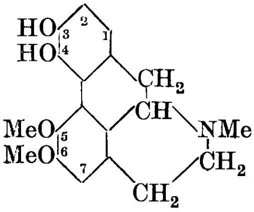
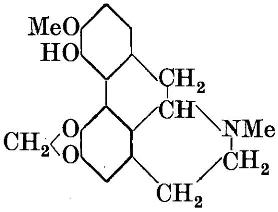
CCCCIV.—*Experiments on the Synthesis of Phenolic Aporphines. Part III. 3-Hydroxy-4 : 5 : 6-trimethoxyaporphine.*

By JOHN MASSON GULLAND, KATHERINE ISOBEL ROSS, and NORMAN BRYCE SMELLIE.

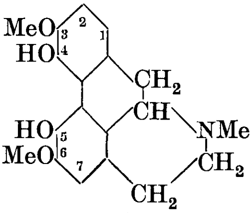
CORYTUBERINE occurs in the roots of *Corydalis* species accompanied by a number of other alkaloids. Gadamer (*Arch. Pharm.*, 1911, **249**, 498, 503, 641) recognised it as an aporphine and assigned to it the structure (I). The positions of its oxygen atoms were first established by the synthesis of its dimethyl ether by Gulland and Haworth (J., 1928, 1834).



(I.)



(II.)



(III.)

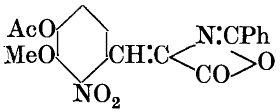
On methylation with diazomethane (Gadamer, *loc. cit.*), corytuberine yielded two monomethyl ethers, corydine and *iso*corydine; the former had also been isolated from *Corydalis* roots, but the latter was at that time purely a synthetic product. Gadamer attempted to deduce the positions of the methyl groups thus introduced from a consideration of the behaviour with faintly alkaline alcoholic iodine solution (Pellagri reaction) of corytuberine, bulbocapnine (Gadamer and Kuntze, *ibid.*, p. 598), and apomorphine. With this reagent, *iso*corydine, bulbocapnine, and apomorphine gave deep green solutions, which Gadamer interpreted as being due to quinhydrone formation. Consequently the *p*-position to the hydroxyl group was regarded as being unsubstituted, and *iso*corydine was believed to be the 4-methyl ether, and corydine the 3-methyl ether, of corytuberine (I). This conclusion seemed to be confirmed when Späth, Holter, and Posega (*Ber.*, 1928, **61**, 322) established the relative positions of the methoxyl and hydroxyl groups in bulbocapnine (II) by oxidising its ethyl ether to 4-methoxy-3-ethoxybenzene-1 : 2-dicarboxylic acid, and Gulland and Haworth (J., 1928, 1132) proved that these groups are in the 3 : 4- and not the 1 : 2-positions in the phenanthrene nucleus by the synthesis of bulbocapnine methyl ether.

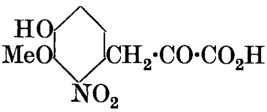
In 1929, however, Go (*J. Pharm. Soc. Japan*, 1929, **49**, 128) concluded that bulbocapnine and corydine, not *iso*corydine, are related, and stated that the ethyl ether of the first is converted into the ethyl ether of the second by demethylenation and methylation of both hydroxyl groups. As a result, Go reversed the constitutions assigned to corydine and *iso*corydine by Gadamer, *iso*corydine being the 3-methyl ether and corydine the 4-methyl ether of corytuberine (I). Go also isolated *iso*corydine from *Corydalis* tubers (*ibid.*, p. 126).

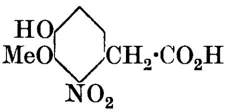
After this paper had been submitted for publication, Späth and Berger (*Ber.*, 1931, **64**, 2038) affirmed that corytuberine has the constitution (III), corydine being the 4-methyl ether and *iso*corydine the 5-methyl ether. The final decision as to the structures to be assigned to these bases can only be made after syntheses of some of the alternatives have been accomplished. The present communication deals with the stages leading to the synthesis of 3-hydroxy-4 : 5 : 6-trimethoxyaporphine, which Gadamer regarded as corydine and Go as *iso*corydine.

