The Aporphine Series. Part I. Developments of the Bischler–Napieralski–Pschorr Synthetic Method. The Synthesis of (±)-iso*Bulbocapnine and* (±)-*Actinodaphnine Methyl Ether.*

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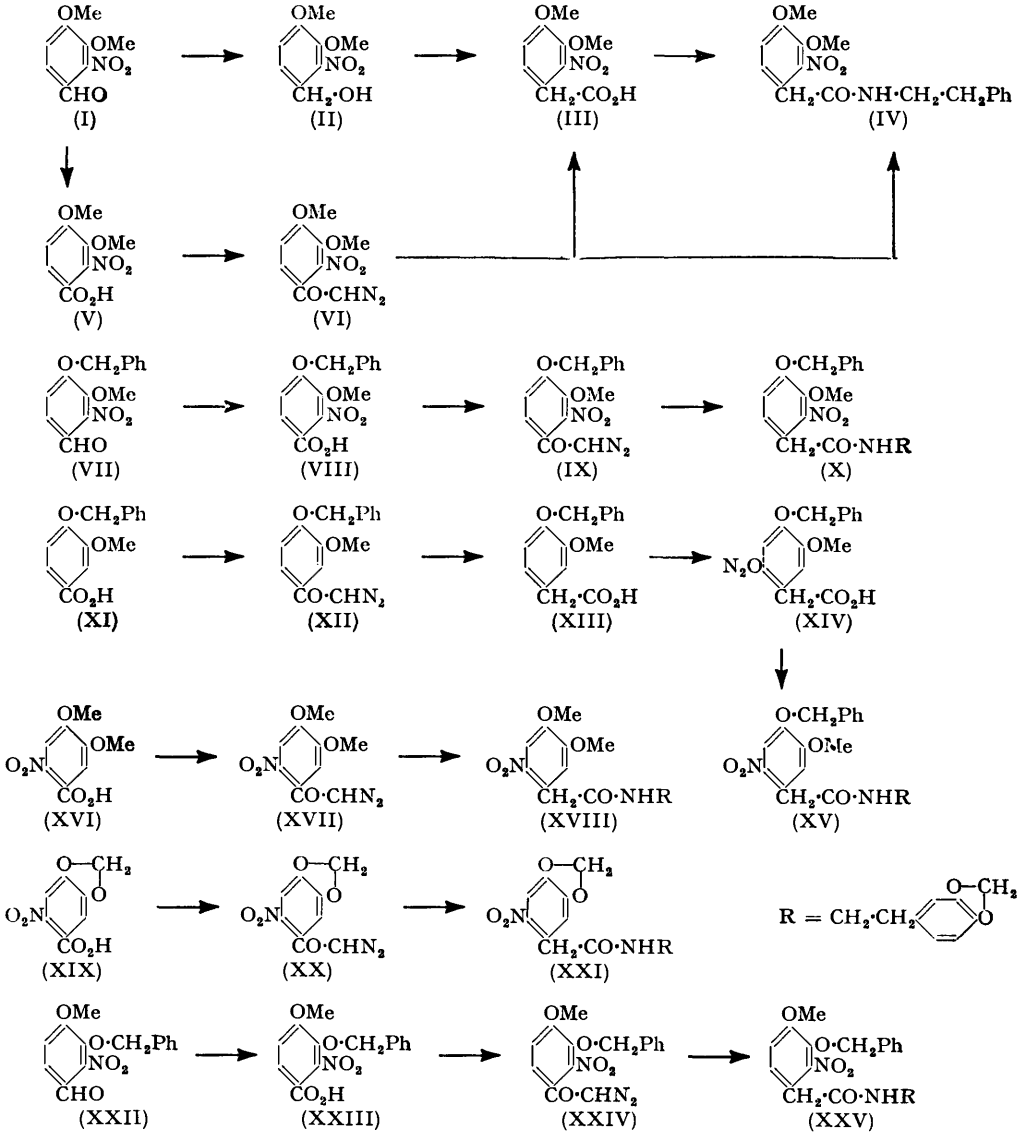
An improved method has been developed for the synthesis of *N*-2-arylethyl-*o*-nitroarylacetamides which is illustrated by the preparation of seven members of this class. Contrary to the claim of Späth and Hromatka, and in agreement with the earlier work of Kay and Pictet, Kondo, and Gulland, Haworth, Virden, and Callow, it has not been possible to convert 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide into a derivative of *iso*quinoline by means of the Bischler–Napieralski reaction. On the other hand, four substituted *N*-2-(3 : 4-methylenedioxyphenyl)ethyl-*o*-nitrophenylacetamides have been converted by means of the successive application of the Bischler–Napieralski and the Pschorr reaction into derivatives of aporphine or noraporphine. In two examples in the aporphine series, in which the benzyl group is used as a protective group, this method has led to the first syntheses of members of the hydroxyaporphine series. The compounds synthesised include (±)-*iso*bulbocapnine and (±)-actinodaphnine methyl ether.

Apart from the synthesis of several aporphine ethers there are few groups of alkaloids in which synthetic work is less satisfactory than in the aporphine group. *apo*Morphine (3 : 4-dihydroxyaporphine) and its dimethyl ether (*apo*-ψ-codeine) have long been recognised as dehydration and rearrangement products of morphine and codeine respectively. Although the constitution of these compounds has been established by degradation, *apo*morphine has never been synthesised and considerable doubt exists concerning the claims for the synthesis of *apo*morphine dimethyl ether made by both Avenarius and Pschorr (*Ber.*, 1929, **62**, 321) and Späth and Hromatka (*ibid.*, p. 325). The validity of the former synthesis was questioned by Gulland and Virden (*J.*, 1929, 1794), and in a later communication (*Chem. and Ind.*, 1938, **16**, 774) Gulland pointed out that the product prepared by Avenarius and Pschorr was not a derivative of *apo*morphine but rather a derivative of tetrahydro-2-methyl*iso*quinoline. Doubt also surrounds the claims of Späth and Hromatka because their method had previously been tried without success by Kay and Pictet (*J.*, 1913, **103**, 947), Kondo (*J. Pharm. Soc., Japan*, 1925, 429), and Gulland, Haworth, Virden, and Callow (*J.*, 1929, 1666). In addition, the identity of the products from the synthetic and the natural source was established with a scission product, and the key intermediate used in this method, namely, 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV), was reported to melt at 98° by Kay and Pictet, at 119° by Kondo, and at 79° and 117° by Späth and Hromatka. Further, although many attempts have been made to synthesise phenolic aporphines, notably by Gulland and his co-workers (*J.*, 1931, 2872, 2881, 2885, 2893), little success attended their efforts. These workers carried out preliminary work with both the benzyl and the ethoxycarbonyl group as protecting groups which could subsequently be removed but the completion of this work, including the description of one phenolic aporphine, has not been published. There is thus no record of an authentic synthesis of a hydroxyaporphine, although Kondo and Ishiwata (*Ber.*, 1931, **64**, 1533) reported the synthesis of 6-hydroxy-3 : 4-dimethoxynoraporphine.

