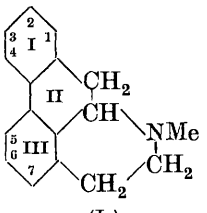
CCCCII.—*Experiments on the Synthesis of Phenolic Aporphines. Part I. An Introduction and the Preparation of Nitro-derivatives of* 3 : 4-*Dihydroxyphenylacetic Acid.*

By JOHN MASSON GULLAND.

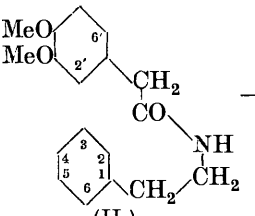
THE alkaloids related to aporphine (I) which occur in nature or are derived from morphine are phenols or phenolic ethers. They may be classified in two main groups, distinguished from each other by the positions of the oxygen atoms in ring I. On the one hand, in glaucine and dicentrine (2OMe), in laurotetanine and boldine (OH, OMe), and in domesticine and *iso*domesticine (OH, OMe, or possibly O_2CH_2), oxygen atoms are linked to positions 2 and 3. On the other hand, in apomorphine (2OH), in corytuberine (2OH or OH, OMe), in *iso*corydine, bulbocapnine, morphothebaine, apo-ψ-codeine, and *iso*thebaine (OH, OMe), in corydine (OH, OMe or 2OMe), and in laurepukine (O_2CH_2 or 2OH), oxygen atoms occupy positions 3 and 4. The sole recorded exceptions to this generalisation are pukateine and laureline, which Barger and Girardet (*Helv. Chim. Acta*, 1931, **14**, 481) have recently shown to contain only one oxygen atom in ring I. These alkaloids, however, are abnormal in other ways, since they, and laurepukine which accompanies them, are lævorotatory, whereas the naturally occurring aporphines have

hitherto been found to be dextrorotatory. Those derived from morphine are lævorotatory.

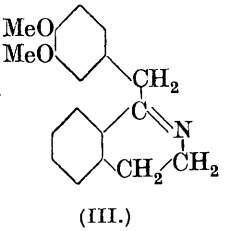
In passing, it may be mentioned that this distinction between natural and derived aporphines lessens the probability that Klee (*Arch. Pharm.*, 1914, **252**, 211) was correct in inferring an actual conversion of thebaine (lævorotatory) into *iso*thebaine (dextrorotatory) in *Papaver orientale* after the period of vigorous growth. Since both alkaloids have in all likelihood the same antecedent components, it is probable that thebaine is destroyed at that time, and that the synthetic activities of the plant produce *iso*thebaine by a somewhat different mechanism from that by which thebaine was originally formed.



(I.)



(II.)

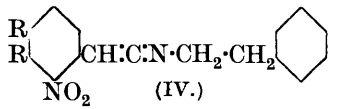


(III.)

NO_2 in 2′ or 6′.
MeO in 5, or 4 : 5, or 5 : 6 or O_2CH_2 in 4 : 5.

In previous memoirs (J., 1928, 581, 1132, 1834, 2083; 1929, 658), a general method was elaborated for the synthesis of ethers of both groups of aporphines, in which the requisite nitrophenylaceto-β-phenylethylamides (II) were converted into nitrobenzyl*iso*quinolines (III) by a modified Bischler–Napieralski reaction, using phosphorus pentachloride to effect the ring-closure. The syntheses were then completed by methylation of the nitrogen atom to the quaternary salt, reduction of the nitro-group and dihydro*iso*quinoline ring, and formation of the phenanthrene nucleus by Pschorr's method.

In each of the cases mentioned above, position 2 of the phenylethylamine nucleus of the amide (II) was rendered reactive by the presence of a *p*-methoxyl or catechol ether group. In the absence of such activation, however, the Bischler–Napieralski reaction fails, and Kay and Pictet (J., 1913, **103**, 950) and Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) obtained only non-basic anhydro-derivatives (IV) and no *iso*quinoline bases.



(IV.)

R = OMe (K. and P.)

R = H (G., O. and S.)