A more economical process has been evolved for the preparation of the 2-nitro-4-hydroxy-3-methoxyphenylacetic acid (VI) required in this synthesis, since the yields by the method described in Part I (this vol., p. 2877) are only moderate on account of the simultaneous formation of the fully demethylated acid. 2-Nitrovanillin yielded *5-keto-2-phenyl-4-(2′-nitro-4′-acetoxy-3′-methoxybenzylidene)-4 : 5-dihydro-oxazole* (IV) when condensed with hippuric acid in presence of acetic anhydride and sodium acetate. This azlactone is abnormal in that the lactone ring is opened by boiling 96% alcohol, *ethyl*

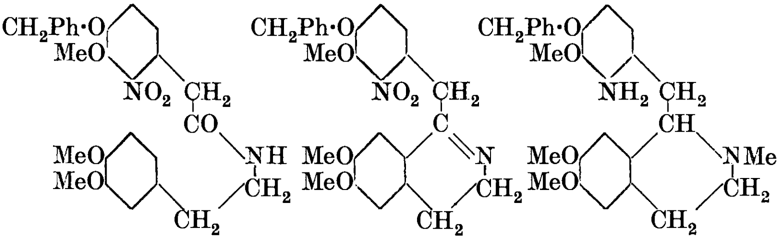
2-*nitro*-4-*acetoxy*-3-*methoxybenzylidenehippurate* being formed. The customary alkaline (sodium hydroxide) hydrolysis of azlactones to α-keto-acids is precluded in this case by the observations of Gulland, Robinson, Scott, and Thornley (J., 1929, 2924) on the hydrolysis of the azlactone derived from 2-nitroveratraldehyde. Boiling alcoholic hydrochloric acid or 50% sulphuric acid merely opened the lactone ring with the formation of 2-*nitro*-4-*hydroxy*-3-*methoxybenzylidenehippuric acid*, but boiling 75% sulphuric acid gave small yields of 2-*nitro*-4-*hydroxy*-3-*methoxyphenylpyruvic acid* (V). Much charring took place, however, and hydrolysis with intermediate strengths of sulphuric acid was therefore investigated. The yields remained unsatisfactory, and recourse had to be made to hydrolysis with alcoholic hydrochloric acid under pressure (compare Avenarius and Pschorr, *Ber.*, 1929, **62**, 321), the maximum yield being 53%. Oxidation of the acid (V) with hydrogen peroxide in alkaline solution yielded the acid (VI), which was benzylated as described in Part I (this vol., p. 2878), and converted into 2′-*nitro* 4′-*benzyloxy*-3′-*methoxyphenylaceto*-β-3 : 4-*dimethoxyphenylethylamide* (VII) by treatment of the acid chloride with homoveratrylamine.


(IV.)


(V.)


(VI.)

The amide (VII) was transformed by phosphorus pentachloride into the sparingly soluble *hydrochloride* of 2′-nitro-4′-benzyloxy-3′ : 6 : 7-trimethoxy-1-benzyl-3 : 4-dihydro*iso*quinoline (VIII), some precautions being required to avoid fission of the benzyl ether. The reduction of the methiodide or methosulphate of this base at first presented some difficulty. Reduction with zinc and hydrochloric acid (*d* 1·2) on the water-bath removed the benzyl group, whereas the substitution of 2*N* for concentrated hydrochloric acid yielded a basic oil, which did not diazotise and couple with β-naphthol and did not therefore contain a primary amino-group. The catalytic reduction of the methochloride of the base (VIII) and, for comparison, of nitropapaverine methochloride was then studied, palladised charcoal being used as catalyst. In the latter case the nitro-group was converted into an amino-group, although the *iso*quinoline ring was not reduced. The methochloride of the base (VIII) on the other hand absorbed a volume of hydrogen sufficient to reduce the nitro-group and the double bond, but the properties of the product were entirely novel for bases of this series and were not in agreement with those of the expected aminobenzyl-*N*-methyltetrahydro*iso*quinoline. Catalytic reduction was therefore abandoned. Ultimately, the reduction was satisfactorily accomplished by means of zinc and hydrochloric acid of *d* 1·16 at 100° or better in ice. 2′-Amino-4′-benzyloxy-3′ : 6 : 7-trimethoxy-1-benzyl-2-methyltetrahydro*iso*quinoline (IX) was an oil, which was characterised by conversion into the sparingly soluble *dipicrolonate*. The completion of the synthesis will be described in a later publication.



