796. *The Aporphine Series. Part II.* Application of the Bischler–Napieralski Reaction to 2-Nitrophenyl-N-phenethylacetamides.†*

By D. H. Hey and A. L. Palluel.

A re-examination of Späth and Hromatka's synthesis of *apo*morphine dimethyl ether (I) has shown that the action of phosphoric oxide on 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) gives a mixture of 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (II) and the phenethylamide of 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = NH·CH_2·CH_2Ph). The former was converted into DL-*apo*morphine dimethyl ether (I); the latter was synthesised independently from 3 : 4-dimethoxy-2-nitrophenylacetic acid and from 3 : 4-dimethoxy-2-nitromandelic acid. The alternative ketenimine and acetylenic structures previously assigned to the neutral by-products formed when the Bischler–Napieralski reaction is applied to certain 2-nitrophenyl-*N*-phenethylacetamides must be rejected.

The synthesis of *apo*morphine dimethyl ether (I) reported by Späth and Hromatka in 1929 [1] has been the subject of considerable interest. Their method had previously been

* Part I, *J.*, 1954, 2246.

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[1] Späth and Hromatka, *Ber.*, 1929, **62**, 326.

attempted by Kay and Pictet [2] and by Kondo [3] without success, and a similar failure was reported by Gulland, Haworth, Virden, and Callow [4] at about the time when Späth and Hromatka announced their success. The stage in the synthesis upon which particular interest is centred, namely, the application of the Bischler–Napieralski reaction to 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) to give 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (II), was reinvestigated by Hey and Lobo.[5] Although a variety of experimental conditions and reagents was used in an attempt to effect ring closure to the dihydro*iso*quinoline, no positive evidence for such ring closure was obtained, but the presence of a trace of a basic product in one experiment led to the further reinvestigation reported in this communication.

It is significant that Späth and Hromatka's synthesis of 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (II) from 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) provided the only known example of the ring closure of an *o*-nitrophenyl-*N*-phenethylacetamide into a 3 : 4-dihydro*iso*quinoline in which the nucleus involved in the ring closure is not activated by the presence of a suitable substituent atom or group (see Whaley and Govindachari [6]). Further, it has been noted by all the groups of workers that, whenever 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) is subjected to the experimental conditions required for the Bischler–Napieralski reaction, there is invariably formed a neutral by-product, which is isomeric with the desired 3 : 4-dihydro*iso*quinoline. Similar neutral products have also been reported by Kondo and Ishiwata [7] in the attempted cyclisation of *N*-(3-bromo-4-methoxyphenethyl)-3 : 4-dimethoxy-2-nitrophenylacetamide, and by Callow, Gulland, and Haworth [8] in that of 3 : 4-dimethoxy-2-nitrophenyl-*N*-*p*-methoxyphenethylacetamide and of a similar compound prepared from β-3-amino-4-methoxyphenethylamine (see also Gulland, Haworth, Virden, and Callow [4]). These neutral compounds have always been represented as either (*a*) keten-imines (*e.g.*: III; R = CH:C:N·CH_2·CH_2Ph) or (*b*) acetylenic compounds (*e.g.*: III; R = C:C·NH·CH_2·CH_2Ph), but adequate experimental evidence to establish one or other of these structures has never been obtained.

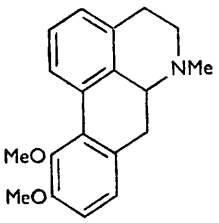
After work had been initiated on a general study of the application of the Bischler–Napieralski reaction to *o*-nitrophenyl-*N*-phenethylacetamides with the double objective of establishing (*a*) the experimental conditions necessary for ring closure to the 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinolines, and (*b*) the identity of the neutral isomeric by-products, it was reported by Govindachari and Nagarajan [9] that, using the conditions of Späth and Hromatka, they had been able to prepare 3 : 4-dihydro-1-2′-nitrobenzyl-*iso*quinoline in about 25% yield from 2-nitrophenyl-*N*-phenethylacetamide. This reaction, which provided only the second example of the ring closure of an *o*-nitrophenyl-*N*-phenethylacetamide involving an unactivated aromatic nucleus, has also been successfully carried out independently by the present authors and has been briefly reported.[10]