It is thus clear that certain aspects of the synthetic work in the aporphine series require further investigation, and with the knowledge now available on the Bischler–Napieralski reaction (see Whaley and Govindachari, *Organic Reactions*, 1951, **6**, 74), on the Pschorr reaction (Hey and Osbond, *J.*, 1949, 3164 and following papers), and on the use of protective groups for phenolic compounds, it would seem that the time is opportune for attacking some of these problems afresh. The present communication is concerned with

the classical synthetic method which involves (*a*) the preparation of a substituted *o*-nitrophenyl-*N*-phenethylacetamide, (*b*) conversion into a 3 : 4-dihydro*iso*quinoline by means of the Bischler–Napieralski reaction, (*c*) methylation and reduction to give a substituted 1-*o*-aminobenzyltetrahydro-2-methyl*iso*quinoline, and finally (*d*) ring closure to the aporphine structure by means of the Pschorr reaction.



The Preparation of the Amides.—The preparation of 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV) has been claimed by several authors. The first synthesis was effected by a ten-stage process from vanillin and the amide was stated to melt at 98° (Kay and Pictet, *loc. cit.*). Later preparations were carried out by Kondo (*loc. cit.*), who reported m. p. 119°, and Späth and Hromatka (*loc. cit.*), who reported the existence of two forms, m. p. 79° and 117°. Two methods of preparation are now described and both lead to a product of m. p. 79°. The first method is based on that of Kay and Pictet (*loc. cit.*) and involves the intermediates (I), (II), and (III) but improvements, reported in

detail in the Experimental section, have been effected at several stages. This improved method was found, in our hands, to be superior to the somewhat similar method described by Slotta and Lauerson (*J. pr. Chem.*, 1934, **139**, 220) for the preparation of 2-nitrohomoveratric acid (III). In the second method 2-nitroveratraldehyde (I) was oxidised to 2-nitroveratric acid (V) by the action of silver oxide, and the acid was converted successively into the acid chloride and the diazo-ketone (VI). The latter, on treatment with phenethylamine in the presence of silver oxide, gave 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV). In addition, the diazo-ketone (VI) with ammonia and silver oxide gave 3 : 4-dimethoxy-2-nitrophenylacetamide, which was converted with nitrous acid into 2-nitrohomoveratric acid (III). The second method of preparation gave inferior yields, although a comparison of the two routes to *o*-nitrophenyl-*N*-phenethylacetamide from *o*-nitrophenylacetic acid through the acid chloride on the one hand, and from *o*-nitro-ω-diazoacetophenone on the other, gave comparable yields.

From these results a general method for the preparation of substituted *N*-2-(3 : 4-methylenedioxyphenyl)ethyl-*o*-nitrophenylacetamides has been developed which involves the conversion of an *o*-nitro-aldehyde into the corresponding carboxylic acid by oxidation with silver oxide, subsequent preparation of the acid chloride and the diazo-ketone, and reaction of the latter with 2-(3 : 4-methylenedioxyphenyl)ethylamine in presence of silver oxide. In this manner, (*a*) 2-nitro-*O*-benzylvanillin (VII) has been converted successively into (VIII), (IX), and 4-benzyloxy-3-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (X); (*b*) 6-nitroveratraldehyde has been converted into 6-nitroveratric acid (XVI), ω-diazo-3 : 4-dimethoxy-6-nitroacetophenone (XVII), and 3 : 4-dimethoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XVIII); (*c*) 6-nitropiperonaldehyde has been converted into 6-nitropiperonylic acid (XIX), the diazo-ketone (XX), and 3 : 4-methylenedioxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)-ethylacetamide (XXI); and (*d*) 2-nitro-*O*-benzyl*iso*vanillin (XXII) has been converted successively into the acid (XXIII), the diazo-ketone (XXIV), and 3-benzyloxy-4-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XXV). In addition, *O*-benzylvanillic acid (XI) has been converted by means of the diazo-ketone (XII) into 4-benzyloxy-3-methoxyphenylacetic acid (XIII), which had been previously prepared by Douglas and Gulland (*J.*, 1931, 2893) by another method. This acid was then nitrated to give (XIV) and converted into 4-benzyloxy-3-methoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XV).

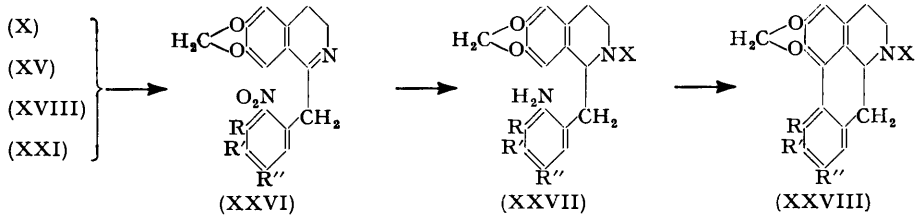
The Bischler–Napieralski–Pschorr Reaction.—Many attempts were made to substantiate the claim made by Späth and Hromatka (*loc. cit.*) to have synthesised apomorphine dimethyl ether from 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV) by successive application of the procedures due to Bischler and Napieralski and to Pschorr. Although a variety of experimental conditions and reagents were used in an attempt to effect ring closure to the dihydro*iso*quinoline no positive evidence for ring closure could be obtained, and the only product isolated was the non-basic dehydration product $C_{18}H_{18}O_4N_2$, as described by Kay and Pictet (*loc. cit.*). These results, as far as the non-formation of an *iso*quinoline is concerned, are in agreement with those of Kay and Pictet, of Gulland, Haworth, Virden, and Callow, and of Kondo (*locc. cit.*). A similar failure at the Bischler–Napieralski stage occurred with *o*-nitrophenyl-*N*-phenethylacetamide and it would appear likely that the presence of an *o*-nitro-group in the phenylacetyl moiety, coupled with the absence of an activating group in the phenethylamino-moiety, makes ring closure to the dihydro*iso*quinoline derivative very difficult, if not impossible. The usefulness of polyphosphoric acid as a reagent to effect the Bischler–Napieralski reaction was demonstrated by the formation of 1-benzyl-3 : 4-dihydro*iso*quinoline from *N*-phenethylphenylacetamide.

The successful conversion of a series of *N*-2-(3 : 4-methylenedioxyphenyl)ethyl-*o*-nitrophenylacetamides into derivatives of aporphine or noraporphine has been achieved in the following four examples.

4-Benzyloxy-3-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (X) was converted into 1-(4-benzyloxy-3-methoxy-2-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline (XXVI; R = MeO, R′ = Ph·CH_2·O, R″ = H) by the action of phosphorus pentachloride in chloroform. The base was converted into the

methiodide, which was then reduced with zinc and hydrochloric acid to 1-(2-amino-4-benzyloxy-3-methoxylbenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline (XXVII; R = MeO, R′ = Ph·CH_2·O, R″ = H, X = Me). Diazotisation of this base with barium nitrite, decomposition with the addition of copper powder, and subsequent debenzylation gave (±)-3-hydroxy-4-methoxy-5 : 6-methylenedioxyaporphine (XXVIII; R = MeO, R′ = HO, R″ = H, X = Me), also known as *iso*bulbocapnine.