(VII.) (VIII.) (IX.)

EXPERIMENTAL.

5-Keto-2-phenyl-4-(2′-nitro-4′-acetoxy-3′-methoxybenzylidene)-4 : 5-dihydro-oxazole (IV).—2-Nitrovanillin (Pisovschi, *Ber.*, 1910, **43**, 2137) was used in this preparation instead of 2-nitroacetvanillin, since the latter, as obtained from the nitration of vanillin, was not easily dried in large quantities and could only be purified with difficulty, probably because it contained 2-nitro-4-acetoxyprotocatechualdehyde as a by-product of the nitration.

A mixture of dry 2-nitrovanillin (22 g.), hippuric acid (22 g.), and acetic anhydride (40 c.c.) was heated to 100° on the water-bath and powdered fused sodium acetate (24 g.) was added. The mixture was heated for 8—10 minutes, much water was added, and the heating was continued for 30 minutes to decompose the acetic anhydride. The solid, a mixture of crystalline azlactone and dark red tar, was collected, treated repeatedly with boiling water, and crystallised from acetone. After being carefully washed with acetone, the *azlactone* formed lustrous, golden-yellow, diamond-shaped plates, m. p. 171—172°; yield, 42% (Found : N, 7·4. $C_{19}H_{14}O_7N_2$ requires N, 7·3%). Several attempts were made to employ larger quantities in one preparation, but the yields were poorer and contained more red colouring matter; the amount of this was also increased if the duration of heating was continued beyond 8—10 minutes.

In the earlier experiments, the initial mixture was heated with alcohol (40 c.c) on the water-bath and cooled, the solid collected, and heated repeatedly with boiling water. On crystallisation from alcohol, the azlactone, m. p. 171°, separated first in small quantity. After the solution had been concentrated, a large amount of *ethyl*

2-*nitro*-4-*acetoxy*-4-*methoxybenzylidenehippurate* separated, and after recrystallisation from alcohol, formed colourless needles, m. p. 149° (Found : C, 58·4; H, 4·7; N, 6·4; OMe + OEt, by Zeisel's method, 16·5. $C_{21}H_{20}O_8N_2$ requires C, 58·8; H, 4·7; N, 6·5; 1OMe + 1OEt, 17·7%). The ester (2 g.) was heated for 5 minutes with 2*N*-sodium hydroxide (15 c.c.) on the water-bath, and acidified with hydrochloric acid. An oily precipitate of 2-nitro-4-hydroxy-3-methoxybenzylidenehippuric acid (see later) separated, and became crystalline on being heated in the acid liquid. It melted at 197—198° (yield, 1·3 g.) after being dried at 100°, and was converted into the azlactone by boiling acetic anhydride.