It is clear that this behaviour is due to activation of the methylene group by the *o*-nitro-group, since the successful conversion of phenylaceto-β-phenylethylamide into 1-benzyl*iso*quinoline has been recorded (Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, **395**, 299). In subsequent memoirs (J., 1929, 1444, 1666) it was shown that the activation of nitrophenylaceto-β-phenylethylamides by a *p*-acylamino-group was insufficient to ensure *iso*quinoline formation, and the conclusion must therefore be drawn that an ethereal oxygen atom in the *p*-position is essential for facile syntheses.

The majority of aporphines are phenolic, and the application of the methods and conclusions outlined above to their synthesis involves practical difficulties which have been surmounted as described in the following publications. The importance of such syntheses in the determination of the constitution of phenolic aporphines is emphasised by the existence of conflicting statements by Gadamer (*Arch. Pharm.*, 1911, **249**, 503), Go (*J. Pharm. Soc. Japan*, 1929, **49**, 128), and Späth and Berger (*Ber.*, 1931, **64**, 2038) as to the constitutions to be assigned to corytuberine and its monomethyl ethers, corydine and *iso*corydine.

It was essential to "protect" hydroxyl groups during the syntheses by replacing their hydrogens by a radical which conforms to the following specifications. First, it must be stable to thionyl chloride and phosphorus pentachloride, in order to withstand the treatment necessary in the earlier stages. Secondly, it must not be removed by hydrochloric acid under the conditions obtaining during the manipulation of the product of the Bischler–Napieralski reaction or during the reduction of the nitro-group and dihydro-*iso*quinoline ring. The sensitivity to aerial oxidation of amino-benzyltetrahydro*iso*quinolines would be greatly enhanced by the presence of a phenolic hydroxyl, and it is doubtful (see Part IV; this vol., p. 2900) if such bases can be diazotised satisfactorily. Thirdly, it must withstand hydrolysis by cold sodium carbonate. Fourthly, it should resemble, as far as possible, a methyl group in its influence on other parts of the molecule. Finally, it must be capable of being removed by comparatively mild reagents at the conclusion of the synthesis. Carbethoxyl and benzyl groups appeared to satisfy these conditions, and to have the additional advantage of being readily introduced into the starting materials.

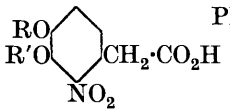
The protection of hydroxyls which would ultimately appear in ring III of the aporphines offers no serious obstacle, and the literature contains syntheses of phenolic *iso*quinolines in which protection has been achieved by carbethoxyl or acetyl groups. Nevertheless, the group ultimately selected for protection of the

nitrophenolic acids, *viz.*, the benzyl group, is possibly more suitable in having greater stability to alkalis.*

The protection of hydroxyls which would ultimately appear in ring I of the aporphine presents greater difficulties on account of the increased susceptibility to hydrolysis of nitrated, as compared with non-nitrated, phenolic ethers. Carbethoxyl groups have been found to afford satisfactory protection to hydroxyls in this category during the Bischler–Napieralski ring-closure (Part II; this vol., p 2881), but their use in aporphine syntheses has had to be abandoned owing to unexpected results in the reduction of the ethylcarbonatonitrobenzyl*iso*quinoline methiodides. On the other hand, protection by the benzyl group is satisfactory, and the isomeric 2′-amino- and 6′-amino-3′ : 6 : 7-trimethoxy-4′-benzyloxy-1-benzyl-2-methyltetrahydro*iso*quinolines have been prepared (Parts III and IV). The latter has been converted into the corresponding phenolic aporphine, and the syntheses of other phenolic aporphines along these lines are in progress.

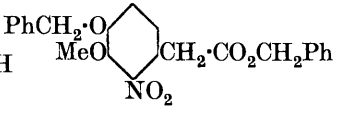
The close similarity in manipulation of the stages of these syntheses warrants the assumption that the procedure described may be regarded as standard and generally applicable. It will be noted that nitrophenolic phenylacetic acids have been selected in which the hydroxyl and the nitro-group occupy *m*-positions relatively to each other. Maximal instability of the benzyl ether to acid reagents has thus been ensured in order to test as searchingly as possible the general validity of the method. The risk of fission by acids is less serious when the benzyloxy- and nitro-groups occupy *o*- or *p*-positions. Nitrated benzyl ethers are stable to alkalis under the conditions required in these syntheses.