In similar manner 4-benzyloxy-3-methoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XV) gave (XXVI; R = H, R′ = Ph·CH_2·O, R″ = MeO), (XXVII; R = H, R′ = Ph·CH_2·O, R″ = MeO, X = Me), and (±)-3-hydroxy-2-methoxy-5 : 6-methylenedioxyaporphine (XXVIII; R = H, R′ = HO, R″ = MeO, X = Me); 3 : 4-dimethoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XVIII) gave (XXVI; R = H, R′ = MeO, R″ = MeO), (XXVII; R = H, R′ = MeO, R″ = MeO, X = H), and (±)-2 : 3-dimethoxy-5 : 6-methylenedioxynoraporphine (XXVIII; R = H, R′ = MeO, R″ = MeO, X = H), which is (±)-actinodaphnine methyl ether; and 3 : 4-methylenedioxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide



(XXI) gave (XXVI; R = H, R′R″ = ·O·CH_2·O·), (XXVII; R = H, R′R″ = ·O·CH_2·O·, X = Me), and (±)-2 : 3-5 : 6-bismethylenedioxyaporphine (XXVIII; R = H, R′R″ = ·O·CH_2·O·, X = Me). Preliminary attempts to effect ring closure with 3-benzyloxy-4-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XXV) and phosphorus pentachloride resulted in debenzylation.

The above examples include the synthesis of two phenolic aporphines, one aporphine ether, and one noraporphine ether. The aporphine ether which corresponds with the last-named compound, namely (±)-dicentrine, was synthesised by Haworth, Perkin, and Rankin (*J.*, 1925, **127**, 2022).

Experimental

Preparation of amides.

3 : 4-*Dimethoxy*-2-*nitrophenyl*-N-*phenethylacetamide* (IV).—*Method* (*a*). *O*-Acetylvanillin was nitrated by Pschorr and Sumuleanu's method (*Ber.*, 1899, **32**, 3405), but at −12° to −20°, to give in 80% yield *O*-acetyl-2-nitrovanillin, which was hydrolysed by boiling with dilute hydrochloric acid for 2 hr. 2-Nitrovanillin separated in yellow needles, m. p. 137°, in 80% overall yield. To an ice-cold solution of 2-nitrovanillin (50 g.) in methyl alcohol (100 c.c.) and methyl sulphate (63 g.) was added 30% aqueous sodium hydroxide (75 c.c.) dropwise with stirring. The mixture was then heated to the b. p. and methyl sulphate (20 g.) was added followed by 30% aqueous sodium hydroxide (20 c.c.). This procedure was repeated twice. On cooling, 2-nitroveratraldehyde separated, which crystallised from alcohol in pale yellow needles (46·5 g.), m. p. 54—56°. For the conversion of 2-nitroveratraldehyde into 3 : 4-dimethoxy-2-nitrobenzyl alcohol the following methods proved superior to that of Kay and Pictet (*loc. cit.*): (i) A solution of 2-nitroveratraldehyde (10 g.) in dry *iso*propyl alcohol (200 c.c.), added to a solution of aluminium *iso*propoxide (5 g.) in *iso*propyl alcohol (50 c.c.), was distilled at the rate of 2—3 drops a minute, the total volume of the solution being kept constant until the distillate was free from acetone (36 hr.). Excess of *iso*propyl alcohol was removed by distillation and the residue warmed to 50° with 10% sulphuric acid. 3 : 4-Dimethoxy-2-nitrobenzyl alcohol (7·5 g.) was collected and crystallised from alcohol in yellow needles, m. p. 66—68°. (ii) (cf. Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905.) A solution of 2-nitroveratraldehyde (20 g.) in methyl alcohol (100 c.c.) and 40% formaldehyde solution (10 c.c.) was heated to 70° and 50% aqueous sodium hydroxide (15 c.c.) was added at such a rate that the temperature did not exceed 75°. After being boiled under reflux for 1 hr., the mixture was cooled and water

(100 c.c.) was added. The 3 : 4-dimethoxy-2-nitrobenzyl alcohol (16 g.) which separated crystallised from alcohol in yellow needles, m. p. 66—68°. Acidification of the filtrate gave 2-nitroveratric acid (0·7 g.), m. p. 200—202°. The alcohol (10 g.) was added in small portions to thionyl chloride (20 g.), cooled in ice. When the initial vigorous reaction had ceased, the solution was boiled under reflux for ½ hr., cooled, and poured on ice (200 g.). The 3 : 4-dimethoxy-2-nitrobenzyl chloride was collected, dried, and dissolved in benzene (15 c.c.). Addition of light petroleum (b. p. 60—80°) precipitated 3 : 4-dimethoxy-2-nitrobenzyl chloride (9 g.) in needles, m. p. 57—58°, which was converted into 3 : 4-dimethoxy-2-nitrobenzyl cyanide (7·5 g.), m. p. 68—69°, by boiling it in alcohol (170 c.c.) with aqueous potassium cyanide (18 g. in 15 c.c.) (cf. Kay and Pictet, *loc. cit.*). The cyanide (15 g.) was converted into 2-nitrohomoveratric acid (10 g.), m. p. 146°, and thence through the acid chloride into 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (10 g.), white needles, m. p. 79° (from alcohol) (Found: C, 62·6; H, 5·8; N, 8·0. Calc. for $C_{18}H_{20}O_5N_2$: C, 62·8; H, 5·8; N, 8·1%), as described by Kay and Pictet, who recorded m. p. 98° (from toluene) for this compound. Späth and Hromatka (*loc. cit.*) have recorded m. p. 79°.

Method (*b*). 2-Nitroveratraldehyde, prepared as in method (*a*), was oxidised to 2-nitroveratric acid by the following method, which is much superior to that of Pschorr and Sumuleanu (*loc. cit.*). Silver oxide (15 g.) was added to a suspension of 2-nitroveratraldehyde (10 g.) in 2% aqueous sodium hydroxide (200 c.c.) at 70° and the mixture was then boiled under reflux for 4 hr. After filtration of the hot solution acidification liberated 2-nitroveratric acid (9 g.), which separated on cooling in yellow leaflets, m. p. 201—202°. In an alternative procedure 15% aqueous sodium hydroxide was slowly added to a boiling suspension of 2-nitroveratraldehyde (10 g.) in a solution of silver nitrate (16 g.) in water (200 c.c.). Boiling under reflux was continued until the silver mirror initially formed had disintegrated and the product was worked up as before, to give 2-nitroveratric acid (9 g.), m. p. 201—202°. 2-Nitroveratric acid (10 g.) was converted into 2-nitroveratroyl chloride (9 g.), m. p. 73°, by Pisovschi's method (*Ber.*, 1910, **43**, 2141). A solution of the acid chloride (9 g.) in dry benzene (20 c.c.) was added to ethereal diazomethane, prepared from nitrosomethylurea (20 g.), at 0—5°. After 3 hr. the *ω-diazo-3 : 4-dimethoxy-2-nitroacetophenone* (8 g.), which separated, was collected and crystallised from dry benzene, giving very pale yellow needles, m. p. 116° (decomp.) (Found: C, 48·1; H, 3·7. $C_{10}H_9O_5N_3$ requires C, 47·8; H, 3·6%). Phenethylamine (3 g.) and silver oxide (0·5 g.) were added to a solution of the diazo-ketone (5 g.) in dry benzene (100 c.c.) at 60°. Evolution of nitrogen was slow and after 10 min. alcohol (1 c.c.) was added and the temperature was kept at 65—70° for 2 hr. After filtration light petroleum (b. p. 60—80°) was added to the cooled filtrate until a small quantity of a dark oil began to separate. The clear solution was decanted from the oil and the operation was repeated with the addition of more light petroleum. The solution which was then considerably paler was diluted with an excess of light petroleum (b. p. 60—80°), which precipitated a red oil which solidified at 0°. The solid product was dissolved in alcohol, to which water was added until a slight turbidity appeared. After the addition of charcoal the mixture was boiled under reflux and filtered. The yellow filtrate, on cooling, deposited an oil which solidified (2 g.; m. p. 62—67°). Three recrystallisations from alcohol gave 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (0·5 g.) in white needles, m. p. 79°, undepressed on admixture with the product prepared by method (*a*) above.