Hydrolyses of the Azlactone.—2-*Nitro*-4-*hydroxy*-3-*methoxyphenylpyruvic acid* (V). The early experiments were carried out in pressure bottles, but later the following procedure was adopted. The azlactone (60 g.) and aqueous-alcoholic hydrochloric acid (600 c.c.; prepared by mixing 2 parts by volume of saturated alcoholic hydrogen chloride with 1 part of the concentrated acid, *d* 1·2) were heated for 15 hours at 100° in an acid-proof enamelled autoclave, the pressure remaining at about 13 kg./cm.^{2} throughout the reaction. The contents of the vessel were mixed with a little water, and extracted repeatedly with ether. This extract was filtered from dirt, and shaken with successive quantities of 2*N*-sodium hydroxide until all the α-keto-acid and its ethyl ester had been removed as indicated by the absence of deep red colour. The alkaline solution, which also contained benzoic acid, was kept at room temperature for 30 minutes to hydrolyse the ester of the keto-acid, and was then saturated with sulphur dioxide, and freed from benzoic acid first by filtration and then by extraction with ether. The solution of the bisulphite compound of 2-nitro-4-hydroxy-3-methoxyphenylpyruvic acid was shaken with charcoal, and decomposed by heating on the water-bath in an open basin with a slight excess of concentrated hydrochloric acid; this heating was not prolonged further than necessary. The solution was filtered from the solid (largely sodium chloride) which had separated, and both solid and filtrate were extracted with chloroform to remove impurities. The keto-acid did not dissolve in this solvent, but was then taken up in ether by thorough extraction of the sodium chloride and filtrate. When dried and distilled, the ether left almost pure 2-*nitro*-4-*hydroxy*-3-*methoxyphenylpyruvic acid*, m. p. 180°, which formed yellow needles, m. p. 182°, when crystallised from benzene and acetic acid or from water and concentrated hydrochloric acid (Found : N, 5·3. $C_{10}H_9O_7N$ requires N, 5·5%). It dissolved readily in water, ether, ethyl and methyl alcohols, and glacial acetic acid, but was insoluble in chloroform and benzene. The solution in alkali was very deep red.

With baryta. This reagent has proved useful in other cases (see Part IV; this vol., p. 2902). The azlactone (1·0 g.), barium hydroxide (2·2 g.; 5 mols.), water (10 c.c.), and alcohol (1·5 c.c., to prevent frothing) were heated under reflux for 12 hours in an oil-bath at 110—120°. The evolution of ammonia had then ceased, and the mixture was cooled and filtered. The colour reactions of the filtrate showed the probable presence of an isatin (compare Gulland, Robinson, Scott, and Thornley, *loc. cit.*), but no homogeneous material could be isolated from this or from the residue.

With sulphuric acid. (i) The azlactone (1·5 g.) and sulphuric acid (15 c.c. of 50% by weight) were heated on the water-bath for 16 hours. The mixture was filtered, and both solid and filtrate were extracted thoroughly with ether. The extract was filtered, and shaken repeatedly with sodium hydroxide solution, which became deep red. The alkaline solution was saturated with sulphur dioxide, and the solid collected and dried at 100°. It was treated with boiling light petroleum to remove traces of benzoic acid, and crystallised from dilute alcohol. 2-*Nitro*-α-*benzamido*-4-*hydroxy*-3-*methoxycinnamic acid* formed colourless needles, m. p. 197—198° (Found : N, 7·8. $C_{17}H_{14}O_7N_2$ requires N, 7·8%), which were converted into the azlactone by boiling acetic anhydride. The solution in alkali was deep red.

The filtrate from the sulphur dioxide precipitation (see above) was treated as in the hydrolysis with alcoholic hydrochloric acid, but only a trace of oily material was obtained as the final product.

(ii) A similar experiment using 75% sulphuric acid was then carried out. The azlactone dissolved in a few minutes, and after 5 hours a sublimate of benzoic acid covered the end of the condenser and upper part of the flask. The contents were worked up as before, and no precipitate of 2-nitro-α-benzamido-4-hydroxy-3-methoxycinnamic acid separated when sulphur dioxide was passed into the solution; the slight precipitate which did separate consisted of benzoic acid. The final product was an acidic oil, consisting largely of the α-keto-acid, but the amount was very small, owing to the extensive charring which had occurred during the hydrolysis.

(iii) Similar experiments with 70% and 60% sulphuric acid were more successful, the reaction being stopped in each case when a considerable amount of benzoic acid had sublimed—3·5 and 6·5 hours respectively. Both were worked up as before, and in each case small amounts of 2-nitro-α-benzamido-4-hydroxy-3-methoxycinnamic acid were obtained. The major portion of the product was the α-keto-acid, however, the yield in the former case being slightly larger, but the amounts obtained did not justify large-scale preparations.