It has now been found that when 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (III; R = CH_2·CO·NH·CH_2·CH_2Ph) is boiled under reflux in toluene solution in the presence of phosphoric oxide the product consists of a mixture of approximately equal parts of a neutral compound and 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro-*iso*quinoline (II). The isolation of the latter compound was assisted by the solubility of its hydrochloride in chloroform. When the same ring-closure was attempted with phosphorus pentachloride in boiling benzene solution the sole identified product was the neutral compound referred to above, which has now been shown to be the phenethylamide (IV;

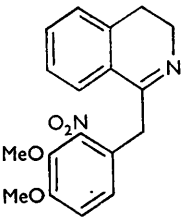
[2] Kay and Pictet, *J.*, 1913, 947.
[3] Kondo, *J. Pharm. Soc. Japan*, 1925, **519**, 429.
[4] Gulland, Haworth, Virden, and Callow, *J.*, 1926, 1666.
[5] Hey and Lobo, *J.*, 1954, 2246.
[6] Whaley and Govindachari, *Organic Reactions*, Vol. VI, p. 97.
[7] Kondo and Ishiwata, *Ber.*, 1931, **64**, 1533.
[8] Callow, Gulland, and Haworth, *J.*, 1929, 1444.
[9] Govindachari and Nagarajan, *Chem. and Ind.*, 1954, 1358.
[10] Hey and Palluel, *Chem. and Ind.*, 1955, 40.

R = NH·CH_2·CH_2Ph) of 6 : 7-dimethoxyanthranil-3-carboxylic acid (4 : 5-dimethoxyanthroxanic acid).

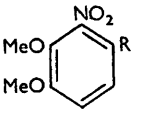
The evidence for this structure is based on the fact that hydrolysis of the neutral compound with acid gave phenethylamine, whereas hydrolysis with alcoholic potassium hydroxide gave some phenethylamine and 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = OH). If the neutral compound had either the keten-imine structure or the



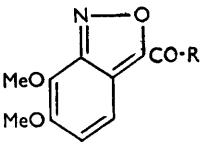
(I)



(II)



(III)



(IV)

acetylenic structure, hydrolysis would lead to 3 : 4-dimethoxy-2-nitrophenylacetic acid. This acid was never found. Further, reduction of the neutral compound with zinc and hydrochloric acid gave the phenethylamide of 2-amino-3 : 4-dimethoxyphenylglyoxylic acid (2 : 3-dimethoxyisatinic acid). On the alternative formulations reduction should lead to 2-(2-amino-3 : 4-dimethoxyphenyl)-2-phenylethylamine. The identity of the 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = OH) has been confirmed by two independent syntheses of this acid (*a*) from 3 : 4-dimethoxy-2-nitrophenylacetic acid by Gulland's method [11] and (*b*) from 3 : 4-dimethoxy-2-nitromandelic acid by the method of Gulland, Robinson, Scott, and Thornley.[12] The identity of the three acids has been further confirmed by infrared and ultraviolet spectroscopy. The synthetic acid thus obtained has also been converted into its phenethylamide, which was shown to be identical with the neutral product obtained in the application of the Bischler–Napieralski reaction to 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide. The isolation of 6 : 7-dimethoxyanthranil-3-carboxylic acid on alkaline hydrolysis of the neutral compound is not in itself proof of the anthranil structure for the neutral compound because 3 : 4-dimethoxy-2-nitrophenylacetic acid also gives the anthranil-carboxylic acid on treatment with alkali, but the synthesis of the neutral compound from 6 : 7-dimethoxyanthranil-3-carboxylic acid, as reported above, establishes its structure beyond all doubt.