To a portion of the diazo-ketone (1 g.) in dioxan (15 c.c.) were added a solution of ammonia (*d* 0·880; 5 c.c.) in water (5 c.c.) and then silver oxide (0·2 g.) and alcohol (0·5 c.c.). The mixture was kept at 50° for 1 hr. Nitrogen was evolved and after being boiled under reflux for ½ hr. the mixture was filtered. Water was added to the filtrate (until turbidity was produced) and the whole was then boiled with charcoal and filtered. 3 : 4-Dimethoxy-2-nitrophenylacetamide (0·22 g.) which separated on cooling formed needles, m. p. 150—151°, from hot water (cf. Gulland and Virden, *J.*, 1929, 1803). When a solution of sodium nitrite (0·3 g.) in water (3 c.c.) was added slowly to a solution of the amide (1 g.) in concentrated sulphuric acid (5 c.c.), cooled in ice, nitrogen was liberated with evolution of heat. When the reaction had subsided water (25 c.c.) was added and the solution was boiled under reflux for 15 min. On cooling, 2-nitrohomoveratric acid (0·7 g.) separated, which crystallised from hot water in white leaflets, m. p. 144—146°, identical with the product obtained above from the hydrolysis of 3 : 4-dimethoxy-2-nitrobenzyl cyanide.

o-*Nitrophenyl*-N-*phenethylacetamide.*—*Method* (*a*). *o*-Nitrophenylacetic acid (10 g.) in dry benzene (20 c.c.) was boiled under reflux for 2 hr. with thionyl chloride (12 g.). Excess of thionyl chloride and benzene were removed under reduced pressure and the residual *o*-nitrophenylacetyl chloride was redissolved in benzene (30 c.c.) and added in small portions to

a suspension of phenethylamine (8 g.) in water (20 c.c.) cooled in ice. Aqueous sodium hydroxide (10%; 20 c.c.) was added, and after 15 min. the benzene layer was separated, washed with dilute hydrochloric acid, and dried. Addition of light petroleum (b. p. 60—80°) deposited *o*-nitrophenyl-*N*-phenethylacetamide (12 g.), which separated from aqueous alcohol in needles, m. p. 98—99° (cf. Kay and Pictet, *loc. cit.*).

Method (*b*). To a solution of ω-diazo-*o*-nitroacetophenone (13 g.) (Arndt, Eistert, and Partale, *Ber.*, 1927, **60**, 1366) in benzene (100 c.c.) were added phenethylamine (9 g.), silver oxide (0·5 g.), and alcohol (2 c.c.). After being kept for 1 hr. at 70° the mixture was boiled under reflux for ½ hr. and filtered. Light petroleum (b. p. 60—80°) was added to the brown filtrate until a small quantity of dark oil separated, and the clear solution was then decanted. Further addition of light petroleum precipitated a brown oil which solidified. Recrystallisation from benzene gave *o*-nitrophenyl-*N*-phenethylacetamide (10 g.) in pale yellow needles, m. p. 98—99°, identical with the product prepared by method (*a*) above.

4-Benzyloxy-3-methoxy-2-nitrophenyl-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (X).—A mixture of 2-nitrovanillin (10 g.), dioxan (40 c.c.), benzyl chloride (9 g.), potassium carbonate (5 g.), and water (7 c.c.) was boiled under reflux for 4 hr. and then poured into water (200 c.c.) and distilled with steam until the distillate was clear. The oil which separated on cooling solidified. Crystallisation from alcohol, after treatment with charcoal, gave *O-benzyl-2-nitrovanillin* (13 g.) in needles, m. p. 108—109° (Found: C, 62·6; H, 4·5; N, 4·7. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·5; N, 4·9%). A mixture of this (10 g.), sodium carbonate (4 g.), silver oxide (9 g.), and water (200 c.c.) was boiled under reflux for 4 hr. When cold, the mixture was filtered and the residue was boiled with water (200 c.c.) and filtered hot. On cooling, sodium *O*-benzyl-2-nitrovanillate separated in plates. This was collected and dissolved in boiling water. On acidification, *O-benzyl-2-nitrovanillic acid* (9 g.) separated, which crystallised from alcohol in needles, m. p. 183—184° (Found: C, 60·0; H, 4·5. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3%). A small quantity of *O*-benzyl-2-nitrovanillic acid was also recovered by acidification of the original filtrate. In an alternative procedure a mixture of 2-nitrovanillin (20 g.), silver nitrate (25 g.), and water (200 c.c.) was heated to 80° and 25% aqueous sodium hydroxide (50 c.c.) was added. Boiling under reflux was continued until the silver mirror initially formed was completely disintegrated (1—1½ hr.). The mixture was worked up as before and gave *O*-benzyl-2-nitrovanillic acid (18 g.), m. p. 183—184°. *O*-Benzyl-2-nitrovanillic acid (12 g.) was added in small portions to a suspension of phosphorus pentachloride (9 g.) in dry chloroform (30 c.c.), and the mixture was set aside for ½ hr. after the acid had dissolved. After filtration, the solvent was removed at 30° under reduced pressure and cold dry ether (20 c.c.) was added to the residue. The granular 4-benzyloxy-3-methoxy-2-nitrobenzoyl chloride (11 g.) was collected, washed with cold ether, and dried. After crystallisation from benzene it was obtained in needles, m. p. 108°. The acid chloride (15 g.) in dry benzene (50 c.c.) was added in portions, with shaking, to a solution of diazomethane in ether (prepared from 20 g. of nitrosomethylurea) at 5°. After 3 hr. the diazo-ketone was collected and dried by suction. Crystallisation from benzene gave *4-benzyloxy-ω-diazo-3-methoxy-2-nitroacetophenone* (14 g.) in pale yellow needles, m. p. 152—154° (decomp.) (Found: C, 58·8; H, 4·0. $C_{16}H_{13}O_5N_3$ requires C, 58·7; H, 4·2%). 2-(3 : 4-Methylenedioxyphenyl)ethylamine (4·5 g.; prepared as described by Decker, *Annalen*, 1913, **395**, 291) and silver oxide (0·5 g.) were added to a solution of freshly prepared 4-benzyloxy-ω-diazo-3-methoxy-2-nitroacetophenone (8 g.) in benzene (200 c.c.) at 65°. Nitrogen was evolved gently at this temperature which should not be exceeded, and after 2 hr. a further quantity of silver oxide (0·5 g.) was added and the mixture was boiled under reflux for ½ hr. After filtration the solution was concentrated to small bulk, and light petroleum (b. p. 60—80°) was added to the cold solution until a small quantity of brown oil separated which solidified. Further light petroleum was then added to complete the separation. The solid was collected and dissolved in boiling glacial acetic acid (6 c.c.). After 2 hr. the solid which had separated was collected under suction, pressed free from mother-liquor, and washed with cold glacial acetic acid (3 c.c.). Several recrystallisations from aqueous alcohol (with charcoal) gave *4-benzyloxy-3-methoxy-2-nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (4·7 g.) in needles, m. p. 123—124° (Found: C, 64·3; H, 5·0; N, 5·9. $C_{25}H_{24}O_7N_2$ requires C, 64·7; H, 5·2; N, 6·0%).