The synthesis of those phenolic aporphines which contain hydroxyl groups in ring I necessitated the preparation of 2-*nitro*-3 : 4-*dihydroxyphenylacetic acid* (V), 2-*nitro*-4-*hydroxy*-3-*methoxyphenylacetic acid* (VI), and the isomeric 2-nitro-3-hydroxy-4-methoxyphenylacetic acid (VII).

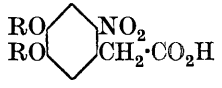


(V.), (VI.), (VII.)

(V) R = R′ = H;
(VI) R = H, R′ = Me;
(VII) R = Me, R′ = H.



(VIII.)



(IX.), (X.)

(IX) R = H;
(X) R = Me.

* Since this was written, Kondo and Ishiwata (*Ber.*, 1931, **64**, 1533) have described the synthesis of 6-hydroxy-3 : 4-dimethoxy*nor*aporphine from 2-nitro-3 : 4-dimethoxyphenylacetic acid and *m*-benzyloxy-β-phenylethylamine.

The demethylation of 2-nitro-3 : 4-dimethoxyphenylacetic acid (V; R = R′ = Me) (Gulland and Haworth, J., 1928, 1132) was therefore studied. This reaction proved to be difficult to control, but conditions have been defined by which the acids (V) and (VI) may be obtained simultaneously by the action of boiling hydrobromic acid. These acids readily yielded *2-nitro-3 : 4-diethylcarbonatophenylacetic acid* and *2-nitro-3-methoxy-4-ethylcarbonatophenylacetic acid* respectively when shaken with chloroformic ester and sodium hydroxide solution. These derivatives are extremely unstable to alkalis, the parent acids being regenerated, but are relatively resistant to concentrated hydrochloric acid, even when boiling.

2-Nitro-4-benzyloxy-3-methoxyphenylacetic acid and *2-nitro-3 : 4-dibenzyloxyphenylacetic acid* were prepared, although only in moderate yield, by heating the acids with benzyl chloride and sodium carbonate solution. The predominating products of the reaction were, however, the corresponding benzyl esters, *e.g.*, *benzyl 2-nitro-4-benzyloxy-3-methoxyphenylacetate* (VIII), from which the acids were obtained by short alkaline hydrolysis. The action of benzyl chloride on phenylacetic acids has been studied more closely in Part II (this vol., p. 2882), and esterification appears to be a normal occurrence under conditions comparable with those outlined above.

The preparation of 2-nitro-3-hydroxy-4-methoxyphenylacetic acid (VII) by partial methylation of the acid (V) with methyl sulphate and aqueous sodium hydroxide was unsuccessful, no alkylation occurring at room temperature and methylation of both hydroxyls taking place on warming. Attempts to effect alkaline hydrolysis of the methoxyl in position 3 (*ortho* to the nitro-group) of 2-nitro-3 : 4-dimethoxyphenylacetic acid were also fruitless, *5 : 6-dimethoxyanthranilcarboxylic acid* being the sole product. The reaction followed a course of internal oxidation-reduction analogous to that described by Gulland, Robinson, Scott, and Thornley (J., 1929, 2924) in the case of an allied compound. The most convenient preparation of the acid (VII) would therefore start from 2-nitro-*iso*vanillin and follow the improved synthesis of the acid (VI) as detailed in Part III (this vol., p. 2886).

The synthesis of phenolic aporphines which contain hydroxyl groups in positions 2 and 3 of ring I requires the preparation of *6-nitro-3 : 4-dihydroxyphenylacetic acid* (IX) and its two monomethyl ethers. Demethylation of 6-nitro-3 : 4-dimethoxyphenylacetic acid (X) (Callow, Gulland, and Haworth, J., 1929, 658) by boiling hydrobromic acid afforded a poor yield of the acid (IX), together with traces of the 3-methyl ether (see Part IV; this vol., p. 2898), which were extremely difficult to obtain in pure condition.