When 3 : 4-dimethoxy-2-nitrophenyl-*N*-*iso*propylacetamide (III; R = CH_2·CO·NHPr^i), which cannot undergo the Bischler–Napieralski reaction, was boiled in benzene solution with phosphorus pentachloride, the *iso*propylamide of 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = NHPr^i) was obtained in good yield. The ultraviolet absorption spectrum of this compound showed bands of maximum absorption at 237·5 and 295 mμ, identical with those observed for 6 : 7-dimethoxyanthranil-3-carboxylic acid and the neutral compound from the Bischler–Napieralski reaction.

The infrared spectrum of the neutral compound from the Bischler–Napieralski reaction indicates the presence of an amide group and shows the complete absence of significant absorption between the C–H stretching frequencies at 3·46 μ and a strong absorption band at 6·00 μ. Since it is precisely in this region that the characteristic absorption bands of the triple carbon–carbon bond (4·5—5·1 μ) and of the keten-imine structure (4·87—5·00 μ), as reported by Stevens and French,[13] reside, it is reasonable to assume that these structural features are absent. The ultraviolet spectrum also shows the absence of the keten-imine structure (cf. Stevens and French [13]).

The formation of anthranils (3 : 4-benzo*iso*oxazoles) by *cyclo*dehydration of aromatic compounds containing a nitro-group and a methylene group at adjacent nuclear positions is well known. Anthranil itself is formed from *o*-nitrotoluene on treatment with alkali,[14]

[11] Gulland, *J.*, 1931, 2872.
[12] Gulland, Robinson, Scott, and Thornley, *J.*, 1929, 2924.
[13] Stevens and French, *J. Amer. Chem. Soc.*, 1953, **75**, 657; 1954, **76**, 4398.
[14] Scholl, *Monatsh.*, 1913, **34**, 1016.

and phenylanthranil can be obtained when *o*-nitrodiphenylmethane is heated alone or in the presence of aluminium chloride or sulphuric acid.[15] Similar compounds can also be obtained by the mild reduction of a nitro-group which is *ortho* to a carbonyl group, *e.g.*, *o*-nitrobenzaldehyde and *o*-nitroacetophenone. Anthranil-3-carboxylic acid has been prepared (*a*) by the action of heat on *o*-nitroepoxycinnamic acid,[16] (*b*) by the mild reduction of *o*-nitromandelic acid or nitrile,[17] and (*c*) from *o*-nitrophenylacetic acid by mild reduction and cyclisation to 1 : 2-dioxindole followed by treatment with nitrous acid and rearrangement under acidic conditions.[18] When reduced with ferrous sulphate and ammonia anthranil-3-carboxylic acid gives isatinic acid and then isatin by *cyclo*dehydration. 6 : 7-Dimethoxyanthranil-3-carboxylic acid (IV; R = OH) was reported by Gulland [11] to be the sole product of the attempted demethylation of 3 : 4-dimethoxy-2-nitrophenylacetic acid (III; R = CH_2·CO_2H) by prolonged boiling with alkali. A similar product had previously been isolated by Gulland, Robinson, Scott, and Thornley,[12] together with 6 : 7-dimethoxyisatin, from the reduction of 3 : 4-dimethoxy-2-nitromandelic acid [III; R = CH(OH)·CO_2H] with sodium amalgam, but this compound was provisionally formulated as a derivative of azobenzene. The reaction of 6 : 7-dimethoxyanthranil-3-carboxylic acid (IV; R = OH) with ferrous sulphate and ammonia gives 6 : 7-dimethoxyisatin.

The identity of the 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (II) was confirmed by conversion into the methiodide, followed by reduction to 1-(2-amino-3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline, which was characterised as the dipicrolonate, with subsequent diazotisation and ring closure by the Pschorr procedure to give (±)-*apo*morphine dimethyl ether (I). The latter was characterised as the hydrochloride and methiodide and the ultraviolet absorption spectrum of the hydrochloride was identical with that of (−)-*apo*morphine dimethyl ether hydrochloride prepared from (−)-*apo*morphine hydrochloride. Späth and Hromatka [1] identified their synthetic racemic *apo*morphine dimethyl ether with the corresponding compound obtained from the natural product by the conversion of both into *N*-benzoyl-β-(5 : 6-dimethoxyphenanthryl)-*N*-methylethylamine. Attempts made by Späth and Hromatka to racemise (−)-*apo*morphine dimethyl ether were unsuccessful.