4-Benzyloxy-3-methoxy-6-nitrophenyl-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (XV).—To a vigorously boiling mixture of *O*-benzylvanillin (20 g.; Dickinson, Heilbron, and Irving, *J.*, 1927, 1895), silver nitrate (32 g.), and water (150 c.c.), 40% aqueous sodium hydroxide (50 c.c.) was slowly added. After being boiled under reflux for 1 hr. the mixture was filtered and the filtrate acidified. Recrystallisation of the separated solid from benzene gave O-*benzyl*-

vanillic acid (19 g.) in needles, m. p. 171—172° (Found : C, 69·4; H, 5·2. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%). This acid (12 g.) was converted into the acid chloride (11 g.), m. p. 65—66°, as described above for the preparation of *O*-benzyl-2-nitrovanillic acid except that the solvent was removed below 30°. The acid chloride (11 g.) was in turn converted by the method described above for the 2-nitro-compound into 4-*benzyloxy*-ω-*diazo*-3-*methoxyacetophenone* (10 g.), pale yellow needles, m. p. 98—99° (decomp.; from alcohol) (Found : C, 67·9; H, 4·8. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0%). Silver oxide (0·5 g.) was added to a solution of the diazo-ketone (10 g.) in dioxan (50 c.c.) and ammonia (*d* 0·880; 20 c.c.), and the mixture was heated at 80° for 2 hr., filtered, and poured into water (100 c.c.). Recrystallisation of the solid which separated gave 4-*benzyloxy*-3-*methoxyphenylacetamide* (8 g.), which separated from hot water in plates, m. p. 133—134° (Found : C, 70·6; H, 6·1. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3%). Hydrolysis of the amide (6 g.) with boiling 10% aqueous sodium hydroxide gave 4-benzyloxy-3-methoxyphenylacetic acid (5 g.), which separated from benzene in prisms, m. p. 114—116°. The m. p. was not depressed on admixture with a specimen of the acid (m. p. 115—116°) prepared from 4-benzyloxy-3-methoxyphenylpyruvic acid by Douglas and Gulland's method (*J.*, 1931, 2897). Nitration by Douglas and Gulland's method gave 4-benzyloxy-3-methoxy-6-nitrophenylacetic acid in needles, m. p. 222°. The crude acid (6 g.) was converted into the acid chloride, as described above for the preparation of 4-benzyloxy-3-methoxy-2-nitrobenzoyl chloride, which in turn was added to a solution of 2-(3 : 4-methylenedioxyphenyl)ethylamine (4 g.) in chloroform (30 c.c.) at 0°. After 10 min. 5% aqueous sodium hydroxide (40 c.c.) was added and finally chloroform (50 c.c.). The chloroform layer was washed with dilute hydrochloric acid and dried, and the solvent was removed. Crystallisation of the residue from ethylene dichloride and then from alcohol gave 4-*benzyloxy*-3-*methoxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (5 g.) in needles, m. p. 195—197° (Found : C, 64·6; H, 5·0. $C_{25}H_{24}O_7N_2$ requires C, 64·8; H, 4·9%).

3 : 4-*Dimethoxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (XVIII).—Veratraldehyde was converted into 6-nitroveratraldehyde by Pschorr and Sumuleanu's method (*Ber.*, 1899, **32**, 3412). A solution of sodium hydroxide (15 g.) in water (50 c.c.) was added slowly to a mixture of 6-nitroveratraldehyde (25 g.), silver nitrate (40 g.), and water (200 c.c.) boiling under reflux. After further boiling for 1½ hr. the mixture was filtered and to the filtrate acid was added until the solution was only just alkaline. This solution was heated with charcoal and filtered. Acidification of the hot filtrate precipitated 6-nitroveratric acid (20 g.), yellow leaflets, m. p. 186° (from hot water). Simonsen and Rau (*J.*, 1918, **113**, 26) record m. p. 185—187°. 6-Nitroveratric acid (15 g.) was converted into the acid chloride (14·5 g.), m. p. 120—122°, by the method described above for *O*-benzyl-2-nitrovanillic acid. From the acid chloride (13 g.) in dioxan (40 c.c.) and ethereal diazomethane (200 c.c.), prepared from nitrosomethylurea (25 g.), at 0—5°, there was obtained ω-diazo-3 : 4-dimethoxy-6-nitroacetophenone (11·5 g.), in yellow needles, m. p. 157—158° (decomp.; from dioxan), which was too unstable for analysis. 2-(3 : 4-Methylenedioxyphenyl)ethylamine (7 g.) and silver oxide (0·5 g.) were added to a solution of the diazo-ketone (10·5 g.) in dioxan (150 c.c.) at 60°. Nitrogen was evolved and after 2 hr. more silver oxide (0·5 g.) was added and the temperature was raised to 100° for 10 min. After filtration the filtrate was cooled to 0° and the solid which separated was collected and washed with ice-cold methyl alcohol. Recrystallisation from ethylene dichloride gave 3 : 4-*dimethoxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (9·5 g.) in plates, m. p. 199—201° (Found : C, 58·1; H, 5·1; N, 6·8. $C_{19}H_{20}O_7N_2$ requires C, 58·8; H, 5·2; N, 7·2%).