Alkaline hydrolysis of the acid (X) appears to be excluded by analogy with the corresponding 2-nitro-derivative (see above), and attempted demethylation of the methoxyl in position 3 by boiling aniline (compare Klemenc, *Sitzungsber. Akad. Wissenschaft.*, 1912, **121**, 83) yielded only 6-*nitro*-3 : 4-*dimethoxyphenylacetanilide*. The preparation of the acid (IX) and of its 4-methyl ether would therefore be most readily achieved by nitration of the corresponding benzyloxyphenylacetic acids as described in Part IV in the case of the 3-methyl ether.

EXPERIMENTAL.

The Demethylation of 2-*Nitro*-3 : 4-*dimethoxyphenylacetic Acid.*—The yields in this process depend on the intensity and duration of heating, and the following description is typical.

A mixture of the acid (10 g.) and concentrated hydrobromic acid (70 c.c. of *d* 1·5) was raised rapidly to the boiling point by heating over a free flame, and the solution was maintained for 15 minutes at such a temperature that gentle ebullition occurred. The dark red solution was cooled in ice, and after 2 hours 2-nitro-4-hydroxy-3-methoxyphenylacetic acid was collected, washed with hydrobromic acid and then with water, and crystallised from water (yield, 2·2 g.).

The filtrate from this reaction contained 2-nitro-3 : 4-dihydroxyphenylacetic acid, which was isolated by diluting the solution with water (200 c.c.), filtering it from a little amorphous material, and extracting it repeatedly with ethyl acetate. The extracts were dried with sodium sulphate, and the ethyl acetate was removed by distillation, reduced pressure being finally employed to remove as much acetic acid as possible. The residual red oil solidified, and after being rubbed with benzene, in which it was insoluble, the crystals of 2-nitro-3 : 4-dihydroxyphenylacetic acid were collected (5·5 g.).

2-*Nitro*-4-*hydroxy*-3-*methoxyphenylacetic acid* formed orange-yellow needles when crystallised from water and shining orange leaflets when crystallised from toluene; both specimens melted at 161° (Found: C, 47·6; H, 3·9. $C_9H_9O_6N$ requires C, 47·6; H, 3·9%). This acid dissolved readily in alcohol, formed an orange solution in sodium hydroxide, and developed a feeble green colour with alcoholic ferric chloride.

2-*Nitro*-3 : 4-*dihydroxyphenylacetic acid*, when crystallised from xylene, formed orange-yellow needles, m. p. 171°, which were readily soluble in water and in alcohol, and developed an intense blue-green colour with alcoholic ferric chloride, which changed to reddish-violet on addition of a trace of aqueous sodium carbonate (Found: C, 45·5; H, 3·5. $C_8H_7O_6N$ requires C, 45·1; H, 3·3%). The solution in alkali was crimson.

2-*Nitro*-3-*methoxy*-4-*ethylcarbonatophenylacetic Acid.*—The phen-

olic acid (10 g.), dissolved in water (30 c.c.) and dilute aqueous sodium hydroxide (50 c.c. of 10%), was cooled in ice and shaken with chloroformic ester (10 g., added in two batches). The solution remained alkaline, and the red colour was discharged in the course of a few minutes. Excess of dilute hydrochloric acid was added, the liberated oil taken up in ether, and the ethereal extract shaken repeatedly with small quantities of ice-cold potassium bicarbonate solution. Acidification of this solution yielded the desired acid as an oil which rapidly crystallised; it was dried on porous tile (11·4 g.) and recrystallised from benzene by dissolution in the solvent (charcoal), filtration, and concentration until crystals began to separate. *2-Nitro-3-methoxy-4-ethylcarbonatophenylacetic acid* formed colourless diamond-shaped tablets, which melted at 110—118° while losing solvent of crystallisation, and at 132—133° after being heated at 110° (Found: loss at 110°, 11·7. $C_{12}H_{13}O_8N,\frac{1}{2}C_6H_6$ requires loss, 11·5%. Found: C, 48·1; H, 4·3. $C_{12}H_{13}O_8N$ requires C, 48·1; H, 4·3%). It was rather readily soluble in the usual solvents, and dissolved in 2*N*-sodium carbonate to form a colourless solution. The carbethoxy-group was instantly hydrolysed by cold 2*N*-sodium hydroxide, but the acid was not affected by heating at 100° in 2*N*-hydrochloric acid for 20 minutes or in the concentrated acid for a shorter period.