When a solution of 2-nitrophenyl-*N*-phenethylacetamide was boiled in toluene solution in the presence of phosphoric oxide it gave an unidentified brown gum as the main product, but 3 : 4-dihydro-1-(2-nitrobenzyl)*iso*quinoline was isolated in small yield.

Experimental

Application of the Bischler–Napieralski Reaction to 3 : 4-*Dimethoxy*-2-*nitrophenyl*-N-*phenethylacetamide.*—(a) *With phosphoric oxide.* A solution of the amide (3 g.; Hey and Lobo [5]) in toluene (50 c.c.) was added to a suspension of phosphoric oxide (18 g.) in toluene (50 c.c.), and the mixture was boiled under reflux for 1 hr. The toluene was separated by decantation and the residual solid cake was broken up and washed twice by decantation with boiling benzene. Evaporation of the combined toluene and benzene solutions left a crystalline residue (0·62 g.), which on crystallisation from methanol gave 6 : 7-*dimethoxy*-N-*phenethylanthranil*-3-*carboxyamide* in fine yellow needles, m. p. 123—124° (Found: C, 66·1; H, 5·6; N, 8·8. $C_{18}H_{18}O_4N_2$ requires C, 66·2; H, 5·5; N, 8·6%). This compound was insoluble in dilute and concentrated hydrochloric acid and failed to yield a picrate. After being boiled with zinc and hydrochloric acid the resulting solution was capable of diazotisation and the diazonium solution gave a bright orange precipitate with alkaline β-naphthol. Kay and Pictet [2] reported m. p. 129° for this neutral compound. Späth and Hromatka [1] reported 124—126° and Hey and Lobo [5] m. p. 124—125°. The solid residue containing phosphoric oxide was decomposed with ice and dilute hydrochloric acid, and the aqueous solution was extracted once with benzene and several times with chloroform. Evaporation of the chloroform extracts left white crystals (0·64 g.), which on recrystallisation from ethanol containing a drop of concentrated hydrochloric acid gave the *hydrochloride* of 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline in fine needles, m. p. 220—221° (Found: C, 59·55; H, 5·4; N, 7·5. $C_{18}H_{18}O_4N_2$,HCl requires C, 59·5; H, 5·5;

[15] Kliegl, *Ber.*, 1909, **42**, 591.
[16] Schillinger and Wleügel, *Ber.*, 1883, **16**, 2226.
[17] Heller, *Ber.*, 1906, **39**, 2344.
[18] Reissert, *Ber.*, 1908, **41**, 3921.

N, 7·9%). In a second experiment the amide (1 g.) gave 6 : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·22 g.) in yellow needles (from ethanol), m. p. 123—124°, and, by ether-extraction of the basified aqueous solution, 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline (0·26 g.), m. p. 115—121°, as a buff amorphous solid from aqueous methanol. Späth and Hromatka [1] reported m. p. 129° for this base. The *picrate*, prepared in the normal manner, separated from methanol in yellow-brown needles m. p. 166—167° (Found : C, 51·6; H, 4·0. $C_{18}H_{18}O_4N_2,C_6H_3O_7N_3$ requires C, 51·9; H, 3·8%). A solution of the free base (0·52 g.) in methanol (15 c.c.) was boiled under reflux for 2 hr. with methyl iodide (7 c.c.). Subsequent evaporation of the solvent and excess of methyl iodide left 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline methiodide (0·44 g.) in fine yellow needles, m. p. 200° (from ethanol) (Found : I, 27·2. Calc. for $C_{19}H_{21}O_4N_2I$: I, 28·1%). The same methiodide was obtained from the free base isolated from the hydrochloride of m. p. 220—221°. Späth and Hromatka [1] recorded m. p. 203° for the methiodide.