2-Nitro-4-hydroxy-3-methoxyphenylacetic acid (VI) was obtained in over 80% yield when the α-keto-acid was oxidised in alkaline solution by perhydrol, care being taken to avoid much rise in temperature by cooling in a freezing mixture. Next day, the pure product was precipitated with dilute sulphuric acid, and extraction of the mother-liquor with ether yielded a further quantity.

2′-Nitro-4′-benzyloxy-3′-methoxyphenylaceto-β-3 : 4-*dimethoxyphenylethylamide* (VII).—2-Nitro-4-benzyloxy-3-methoxyphenylacetic acid (4 g.; Part I, this vol., p. 2879) in chloroform (40 c.c.) was heated on the water-bath for 1½ hours with thionyl chloride (16 c.c.). The solvent and excess of thionyl chloride were removed at 45° under reduced pressure, and the residual acid chloride was dissolved in dry benzene (20 c.c.) and added to a cooled solution of homoveratrylamine (2·8 g.) in the same solvent. After a few minutes, 2*N*-sodium hydroxide was added, the benzene layer was separated, and after being washed successively with hydrochloric acid and water, was dried and distilled. The residue solidified after several days, and, when crystallised from alcohol, the *amide* formed colourless plates, m. p. 112—113°; yield, 96% (Found: C, 64·9; H, 6·0. $C_{26}H_{28}O_7N_2$ requires C, 65·0; H, 5·8%).

*2′-Nitro-4′-benzyloxy-6 : 7 : 3′-trimethoxy-1-benzyl-3 : 4-dihydro*iso*quinoline Hydrochloride* (VIII).—A solution of the amide (5·1 g.) in chloroform (50 c.c.) was thoroughly cooled in ice and salt, and mixed gradually with powdered phosphorus pentachloride (10 g.). (Careful cooling is essential at this stage; in similar experiments in which the mixing was carried out at room temperature, fission of the benzyl ether group occurred, and little or no hydrochloride could be isolated.) The mixture was left in ice for several hours, and was then kept for 4—7 days at room temperature protected from moisture. Ice (30 g.) was added, and the chloroform and phosphorus oxychloride were removed under reduced pressure at 20—30°. The liquid was decanted from the crystalline, light brown solid, and discarded. The solid was dissolved in boiling alcohol (15 c.c.), mixed with hot hydrochloric acid (20 c.c. of 2*N*), and cooled slowly; rapid cooling is apt to result in the formation of a jelly which does not easily become crystalline. On some occasions the solid obtained from the ring-closure was not crystalline; it was extracted repeatedly with hot water containing a few drops of dilute hydrochloric acid, and the hydrochloride was obtained from the extract by adding 2*N*-hydrochloric acid gradually while the solution cooled. The water-insoluble residue from such experiments usually contained some unchanged amide, which was recovered by recrystallisation from alcohol. *2′-Nitro-4′-benzyloxy-6 : 7 : 3′-trimethoxy-1-benzyl-3 : 4-dihydro*iso*quinoline hydrochloride*, which was obtained in 65% yield, formed colourless needles, m. p. 232—233° (decomp.), when crystallised from a mixture of equal volumes of alcohol and 2*N*-hydrochloric acid (Found: C, 62·5; H, 5·5. $C_{26}H_{26}O_6N_2,HCl$ requires C, 62·5; H, 5·4%). It was readily soluble in alcohol and hot water, but dissolved only very sparingly in dilute hydrochloric acid. The benzyl group was split off by hot concentrated hydrochloric acid.

2′-Nitro-4′-benzyloxy-6 : 7 : 3′-trimethoxy-1-benzyl-3 : 4-dihydro*iso*quinoline was obtained by adding an excess of aqueous ammonia to a solution of the hydrochloride in methyl alcohol, extracting the base with ether, and drying and distilling the solvent. The residual oil slowly crystallised; it then melted at 119°.