The ethereal extract from this preparation contained a pale pink, uncrystallisable oil, which was obtained by distilling the ether and stirring the residue with ligroin so as to dissolve the excess of chloroformic ester. This oil, which may have been ethyl 2-nitro-3-methoxy-4-ethylcarbonatophenylacetate, produced by the introduction of the carbethoxy-group at the reactive methylene group and elimination of the carboxyl of the acid, was converted into the original phenolic acid by heating with dilute alcoholic potash on the water-bath for a few minutes and acidifying the product with hydrochloric acid. Ethyl acetate extracted the acid, which was obtained by distillation of the solvent, and was crystallised from water (yield, 0·6 g.).

Benzylation of 2-Nitro-4-hydroxy-3-methoxyphenylacetic Acid.—No benzylation occurred when the acid was heated with benzyl chloride and powdered potassium carbonate in dry acetone, and the following procedure was therefore adopted. A mixture of the phenolic acid (10 g.) in sodium carbonate solution (300 c.c. of 2*N*) and benzyl chloride (30 c.c.) was boiled under reflux for about 1 hour until the red colour was discharged. The liquid was cooled, extracted with ether to remove the excess of benzyl chloride (see below), and acidified. The oily benzylated acid, which soon crystallised, was dissolved in hot benzene, the solution concentrated, and the crystals

(4·0 g.) which separated on cooling were recrystallised from benzene. *2-Nitro-4-benzyloxy-3-methoxyphenylacetic acid* formed colourless hexagonal plates, m. p. 108—109°, or 144° after being dried at 100° (Found in material dried at 100°: C, 60·8; H, 4·9. $C_{16}H_{15}O_6N$ requires C, 60·6; H, 4·7%). This acid darkened on exposure to light. It formed a colourless solution in alkalis and was stable to boiling sodium hydroxide, but the benzyl group was readily hydrolysed by hot hydrochloric acid.

The ethereal solution (see above) contained *benzyl 2-nitro-4-benzyloxy-3-methoxyphenylacetate* (VIII), which was obtained in crystalline condition (6·4 g.) by drying and distilling the ether, and stirring the residual oil with light petroleum to dissolve the benzyl chloride. On recrystallisation from light petroleum containing a little benzene it formed colourless needles, m. p. 80°, but it crystallised from alcohol in the same form, m. p. 101° (Found: C, 67·4; H, 5·0; N, 3·3. $C_{23}H_{21}O_6N$ requires C, 67·8; H, 5·2; N, 3·4%). The ester (4·4 g.) was hydrolysed by heating under reflux with sodium hydroxide solution (55 c.c. of 2*N*) for 25 minutes. Water (50 c.c.) was added, and the cooled solution acidified with hydrochloric acid. The regenerated acid separated in crystalline condition, m. p. 142°.