(b) *With phosphorus pentachloride.* A solution of the amide (1·7 g.) in benzene (30 c.c.), added to a suspension of phosphorus pentachloride (1 g.) in benzene (30 c.c.), was boiled under reflux. Evolution of hydrogen chloride ceased after 1 hr. and the solvent and phosphorus oxychloride were removed under reduced pressure. Recrystallisation of the crystalline residue from benzene–light petroleum (b. p. 60—80°) gave 6 : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·95 g.) in yellow needles, m. p. 121—123°, both alone and on admixture with the neutral compound prepared by method (*a*) above.

Hydrolysis of 6 : 7-*Dimethoxy*-N-*phenethylanthranil*-3-*carboxyamide.*—(a) *With hydrochloric acid.* 6 : 7-Dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·2 g.) was boiled under reflux with 10% hydrochloric acid (50 c.c.) for 24 hr. The yellow solution was decanted from solid matter, cooled, and extracted with ether. Evaporation of the ether left a residue (0·06 g.) from which no crystalline product could be obtained. The aqueous solution, made alkaline with sodium hydroxide, was shaken with a few drops of benzoyl chloride. *N*-Phenethylbenzamide separated, which after recrystallisation from ethanol had m. p. and mixed m. p. 111—112°.

(b) *With alcoholic potassium hydroxide.* A solution of 6 : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·8 g.) in ethanol (100 c.c.) was boiled under reflux with a solution of potassium hydroxide (20 g.) in ethanol (200 c.c.) for 5 hr. The solution was diluted with water, and most of the alcohol was removed by distillation. The cold aqueous solution was extracted with ether, and the ethereal extract was washed with dilute hydrochloric acid. The acidic washings were shown to contain phenethylamine (0·08 g.) by conversion into *N*-phenethylbenzamide, m. p. 111—112°, as described above. The aqueous alkaline solution was acidified with hydrochloric acid, and on cooling and standing a crystalline acid was deposited (0·2 g.), which on recrystallisation, first from hot water and then from benzene, gave 6 : 7-dimethoxyanthranil-3-carboxylic acid in bright orange needles, m. p. 166—167° (Found : C, 53·4; H, 4·3; N, 6·4. Calc. for $C_{10}H_9O_5N$: C, 53·7; H, 4·0; N, 6·3%). The m. p. was not depressed on admixture with specimens of this acid prepared as described below.

Reduction of 6 : 7-*Dimethoxy*-N-*phenethylanthranil*-3-*carboxyamide.*—(a) *Catalytic.* No hydrogen was absorbed when the amide in methanol–benzene was shaken with palladium on barium sulphate or Adams's catalyst.

(b) *With zinc and hydrochloric acid.* To an ice-cold solution of 6 : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide (0·1 g.) in ethanol (20 c.c.) was added concentrated hydrochloric acid (0·5 c.c.) and zinc dust (0·1 g.) portionwise with agitation. Further small quantities of zinc dust and of concentrated hydrochloric acid, one drop at a time, were added until the solution was colourless. The solution was made alkaline with aqueous ammonia and extracted four times with ether. Evaporation of the extract left a crystalline residue (0·1 g.), which on recrystallisation from ether gave the *phenethylamide* of 2-*amino*-3 : 4-*dimethoxyphenylglyoxylic acid* in needles, m. p. 92—93° (Found : C, 65·4; H, 6·4. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1%). This product gave a positive reaction on diazotisation and coupling with alkaline β-naphthol. The same product was obtained in 60% yield on reduction of the amide with zinc and sulphuric acid.

Anthranil-3-*carboxylic Acid* (*Anthroxanic Acid*).—Anthranil-3-carboxylic acid [needles from hot water; m. p. 196° (decomp.)] (Found : C, 58·5; H, 3·0. Calc. for $C_8H_5O_3N$: C, 58·8; H, 3·0%) was prepared from *o*-nitrophenylacetic acid (Marion and Grassie [19]) by Reissert's method [18] by means of 1 : 2-dioxindole (white needles, m. p. 199—201°, from hot water) (Found : C, 64·0; H, 4·7. Calc. for $C_8H_7O_2N$: C, 64·4; H, 4·7%), and 1-hydroxyisatoxime [yellow amorphous solid from hot water; m. p. 230—231° (decomp.)] (Found : C, 53·8; H, 3·3. Calc.