3 : 4-*Methylenedioxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (XXI).—6-Nitropiperonaldehyde (10 g.) (Salway, *J.*, 1909, **95**, 1163) in 5% aqueous sodium carbonate (200 c.c.) was warmed to 70° and silver oxide (15 g.) added. The mixture was boiled under reflux until the purple colour changed to orange (1 hr.). After filtration and treatment with charcoal, acidification precipitated 6-nitropiperonylic acid, which separated from hot water in yellow plates (5 g.), m. p. 170—172° (cf. Jobst and Hesse, *Annalen*, 1879, **199**, 70). In an alternative preparation piperonaldehyde (30 g.) was oxidised with silver nitrate in alkaline solution, as described above for the oxidation of 6-nitroveratraldehyde, to give piperonylic acid (32 g.), which was then nitrated by Jobst and Hesse's method (*loc. cit.*) to 6-nitropiperonylic acid, m. p. 172°, in 60% yield. A suspension of 6-nitropiperonylic acid (10 g.) in benzene (30 c.c.) was boiled under reflux with thionyl chloride (10 g.) until evolution of hydrogen chloride had ceased. After filtration and evaporation at 70° under reduced pressure, more benzene (20 c.c.) was added and the evaporation repeated. The residual 6-nitropiperonyloyl chloride, obtained as a yellow oil (11 g.), in benzene (20 c.c.) was added to ethereal diazomethane (200 c.c.),

prepared from nitrosomethylurea (20 g.), at 0—5°. Nitrogen was evolved and yellow needles separated. After 3 hr. these were collected and recrystallisation from benzene gave *ω-diazo-3 : 4-methylenedioxy-6-nitroacetophenone* (9·5 g.), m. p. 133—134° (decomp.) (Found: C, 46·1; H, 2·3. $C_9H_5O_5N_3$ requires C, 46·2; H, 2·1%). The diazo-ketone (10 g.) and 2-(3 : 4-methylenedioxyphenyl)ethylamine (7 g.), as for the preparation of (X), gave the *amide* as a grey solid. Recrystallisation from pyridine gave needles (9 g.), m. p. 203—206° (Found: C, 57·8; H, 4·15. $C_{18}H_{16}O_7N_2$ requires C, 58·2; H, 4·3%).

3-Benzyloxy-4-methoxy-2-nitrophenyl-N-*2-(3 : 4-methylenedioxyphenyl)ethylacetamide* (XXV).—A mixture of 2-nitro*iso*vanillin (5 g.; Pschorr and Stöhrer, *Ber.*, 1902, **35**, 4393), alcohol (20 c.c.), water (25 c.c.), benzyl chloride (25 g.), and sodium carbonate (5 g.) was boiled under reflux for 4 hr. Water (80 c.c.) was added and excess of benzyl chloride was removed with steam. The residual oil solidified and crystallisation from alcohol and then from benzene–light petroleum (b. p. 60—80°) gave *O-benzyl-2-nitro*iso*vanillin* (6 g.) in plates, m. p. 102—103° (Found: C, 62·5; H, 4·4. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·5%). In similar manner 6-nitro*iso*vanillin (5 g.) gave its *benzyl ether* (6 g.), plates m. p. 133—134° (Found: C, 62·6; H, 4·4%). *O*-Benzyl-2-nitro*iso*vanillin (5 g.) was oxidised with silver nitrate in alkaline solution as described above for the oxidation of *O*-benzylvanillin. The acid was purified by crystallisation of the sodium salt from hot water. Acidification gave *O-benzyl-2-nitro*iso*vanillic acid* (4 g.), which crystallised from aqueous alcohol in needles, m. p. 186° (Found: C, 59·6; H, 4·25. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3%). This acid (5 g.) was converted into the acid chloride (4·2 g.), needles, m. p. 122—123°, by the method used above with *O*-benzyl-2-nitrovanillic acid, and thence into *3-benzyloxy-ω-diazo-4-methoxy-2-nitroacetophenone* (3·6 g.) by the method used in the previous examples. The diazo-ketone separated from benzene in pale yellow needles, m. p.123—124° (decomp.) (Found: C, 58·9; H, 4·0. $C_{16}H_{13}O_5N_3$ requires C, 58·7; H, 4·2%). The diazo-ketone (7 g.) and 2-(3 : 4-methylenedioxyphenyl)ethylamine (4 g.), by the procedure used for (X), gave the *amide* (4 g.), plates (from aqueous alcohol), m. p. 106—107° (Found: C, 64·9; H, 4·95. $C_{25}H_{24}O_7N_2$ requires C, 64·7; H, 5·2%).

The Bischler–Napieralski–Pschorr reaction.

Attempted Ring Closure of 3 : 4-Dimethoxy-2-nitrophenyl-N-phenethylacetamide and of o-Nitrophenyl-N-phenethylacetamide.—Attempted ring closure of 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (1 g.) with phosphoric oxide in boiling sulphur-free xylene, followed by addition of ice and concentrated hydrochloric acid, gave, on evaporation of the xylene layer, a non-basic compound $C_{18}H_{18}O_4N_2$ (0·5 g.), yellow needles, m. p. 123—124° (from alcohol) (Found: C, 66·6; H, 5·6. Calc. for $C_{18}H_{18}O_4N_2$: C, 66·25; H, 5·5%). Basification of the aqueous acid gave only a slight turbidity (cf. Kay and Pictet, *loc. cit.*, and Callow, Gulland, and Haworth, *J.*, 1929, 1444). Similar results were obtained when concentrated sulphuric acid, fused zinc chloride, phosphorus oxychloride, polyphosphoric acid, and a mixture of phosphorus oxychloride and polyphosphoric acid were used as dehydrating agents in xylene or toluene.

Similar experiments carried out on *o*-nitrophenyl-*N*-phenethylacetamide failed to effect ring-closure, and unchanged amide was in most cases recovered.

Ring Closure of Phenyl-N-phenethylacetamide with Polyphosphoric Acid.—A mixture of polyphosphoric acid (10 g.) and phenyl-*N*-phenethylacetamide (5 g.) in dry xylene (30 c.c.) was boiled under reflux for 1 hr., after whlch it was poured into water (30 c.c.) and heated to 70° with concentrated hydrochloric acid (5 c.c.). The aqueous layer was separated, filtered, made alkaline with aqueous sodium hydroxide, and extracted with ether. Evaporation of the dried extract left 1-benzyl-3 : 4-dihydro*iso*quinoline (1·8 g.), b. p. 174—176°/8 mm. (picrate, m. p. 174—175°) (cf. Pictet and Kay, *Ber.*, 1909, **42**, 1977).

*1-(4-Benzyloxy-3-methoxy-2-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline* (XXVI; R = MeO, R′ = Ph·CH_2·O, R″ = H).—A solution of 4-benzyloxy-3-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (5 g.) in dry alcohol-free chloroform (30 c.c.) to which phosphorus pentachloride (10 g.) had been added was kept in a stoppered flask at room temperature for 4 days. Pressure was released every 12 hr. Crushed ice (100 g.) was added to the ice-cooled mixture and, when the vigorous reaction had subsided, the mixture was allowed to attain room temperature. Chloroform and phosphorus oxychloride were removed at 30° under reduced pressure. The gum which separated was dissolved in hot alcohol (30 c.c.) containing concentrated hydrochloric acid (2 c.c.), boiled with charcoal, and filtered. The substituted iso*quinoline hydrochloride* separated on cooling in pale yellow needles (3·5 g.), m. p. 191—192° (Found: C, 61·9; H, 4·8; N, 6·05; Cl, 7·7.

