on the water-bath for 20 minutes, and then boiled gently over a gauze

for 40 minutes. After the toluene and thionyl chloride had been removed under reduced pressure, the residue was extracted repeatedly with dilute hydrochloric acid, and the extracts were made alkaline with sodium hydroxide and shaken repeatedly with ether. When distilled, the ether left an oil, which was purified by solution in acid, filtration, precipitation with alkali, and extraction with ether. The colourless oil thus obtained in poor yield did not crystallise, and did not condense with the nitrile (IV). A similar experiment in which the toluene solution of the reactants was boiled vigorously for 25 minutes led to the same result.

When a solution of formyl-β-phenylethylmethylamine (4 g.) in concentrated hydrochloric acid (20 c.c.) was boiled under reflux for 4 hours, and evaporated under reduced pressure, the residual β-phenylethylmethylamine hydrochloride obtained crystallised from ether–alcohol in colourless plates, m. p. 157° (Decker and Becker, *Annalen*, 1913, **395**, 362, give m. p. 155—157°).

Attempted Preparation of dl-apo*Morphine Dimethyl Ether. 2-Methyltetrahydro*iso*quinoline Methiodide.* — The experiments described below are typical of a number which were carried out, all of which resulted in the isolation of 2-methyltetrahydro*iso*-quinoline methiodide.

(i) A mixture of the nitrile (IV) (2·0 g.), *iso*quinoline methiodide (2·4 g.), sodium ethoxide solution (12 c.c. of 1·12*N*), and alcohol (23 c.c.) was boiled gently for 15 minutes, and kept at room temperature for 42 hours. After being mixed with concentrated hydrochloric acid (35 c.c.), the solution was boiled for 45 minutes in an open flask, the volume being kept constant by the addition of concentrated hydrochloric acid. During this stage a dark oil separated, but this gradually dissolved and the solution became pale yellow when an excess of tin was added. After the reduction had proceeded for 10 minutes, more concentrated hydrochloric acid (15 c.c.) was added, and heating was continued for 35 minutes. The cooled, filtered solution was made alkaline with concentrated sodium hydroxide solution (ammonia evolved) and extracted with ether. The ethereal solution, after being dried with potassium carbonate and concentrated, yielded a hydrochloride (1·2 g.) as a mixture of gum and needles when treated with hydrogen chloride. The ether was decanted, and the hydrochloride dissolved in dilute sulphuric acid, and titrated with 1·121*N*-sodium nitrite solution (0·6 c.c.; theory, 2·8 c.c.), starch–iodide paper being used. The acid solution, after being treated with nitrite, did not couple with alkaline β-naphthol.

(ii) The course of this experiment was exactly parallel to that just described, but the hydrolysis with acid was carried out under reflux, and the reduction was prolonged for 60 minutes in all. No

dark oil separated in the experiments in which the alcohol was not allowed to boil away. The hydrochloride (1·4 g.) required 1·1 c.c. of 1·121*N*-sodium nitrite solution (theory, 3·24 c.c.).

After treatment with nitrite solution, both solutions (i) and (ii) were mixed with copper-bronze; several hours later, they were filtered, made alkaline with sodium hydroxide, and extracted with ether. The ethereal solution, when dried with potassium carbonate and distilled, yielded an oil which combined with methyl iodide in alcoholic solution to form a crystalline methiodide. This substance, when crystallised from alcohol or purified from traces of yellow impurity by the ethyl acetate–methyl alcohol method (see below), formed plates, m. p. 190° after softening from 187° (Found, by microanalysis : C, 46·1 ; H, 5·8. Calc. for $C_{11}H_{16}NI$: C, 45·7 ; H, 5·5%). There was no depression in melting point of a mixture of this substance with authentic 2-methyltetrahydro*iso*quinoline methiodide ; the mixture and the two specimens, when melted in the same bath and allowed to cool, solidified between 140° and 150°, and re-melted at 190°.