[19] Marion and Grassie, *J. Amer. Chem. Soc.*, 1944, **66**, 1290.

for $C_8H_6O_3N_2$: C, 53·8; H, 3·4%). Reissert gave no m. p. for 1 : 2-dioxindole but reported m. p. 223° for 1-hydroxyisatoxime, and m. p. 196° for anthranil-3-carboxylic acid. For the latter acid Heller [17] reported m. p. 200° and Schillinger and Wleügel [16] m. p. 190—191°. Anthranil-3-carboxylic acid was also obtained in much poorer yield from the reduction of *o*-nitromandelonitrile by Heller's method.[17] Attempts to apply Gulland's method [11] for the preparation of 6 : 7-dimethoxyanthranil-3-carboxylic acid to the preparation of anthranil-3-carboxylic acid from *o*-nitrophenylacetic acid failed. When a solution of anthranil-3-carboxylic acid (0·2 g.) in a slight excess of aqueous ammonia was added to a solution of ferrous sulphate (1 g.) in water and boiled under reflux for 3 hr., subsequent filtration and acidification gave isatin in red needles (0·13 g.), m. p. and mixed m. p. 199—200°.

6 : 7-*Dimethoxyanthranil*-3-*carboxylic Acid*.—This acid [orange needles from benzene; m. p. 168—169° (decomp.)] was prepared from 3 : 4-dimethoxy-2-nitrophenylacetic acid in 31% yield by Gulland's method.[11] It was also obtained in poorer yield from 3 : 4-dimethoxy-2-nitromandelic acid by the method of Gulland, Robinson, Scott, and Thornley.[12] The acid (0·5 g.) in a slight excess of aqueous ammonia (100 c.c.) was added to ferrous sulphate (2·5 g.) in water (50 c.c.) and boiled under reflux for 3 hr. After filtration of the hot solution the cold filtrate was extracted with chloroform, evaporation of which gave 6 : 7-dimethoxyisatin (0·33 g.) in orange needles (from ethanol), m. p. 209—210° (Found: C, 58·3; H, 4·5. Calc. for $C_{10}H_9O_4N$: C, 58·0; H, 4·4%). Gulland, Robinson, Scott, and Thornley [12] gave m. p. 212—213° for this compound. The semicarbazone, prepared in the normal manner, was obtained in pale yellow platelets, m. p. 254° (decomp.), from aqueous alcohol, as recorded by Gulland *et al.*[12]

6 : 7-*Dimethoxy*-N-*phenethylanthranil*-3-*carboxyamide*.—6 : 7-Dimethoxyanthranil-3-carboxylic acid (0·45 g.) was added portionwise to a suspension of phosphorus pentachloride (0·42 g.) in chloroform (30 c.c.). After having been shaken mechanically overnight at room temperature, the mixture was boiled under reflux until a clear solution was obtained (48 hr.). Evaporation of the solvent and phosphorus oxychloride under reduced pressure left a red solid, which was dissolved in boiling ether (50 c.c.). To the boiling solution was added a solution of phenethylamine (1 g.) in dry ether (20 c.c.). After boiling under reflux for 2 hr. the whole was added to water (100 c.c.), and the ethereal layer separated. The aqueous layer was extracted several times with ether and the combined ethereal extracts were washed successively with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water, dried, and evaporated. The crystalline residue (0·33 g.) gave 6 : 7-dimethoxy-*N*-phenethylanthranil-3-carboxyamide in yellow needles, m. p. 121·5—122·5°, from methanol. A mixed m. p. with the neutral product, m. p. 123—124°, obtained from the Bischler–Napieralski reactions with 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide, showed no depression. The infrared and ultraviolet absorption spectra of this compound showed the absence of keten-imine and acetylenic structures.