$C_{25}H_{22}O_6N_2$,HCl requires C, 62·1; H, 4·6; N, 5·8; Cl, 7·6%). The free *base* was liberated by the dropwise addition of dilute aqueous ammonia to a hot alcoholic solution of the hydrochloride. Crystallisation from aqueous alcohol gave the base in off-white needles, m. p. 138—140° (Found: N, 6·6. $C_{25}H_{22}O_6N_2$ requires N, 6·3%). The *methiodide*, prepared by boiling a methyl-alcoholic solution of the base with methyl iodide for 2 hr., separated from methyl alcohol–acetone in pale yellow needles, m. p. 160—161° (Found: N, 4·9. $C_{25}H_{22}O_6N_2,CH_3I$ requires N, 4·9%).

1-(2-*Amino*-4-*benzyloxy*-3-*methoxybenzyl*)-1:2:3:4-*tetrahydro*-2-*methyl*-6:7-*methylenedioxy*isoquinoline (XXVII; R = MeO, R′ = Ph·CH_2·O, R″ = H, X = Me).—Concentrated hydrochloric acid was added to a solution of 1-(4′-benzyloxy-3′-methoxy-2′-nitrobenzyl)-6:7-methylenedioxy*iso*quinoline methiodide (1 g.) in dioxan (20 c.c.) until a faint turbidity appeared. Zinc dust (5 g.) was added in small portions to the ice-cooled mixture until the yellow colour was completely discharged. Water (30 c.c.) was added and the mixture was filtered. The filtrate was covered with a layer of ether in a separating funnel and made alkaline with ammonia, the temperature being kept below 15°. The ether layer was removed and the aqueous layer was extracted a second time with ether. The combined ethereal extracts were dried (K_2CO_3) and the ether removed. The base, which was obtained as a brown oil and which could be diazotised and coupled with β-naphthol, was dissolved in hot alcohol (20 c.c.) and added to a solution of picrolonic acid (1 g.) in boiling alcohol (10 c.c.). On cooling, 1-(2-*amino*-4-*benzyloxy*-3-*methoxybenzyl*)-1:2:3:4-*tetrahydro*-2-*methyl*-6:7-*methylenedioxy*isoquinolinium *dipicrolonate* (0·7 g.) separated, which crystallised from acetone in yellow needles, m. p. 185—186° (Found: C, 57·7; H, 4·95. $C_{26}H_{28}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 57·5; H, 4·6%). A similar reduction was effected with glacial acetic acid (20 c.c.) in place of dioxan (20 c.c.).

(±)-3-*Hydroxy*-4-*methoxy*-5:6-*methylenedioxyaporphine* (iso*Bulbocapnine*) (XXVIII; R = MeO, R′ = HO, R″ = H, X = Me).—A suspension of the above dipicrolonate (1·8 g.) in cold methyl alcohol (20 c.c.) was ground in a mortar with concentrated sulphuric acid (1 c.c.). The precipitated picrolonic acid was filtered off and washed with a small quantity of methyl alcohol, which was added to the filtrate. A solution of barium nitrite (0·34 g.) in water (1 c.c.) was added to the solution, which was kept at 0° for 4 hr., after which catalytic copper powder (0·5 g.) was added. The mixture was boiled under reflux for ½ hr., nitrogen being evolved. After addition of water (20 c.c.) the copper powder and barium sulphate were removed by filtration. The filtrate, in a separating funnel, was covered with a layer of ether and made alkaline with dilute aqueous sodium hydroxide. The ethereal layer was removed and the aqueous layer again extracted several times. The combined ethereal extracts were washed with water and dried (Na_2SO_4). Removal of the ether left a pale brown oil. Concentrated hydrochloric acid (10 c.c.) was added and the solution was warmed to 70° for ½ hr., during which the solution became turbid and benzyl chloride was liberated. Water (15 c.c.) was added to the cold solution, which was then made alkaline with aqueous ammonia and extracted three times with ether (25 c.c.). Removal of the ether from the combined dried (Na_2SO_4) extracts left an almost colourless gum which when scratched under light petroleum (b. p. 40—60°) became crystalline. Recrystallisation from ethylene dichloride–light petroleum (b. p. 40—60°) and then twice from alcohol–ether gave (±)-3-*hydroxy*-4-*methoxy*-5:6-*methylenedioxyaporphine* (40 mg.) in colourless tablets, m. p. 165—166°, soluble in acetic acid and aqueous sodium hydroxide (Found: C, 69·7; H, 5·6. $C_{19}H_{19}O_4N$ requires C, 70·15; H, 5·8%).

1-(4-*Benzyloxy*-3-*methoxy*-6-*nitrobenzyl*)-3:4-*dihydro*-6:7-*methylenedioxy*isoquinoline (XXVI; R = H, R′ = Ph·CH_2·O, R″ = MeO).—By use of the methods previously described 4-benzyloxy-3-methoxy-6-nitrophenyl-*N*-2-(3:4-methylenedioxyphenyl)ethylacetamide (5 g). and phosphorus pentachloride (10 g.) in dry chloroform (30 c.c.) gave the substituted *dihydro*-iso*quinoline hydrochloride* (2·6 g.) in plates, m. p. 224—226° (from alcohol) (Found: Cl, 7·8. $C_{25}H_{22}O_6N_2$,HCl requires Cl, 7·6%). The free *base*, liberated from an alcoholic solution of the hydrochloride with ammonia, crystallised from ethylene dichloride–methyl alcohol in plates, m. p. 164—165° (Found: C, 67·3; H, 4·8. $C_{25}H_{22}O_6N_2$ requires C, 67·1; H, 4·9%). The *methiodide*, prepared as above, separated from acetic acid in yellow needles, m. p. 180—181° (Found: C, 54·5; H, 4·6. $C_{25}H_{22}O_6N_2,CH_3I$ requires C, 54·4; H, 4·4%).

1-(6-*Amino*-4-*benzyloxy*-3-*methoxybenzyl*)-1:2:3:4-*tetrahydro*-2-*methyl*-6:7-*methylenedioxy*isoquinoline (XXVII; R = H, R′ = $PhCH_2$·O, R″ = MeO, X = Me).—The foregoing methiodide (1 g.) was reduced in glacial acetic acid (25 c.c.) with zinc dust (6 g.) as described in the previous example and the *tetrahydro*iso*quinolinium dipicrolonate* (0·8 g.) was obtained in needles, m. p. 176°, from a large volume of alcohol (Found: C, 56·9; H, 4·4. $C_{26}H_{28}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 57·5; H, 4·6%).

(±)-3-*Hydroxy*-2-*methoxy*-5 : 6-*methylenedioxyaporphine* (XXVIII; R = H, R′ = HO, R″ = MeO, X = Me).—By the method described in the previous example the preceding dipicrolonate (2 g.) gave (±)-3-hydroxy-2-methoxy-5 : 6-methylenedioxyaporphine (0·15 g.), which separated from ethylene dichloride–light petroleum (b. p. 40—60°) in needles, m. p. 126—129° after softening at 117°. The base became brown in air and was readily soluble in both acetic acid and aqueous sodium hydroxide. Because of its instability it was analysed as the *picrolonate* which separated from alcohol in yellow needles, m. p. 198—199° (decomp.) (Found : C, 58·8; H, 4·4. $C_{19}H_{19}O_4N,C_{10}H_8O_5N_4$ requires C, 59·1; H, 4·6%).