The methosulphate separated as an oil when the base (0·56 g.) and pure methyl sulphate in dry toluene (20 c.c.) were heated for 1 hour on the water-bath. The toluene was decanted, and the residue soon crystallised, and formed pale yellow needles, m. p. 85°, when recrystallised from water.

The methiodide formed a yellow crystalline precipitate when the base and an excess of methyl iodide were heated under reflux for 30 minutes on the water-bath. Most of the methyl iodide was removed by distillation, and the solid was collected, washed with ether, and dried in a vacuum. It melted at 108° and decomposed at 200°.

Catalytic Reduction of Nitropapaverine Methochloride.—The methiodide was prepared by heating nitropapaverine (Pschorr, *Ber.*, 1904, **37**, 1926) (2 g.) and methyl sulphate (3 g.) in dry toluene (75 c.c.) at 130° for 4 hours. The toluene was decanted, and the residual methosulphate dissolved in hot water and mixed with solid sodium iodide. The methiodide which separated was collected and crystallised from a large volume of hot water, forming yellow prisms, m. p. 225°. The methiodide (0·2 g.) was converted into the methochloride by heating an aqueous solution with fresh silver chloride, and the resulting neutral solution of the methochloride was reduced by shaking with palladised charcoal in an atmosphere of hydrogen. 26 C.c. at N.T.P. were absorbed, corresponding to 97% of the volume required to reduce the nitro-group only of the methochloride. The solution was filtered from the catalyst, and a portion was made alkaline with sodium hydroxide; no precipitate separated, thus indicating that the material was still a metho-salt and that the double bonds had not been reduced. Another portion, after being treated with sulphuric acid and sodium nitrite, formed a red azo-dye when added to an alkaline solution of β-naphthol, thus showing the presence of the amino-group. The aqueous solution evidently contained aminopapaverine methochloride.

*Catalytic Reduction of 2′-Nitro-4′-benzyloxy-6 : 7 : 3′-trimethoxy-1-benzyl-3 : 4-dihydro*iso*quinoline Methochloride.*—The methiodide

(0·4 g.) was converted into the methochloride and reduced by the same method as that used in the case of nitropapaverine methochloride. 56 C.c. of hydrogen were absorbed at N.T.P., being 96% of that required to reduce the nitro-group and the double bond. The solution was filtered from catalyst, and on exposure to the air darkened very rapidly, finally becoming black. On treatment with dilute sulphuric acid and sodium nitrite, a solution was obtained which gave a deep purple coloration on being added to an alkaline solution of β-naphthol; this colour, however, was also produced by the addition of alkali to the solution of the reduced base before treatment with nitrous acid.

*2′-Amino-4′-benzyloxy-6 : 7 : 3′-trimethoxy-1-benzyl-2-methyl-3 : 4-dihydro*iso*quinoline* (IX).—The methiodide of the base (VIII) (1·2 g.), or the methosulphate, was heated with hydrochloric acid (*d* 1·16) on a gently boiling water-bath, and was reduced by the gradual addition of zinc dust until the solution became colourless. The solution was cooled, filtered from excess of zinc, and evaporated to small volume under reduced pressure at 40°. It was rendered alkaline with sodium carbonate solution in an atmosphere of hydrogen, and extracted thoroughly with ether, care being taken to exclude air as far as possible during the process so as to avoid aerial oxidation. The ethereal solution was washed with water, dried with potassium carbonate, and distilled, leaving the base as a pale brown oil. This diazotised and coupled with an alkaline solution of β-naphthol to form a crimson azo-dye. The *dipicrolonate* was obtained by mixing ethereal or alcoholic solutions of the base and picrolonic acid, and crystallised from alcohol, in which it was very sparingly soluble, in yellow needles, m. p. 207° (Found: C, 55·8; H, 5·2; N, 14·0. $C_{27}H_{32}O_4N_2,2C_{10}H_8O_5N_4,2H_2O$ requires C, 55·6; H, 5·1; N, 13·8%).

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, August 26th,* 1931.]