2-Nitro-3 : 4-diethylcarbonatophenylacetic Acid.—2-Nitro-3 : 4-dihydroxyphenylacetic acid (7 g.) was placed in a flask fitted with a mercury-sealed stirrer and swept out by a current of hydrogen. The flask was cooled in ice, and *N*-sodium carbonate solution (100 c.c.) was added. The deep red solution was stirred while chloroformic ester (7·7 c.c.) was run in from a burette; the colour rapidly changed to pale yellow. After 15 minutes, the mixture was extracted with ether to remove the excess of chloroformic ester, and the filtered solution was acidified with ice-cold hydrochloric acid. The resulting semi-solid precipitate was taken up in benzene, and the solution dried. When the benzene solution was evaporated to small volume, *2-nitro-3 : 4-diethylcarbonatophenylacetic acid* crystallised in colourless needles, m. p. 115° after softening at 105°. It formed colourless needles, m. p. 127—128°, when crystallised from dilute acetic acid (Found: C, 47·4; H, 4·3. $C_{14}H_{15}O_{10}N$ requires C, 47·1; H, 4·2%). This acid formed colourless solutions in cold dilute sodium carbonate and bicarbonate, but hydrolysis took place on standing, and was instantaneous in sodium hydroxide. It was recovered unchanged after being heated with boiling concentrated hydrochloric acid for 5 minutes.

2-Nitro-3 : 4-dibenzyloxyphenylacetic Acid.—2-Nitro-3 : 4-dihydroxyphenylacetic acid (1 g.), benzyl chloride (8 g.), and potassium carbonate (4 g.) in water (70 c.c.) were heated under

reflux in a current of hydrogen for 3 hours. The aqueous layer had become lighter in colour, and the mixture remained alkaline. The excess of benzyl chloride and the ester were removed by ether extraction, and the solution was acidified with hydrochloric acid. The resulting oil was taken up in ether, washed, dried, and distilled, and the residue was crystallised by the careful addition of water to an alcoholic solution. 2-*Nitro*-3 : 4-*dibenzyloxyphenylacetic acid* formed long colourless needles, m. p. 85° (Found : C, 67·1; H, 4·9. $C_{22}H_{19}O_6N$ requires C, 67·2; H, 4·8%).

5 : 6-*Dimethoxyanthranilcarboxylic Acid.*—A solution of 2-nitro-3 : 4-dimethoxyphenylacetic acid in *N*-sodium hydroxide was boiled under reflux for 50 hours, and acidified. The resulting yellow precipitate was crystallised from water and then from benzene, and formed orange needles, m. p. 175° (decomp.), which gave a colourless solution in sodium hydroxide (Found : C, 54·1; H, 4·2; N, 6·3. $C_{10}H_9O_5N$ requires C, 53·8; H, 4·0; N, 6·3%).

6-*Nitro*-3 : 4-*dihydroxyphenylacetic Acid.*—A mixture of 6-nitro-3 : 4-dimethoxyphenylacetic acid (2 g.) and hydrobromic acid (20 c.c. of *d* 1·5) was boiled gently under reflux for 5 minutes after all the acid had dissolved. It was then cooled thoroughly in ice; any precipitate of impure 6-nitro-4-hydroxy-3-methoxyphenylacetic acid which separated at this stage was collected. The filtrate was diluted with water and extracted thoroughly with ethyl acetate. After being dried and distilled, the extract yielded a red oil which solidified on being stirred with benzene, and was crystallised from toluene. 6-*Nitro*-3 : 4-*dihydroxyphenylacetic acid* formed yellow needles, m. p. 212° (Found : C, 45·7; H, 3·6. $C_8H_7O_6N$ requires C, 45·1; H, 3·3%). It dissolved readily in water, formed a cherry-red solution in sodium hydroxide, and gave a brilliant dark green coloration with alcoholic ferric chloride.

6-*Nitro*-3 : 4-*dimethoxyphenylacetanilide.*—A solution of 6-nitro-3 : 4-dimethoxyphenylacetic acid (2 g.) in aniline (15 c.c.) was boiled under reflux for 90 minutes. (More prolonged boiling caused marked decomposition.) The product was poured into dilute hydrochloric acid, and the crystalline precipitate collected and recrystallised from alcohol, forming colourless needles, m. p. 201—202°, which were insoluble in boiling sodium hydroxide solution and hydrochloric acid (Found : N, 8·8. $C_{16}H_{16}O_5N_2$ requires N, 8·9%). Extraction of the hydrochloric acid mother-liquors with chloroform yielded a small amount of red oil which probably contained some of the demethylated acid.

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