(iii) A solution of 2-nitro-3 : 4-dimethoxyphenylacetonitrile (3·0 g.), *iso*quinoline methiodide (3·7 g.), and sodium (0·63 g.) in absolute alcohol (30 c.c.) was boiled gently on the water-bath for 15 minutes and then kept at room temperature for 48 hours. Water was added, and the alkaline liquid thoroughly extracted with ether. Carbon dioxide, or hydrochloric acid, precipitated from the aqueous layer a considerable quantity of a reddish-brown amorphous solid, which did not crystallise and has not been examined further. Repeated extraction of the ethereal solution with 2*N*-hydrochloric acid yielded an acid solution of the basic products (see below) and an ethereal solution containing a red oil (1·1 g.), which was soluble in concentrated, but insoluble in dilute, hydrochloric acid, and dissolved readily in the usual organic solvents except ligroin. The acid extract (above) was made alkaline with 30% sodium hydroxide solution, and extracted thoroughly with ether. This ethereal solution was dried with potassium carbonate and evaporated, and the residual red oil (1·3 g.) was heated under reflux with boiling concentrated hydrochloric acid (25 c.c.) for 1½ hours, mixed with more hydrochloric acid (10 c.c.), and reduced for 45 minutes with an excess of tin. The pale yellow solution obtained was decanted from tin, diluted with water, made strongly alkaline with 30% sodium hydroxide solution, and extracted repeatedly with ether. The extract was dried with potassium carbonate, concentrated to 20 c.c., and treated with dry hydrogen chloride. The pale yellow, gummy hydrochloride which separated became partly crystalline on standing over-night; some of the rosettes of colourless needles, after being detached and pressed on porous porcelain, melted at

65—67°, solidified on further heating, and melted at 105°. The mixed crystals and gum (0·7 g.), freed from ether by decantation, were dissolved in 2*N*-sulphuric acid, titrated with sodium nitrite solution (0·1 c.c. of 1·12*N*; theory, 1·8 c.c.) and starch–iodide paper, and treated with copper-bronze. The acid solution was filtered, made alkaline with sodium hydroxide, and the oil was extracted with ether, dried with potassium carbonate, and freed from solvent. The residual oil reacted vigorously with methyl iodide, and the methiodide solidified on rubbing with absolute alcohol, and crystallised from the same solvent in colourless plates, m. p. 189°, alone or mixed with an authentic specimen of 2-methyltetrahydro-*iso*quinoline methiodide (Found : C, 45·4; H, 5·4%).

For comparison, 2-methyltetrahydro*iso*quinoline methiodide was prepared by reducing *iso*quinoline methiodide (2 g.) in concentrated hydrochloric acid (15 c.c.) and water (5 c.c.) with excess of zinc, and acting with methyl iodide on the 2-methyltetrahydro*iso*quinoline thus obtained. This methiodide, even when crystallised repeatedly from alcohol, melted at 190° after softening at 187°, but it was freed from a trace of a yellow impurity as follows. The methiodide was suspended in boiling ethyl acetate and just brought into solution by adding drops of methyl alcohol. On cooling, the impurity separated, and the filtered solution deposited the methiodide when boiled to remove methyl alcohol. One crystallisation from alcohol yielded the methiodide in plates, m. p. 192° (corr.) (Found : C, 46·1; H, 5·4%).

2-*Nitro*-3 : 4-*dimethoxyphenylacetamide* was first isolated from the methyl-alcoholic mother-liquor of the crystallisation of crude 2-nitro-3 : 4-dimethoxyphenylacetonitrile, but it was later obtained more readily by pouring the product of the interaction of 2-nitro-3 : 4-dimethoxybenzyl chloride with potassium cyanide into water, collecting the crystalline nitrile, and extracting the amide from the filtrate by means of chloroform. When distilled, this extract yielded 2-nitro-3 : 4-dimethoxyphenylacetamide, which crystallised from alcohol in colourless needles, m. p. 151—153° (Found : C, 49·7; H, 4·6. $C_{10}H_{12}O_5N_2$ requires C, 50·0; H, 5·0%). It was sparingly soluble in benzene, ligroin, and dilute acetic acid, and was hydrolysed to 2-nitro-3 : 4-dimethoxyphenylacetic acid by short treatment with boiling sodium hydroxide solution.

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