1-(3 : 4-*Dimethoxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline (XXVI; R = H, R′ = MeO, R″ = MeO).—By the methods described above, 3 : 4-dimethoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (9 g.) and phosphorus pentachloride (15 g.) in dry chloroform (30 c.c.) gave 1-(3 : 4-*dimethoxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline *hydrochloride* (5 g.), which separated from dilute hydrochloric acid in yellow plates, m. p. 213—214° (Found : Cl, 9·1. $C_{19}H_{18}O_6N_2$,HCl requires Cl, 8·7%). The free *base*, liberated with ammonia, was obtained in white leaflets, m. p. 198—202° (darkening at 195°), from alcohol containing a small quantity of ethylene dichloride (Found : C, 61·4; H, 5·0. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9%). The *methiodide*, prepared as described in the previous examples, separated from acetic acid in yellow needles, m. p. 208—209° (Found : I, 25·0. $C_{19}H_{18}O_6N_2,CH_3I$ requires I, 25·2%). Reduction of the methiodide (1 g.) with zinc dust (6 g.) in dilute hydrochloric acid (1 : 1; 30 c.c.) as described above, gave 1-(6-amino-3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline dihydrochloride (0·2 g.), m. p. 249—250° (decomp.). Haworth, Perkin, and Rankin (*J.*, 1925, **127**, 2022) record m. p. 250° (decomp.) for this compound prepared by another method.

1-(6-*Amino*-3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy*isoquinoline (XXVII; R = H, R′ = MeO, R″ = MeO, X = H).—Zinc dust (4 g.) was added in small portions to a hot solution of 1-(3 : 4-dimethoxy-6-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline (1 g.) in a mixture of water (15 c.c.) and concentrated hydrochloric acid (15 c.c.). When the yellow colour was discharged the mixture was cooled, filtered, transferred to a separating funnel, and covered with ether. Concentrated aqueous ammonia was then added until the precipitated zinc hydroxide had dissolved. The white solid which remained undissolved was collected, but darkened on exposure to air. It was dissolved in alcohol, filtered, and added to a boiling alcoholic solution (10 c.c.) of picrolonic acid (1 g.). On cooling, the *tetrahydro*isoquinolinium *dipicrolonate* separated; it (0·5 g.) had m. p. 170—190°, depending on rate of heating (Found : C, 53·6; H, 4·5. $C_{19}H_{22}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 53·8; H, 4·5%).

(±)-2 : 3-*Dimethoxy*-5 : 6-*methylenedioxynoraporphine* (*Actinodaphnine Methyl Ether*) (XXVIII; R = H, R′ = MeO, R″ = MeO, X = H).—A solution of 1-(3 : 4-dimethoxy-6-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline (2 g.) in dilute hydrochloric acid (1 : 1; 30 c.c.) was reduced with zinc dust (5 g.) as described above. After filtration the solution was cooled to 0° and diazotised with a solution of barium nitrite (0·52 g.) in water (2 c.c.). The diazonium solution was set aside for 15 min. and then kept at 60° until evolution of nitrogen was complete (1 hr.). The dark solution was heated to the b. p. and zinc dust (1 g.) was added. The solution, which became yellow, was made alkaline with ammonia and extracted several times with ether. The combined extracts were washed successively with aqueous sodium hydroxide and with water. Removal of the ether from the dried (K_2CO_3) extract left a green gum. This was dissolved in a warm mixture of ethylene dichloride and light petroleum (b. p. 60—80°), and the green oil which separated on cooling was removed by decantation. This operation was repeated with the addition of more light petroleum until a clear and almost colourless solution was obtained. Evaporation of the solvent then left a colourless gum which solidified. Recrystallisation from ether–alcohol (3 : 1) gave (±)-2 : 3-*dimethoxy*-5 : 6-*methylenedioxynoraporphine* (0·1 g.) in white needles, m. p. 114—115° (Found : C, 70·6; H, 5·7. $C_{19}H_{19}O_4N$ requires C, 70·15; H, 5·8%).

1-(3 : 4-*Methylenedioxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline (XXVI; R = H, R′R″ = ·O·CH_2·O·).—A suspension of 3 : 4-methylenedioxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (8 g.) in dry chloroform (30 c.c.) with phosphorus pentachloride (15 g.) was kept for 4 days at 0°. Crushed ice (50 g.) was added and the chloroform and phosphorus oxychloride were removed under reduced pressure at 50°. The dark aqueous solution was made nearly neutral with ammonia, boiled with charcoal, and filtered. Addition of further ammonia to the filtrate precipitated a mauve-coloured oil, which solidified to an amorphous powder. This was dissolved in acetic acid (10 c.c.) and alcohol (10 c.c.),

boiled with charcoal, and filtered. Basification of the filtrate with dilute aqueous ammonia precipitated the *dihydroisoquinoline* (1·9 g.), which crystallised from methyl alcohol containing a small quantity of ethylene dichloride in plates, m. p. 159° (decomp.) (Found : C, 60·7; H, 3·8. $C_{18}H_{14}O_6N_2$ requires C, 61·0; H, 4·0%). The same product was obtained in poorer yield by Barger and Weitnauer's method (*Helv. Chim. Acta*, 1939, **22**, 1039). The *methiodide*, prepared as in the preceding examples, crystallised from methyl alcohol containing a small quantity of acetone in yellow needles, m. p. 228—229° (Found : I, 25·9. $C_{18}H_{14}O_6N_2,CH_3I$ requires I, 25·6%).

1-(6-*Amino*-3 : 4-*methylenedioxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-6 : 7-*methylenedioxy*-iso*quinoline* (XXVII; R = H, R'R'' = ·O·CH_2·O·, X = Me).—To a suspension of the above methiodide (2 g.) in a mixture of concentrated hydrochloric acid (15 c.c.) and water (15 c.c.) at 40°, was added zinc dust (5 g.) in small portions. The temperature rose to 80° and the solution was then boiled and more zinc dust (1 g.) added. After filtration the base was liberated with ammonia under ether as in the previous examples, and converted into the dipicrolonate. Crystallisation from a large quantity of alcohol gave the *tetrahydroisoquinolinium dipicrolonate* (2 g.) in yellowish plates, m. p. 169° (decomp.) (Found : C, 53·5; H, 4·4. $C_{19}H_{20}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 53·6; H, 4·15%).

(±)-2 : 3-5 : 6-*Bismethylenedioxyaporphine* (XXVIII; R = H, R'R'' = ·O·CH_2·O·, X = Me).—The above dipicrolonate (2 g.), by the methods described in the previous examples gave, on evaporation of the dried (Na_2SO_4) ethereal extract, a pale yellow gum which solidified. Crystallisation several times from alcohol–ether (1 : 1) gave (±)-2 : 3-5 : 6-*bismethylenedioxy-aporphine* (50 mg.) in needles, m. p. 181—182° (Found : C, 70·5; H, 5·5. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3%).

Preliminary attempts to convert 3-benzyloxy-4-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide into 1-(3-benzyloxy-4-methoxy-2-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline by the use of phosphorus pentachloride in chloroform, as in the previous examples, resulted in debenzylation.

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