3 : 4-*Dimethoxy*-2-*nitrophenyl*-N-iso*propylacetamide*.—3 : 4-Dimethoxy-2-nitrophenylacetic acid (2 g.) was added portionwise to a suspension of phosphorus pentachloride (2·2 g.) in dry chloroform (15 c.c.), and the mixture was set aside with occasional shaking until a homogeneous solution was obtained. Evaporation of the solvent and phosphorus oxychloride under reduced pressure left the acid chloride in fine needles, which were dissolved in dry ether (50 c.c.) and added with cooling to a solution of *iso*propylamine (5 g.) in ether (20 c.c.). After boiling under reflux for 1 hr. the mixture was added to an excess of dilute hydrochloric acid, and the ethereal layer was separated. The aqueous layer was further extracted with ether and the combined ethereal solution was washed successively with dilute acid, dilute alkali, and water. Evaporation of the dried solvent left 3 : 4-*dimethoxy*-2-*nitrophenyl*-N-iso*propylacetamide* (2·1 g.), which crystallised from benzene–light petroleum (b. p. 60—80°) in buff needles, m. p. 103—104° (Found: C, 55·7; H, 6·6. $C_{13}H_{18}O_5N_2$ requires C, 55·5; H, 6·4%).

6 : 7-*Dimethoxy*-N-iso*propylanthranil*-3-*carboxyamide*.—A solution of 3 : 4-dimethoxy-2-nitrophenyl-*N*-*iso*propylacetamide (1 g.) in dry benzene (50 c.c.) was boiled under reflux for 1 hr. with phosphorus pentachloride (0·7 g.). Evaporation of the solvent and phosphorus oxychloride left a yellow oil, which was dissolved in benzene and chromatographed on an alumina column. Evaporation of the benzene eluates left 6 : 7-*dimethoxy*-N-iso*propylanthranil*-3-*carboxyamide* as a crystalline residue (0·7 g.), which separated from aqueous ethanol in yellow platelets, m. p. 92—93° (Found: C, 59·2; H, 6·1. $C_{13}H_{16}O_4N_2$ requires C, 59·9; H, 6·1%). The ultraviolet absorption spectrum of this compound showed bands at 237·5 and 295 mμ, identical with those observed in 6 : 7-dimethoxyanthranil-3-carboxylic acid and its phenethylamide.

(±)-apo*Morphine Dimethyl Ether*.—A suspension of 1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro*iso*quinoline methiodide (0·8 g.) (prepared as described above) in ethanol (30 c.c.) was boiled under reflux for 0·5 hr. with concentrated hydrochloric acid (15 c.c.) and zinc dust (4 g.). The colour of the solution changed from yellow to green and was finally discharged. A sample of the solution gave a positive reaction on diazotisation and addition to alkaline β-naphthol. The cooled filtered solution was extracted with ether, and the aqueous layer was then made alkaline with aqueous sodium hydroxide and repeatedly extracted with ether. Evaporation of the ether gave 1-(2-amino-3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline (0·5 g.) as a pale brown oil with a blue fluorescence. The *dipicrolonate*, formed in ethanol in the normal manner, separated from a large volume of ethanol in orange-yellow needles, m. p. 189—190° (Found : C, 55·35; H, 4·9; N, 16·8. $C_{19}H_{24}O_2N_2,2C_{10}H_8O_5N_4$ requires C, 55·7; H, 4·8; N, 16·7%). A suspension of this dipicrolonate (1·5 g.) in cold methanol (7·5 c.c.) was ground with a cold solution of concentrated sulphuric acid (1·5 c.c.) in methanol (7·5 c.c.). The precipitated picrolonic acid (0·89 g.) was filtered off and the filtrate was cooled to 0° and diazotised with a solution of sodium nitrite (0·123 g.) in water (2 c.c.). After 12 hr. in the refrigerator, copper powder was added and nitrogen was evolved. After 1 hr. the mixture was boiled under reflux, filtered, cooled, diluted with water, made alkaline with ammonia, and extracted with ether. The brown residue obtained on evaporation was dissolved in hydrochloric acid and extracted successively with ether and chloroform. (±)-apo*Morphine dimethyl ether hydrochloride*, obtained from the chloroform extract on evaporation, crystallised from ethanol–ether in fine needles (0·1 g.), m. p. 212—218° (decomp.) (Found : C, 66·6; H, 6·7. $C_{19}H_{21}O_2N,HCl,\frac{1}{2}H_2O$ requires C, 66·8; H, 6·7%). A portion of the hydrochloride (0·02 g.) in water was neutralised with aqueous ammonia and extracted with ether. Evaporation of the dried extract gave DL-*apo*morphine dimethyl ether as a pale brown gum, which was dissolved in dry chloroform to which an excess of methyl iodide (5 c.c.) was added. (±)-apo*Morphine dimethyl ether methiodide* separated, m. p. 218—220° (decomp.) (Found : C, 54·0; H, 5·7; N, 3·1 $C_{20}H_{24}O_2NI,\frac{1}{2}H_2O$ requires C, 53·8; H, 5·6; N, 3·1%). For comparison a specimen of (−)-*apo*-morphine dimethyl ether hydrochloride was prepared from *apo*morphine hydrochloride B.P. by methylation with diazomethane. It separated from ethanol–ether in needles, m. p. 220—225° (Found : C, 66·7; H, 6·4. Calc. for $C_{19}H_{21}O_2N,HCl,\frac{1}{2}H_2O$: C, 66·8; H, 6·7%). (−)-*apo*-Morphine dimethyl ether methiodide, prepared from the hydrochloride as described above for the racemic compound, had m. p. 210—212° (decomp.) (Found : C, 54·0; H, 5·6; N, 3·1. Calc. for $C_{20}H_{24}O_2NI,\frac{1}{2}H_2O$: C, 53·8; H, 5·6; N, 3·1%). Pschorr, Jaeckel, and Fecht [20] recorded the preparation of (−)-*apo*morphine dimethyl ether hydrochloride but gave no m. p. The same authors reported m. p. 195—205° for the methiodide. The ultraviolet absorption spectrum of the (±)-*apo*morphine dimethyl ether hydrochloride and that of the (−)-form were indistinguishable.

3 : 4-*Dihydro*-1-2′-*nitrobenzyl*iso*quinoline*.—A solution of *o*-nitrophenyl-*N*-phenethylacetamide (1 g.; Hey and Lobo [5]) in dry toluene (30 c.c.), added to a suspension of phosphoric oxide (6 g.) in toluene (20 c.c.), was boiled under reflux for 17 hr., further quantities of phosphoric oxide (4 g.) being added during the first 2 hr. The solvent was separated by decantation and the solid matter was washed three times by decantation with hot toluene (150 c.c.). The residual solid was treated with crushed ice (100 g.) and concentrated hydrochloric acid (10 c.c.), and the mixture was heated to boiling and then cooled and repeatedly extracted with benzene. Evaporation of the combined toluene and benzene solution gave a dark brown gum (0·41 g.). The aqueous acid solution was filtered (charcoal), made alkaline with aqueous sodium hydroxide, and extracted with ether. Evaporation of the dried ethereal extract left a red gum, which solidified on trituration with methanol. 3 : 4-Dihydro-1-2′-nitrobenzyl*iso*quinoline (0·23 g.) separated from methanol as a pale buff amorphous solid, m. p. 115—116°. The *picrate*, prepared in the normal manner, separated from methanol in fine yellow needles, m. p. 186—187° (Found : C, 53·2; H, 3·3. $C_{16}H_{14}O_2N_2,C_6H_3O_7N_3$ requires C, 53·3; H, 3·4%). The methiodide separated from ethanol in yellow needles, m. p. 215—216° (decomp.). Govindachari and Nagarajan [9] reported m. p. 115—116° for 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinoline and m. p. 209° (decomp.) for the methiodide.

Spectroscopic measurements were carried out on a Unicam S.P. 500 quartz spectrometer and on a Grubb-Parsons double-beam infrared spectrometer.

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[20] Pschorr, Jaeckel, and Fecht, *Ber.*, 1902, **35**, 4387.