CCCCIII.—*Experiments on the Synthesis of Phenolic Aporphines. Part II. The Protection of Hydroxyls by the Carbethoxyl Group, and the Action of Benzyl Chloride on Nitrophenylacetic Acids.*

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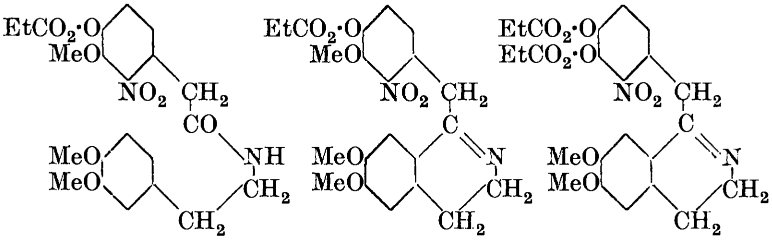
Two parallel investigations were carried out to test the possibility of employing the carbethoxy-group during aporphine syntheses as a protective radical for those hydroxyl groups which would ultimately make their appearance in ring I of the aporphine.

In one of these researches, 2′-nitro-3′-methoxy-4′-ethylcarbonatophenylaceto-β-3 : 4-dimethoxyphenylethylamide (I) was prepared by the interaction of homoveratrylamine and 2-*nitro*-3-*methoxy*-4-*ethylcarbonatophenylacetyl chloride*, and converted into 2′-*nitro*-3′ : 6 : 7 - *trimethoxy* - 4′ - *ethylcarbonato* - 1 - *benzyl* - 3 : 4 - *dihydro*iso*quinoline* (II) by the action of phosphorus pentachloride in chloroform. In the second investigation, 2′-*nitro*-6 : 7-*dimethoxy*-3′ : 4′-*diethylcarbonato*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline* (III) was prepared from the corresponding amide by a similar reaction.


(I.) (II.) (III.)

The *methiodides* of the bases (II) and (III) were readily obtained by heating with methyl iodide. Unexpectedly, they defied all efforts to convert them into the corresponding aminobenzyl-*N*-methyltetrahydro*iso*quinolines in the next stage of the synthesis. Zinc and hydrochloric acid, the reagents normally employed for the reduction, were ineffective, despite wide variations in the concentration of acid and of methiodide, in the temperature, and in the rate of addition of zinc dust. Experiments using stannous chloride or tin and hydrochloric acid, hydrogen and colloidal palladium, and sodium hydrosulphite were equally unsuccessful. Reduction of the nitro-group undoubtedly occurred, but the products were basic oils which contained neither primary amino-groups (failure to couple with β-naphthol after diazotisation) nor secondary amino-groups (failure to give Liebermann's nitroso-reaction), and which did not appear to contain an indole nucleus. These tests are not absolutely conclusive, but in the absence of crystalline derivatives, which have not yet been obtained, the nature of these compounds has not been determined.

It was concluded that the carbethoxy-group, though efficient as a protective radical during the Bischler–Napieralski reaction, is unsuited for standard use during aporphine syntheses.

During the conversion of 2-nitro-4-hydroxy-3-methoxyphenylacetic acid and 2-nitro-3 : 4-dihydroxyphenylacetic acid into the corresponding mono- and di-benzyl ethers (Part I; this vol., p. 2879), a considerable proportion of the benzyl ethers also underwent esterification to the benzyl esters. Partly in the hope of ascertaining how to avoid the formation of this by-product, and partly to determine the conditions under which esterification occurred, a rough study was made of the action of benzyl chloride on hot sodium carbonate solutions of phenylacetic acid, *p*-nitrophenylacetic acid, and 6-nitro-3 : 4-dimethoxyphenylacetic acid.

Under the conditions investigated, phenylacetic acid formed no ester, but the nitrated acids yielded varying proportions of their benzyl esters. A high concentration of sodium carbonate reduced the amount of ester formed, as also did a weakly acid solution; esterification was more extensive in faintly alkaline solution. The proportion of benzyl chloride used has apparently little effect on the yield of ester.

EXPERIMENTAL.

2′-*Nitro*-3′ : 6 : 7-*trimethoxy*-4′-*ethylcarbonato*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline* (II).—2-Nitro-3-methoxy-4-ethylcarbonatophenylacetyl chloride was prepared by heating on the water-bath under reflux for 30 minutes a solution of the acid (2·8 g.) (Part I; this vol., p. 2877) and thionyl chloride (2·2 c.c.) in chloroform (15 c.c.). After the solvent and excess of thionyl chloride had been distilled under reduced pressure, the residual acid chloride, a pale orange-coloured oil, was dissolved in dry benzene (15 c.c.) and added to a cooled solution of β-3 : 4-dimethoxyphenylethylamine (2·2 g.) in dry benzene (15 c.c.). The amide hydrochloride separated as a yellow gum, and 5 minutes later, dilute sodium carbonate solution was added. The benzene layer was separated, and the aqueous layer was extracted once with benzene; the mixed benzene solutions were washed with dilute hydrochloric acid and then with water, and dried with sodium sulphate. After the benzene had been evaporated, 2′-nitro-3′-methoxy-4′-ethylcarbonatophenylaceto-β-3 : 4-dimethoxyphenylethylamide (I) remained as an oil which could not be crystallised.

This amide (3·9 g.) was dissolved in chloroform (35 c.c.) and treated with powdered phosphorus pentachloride (5 g.). The mixture, protected from moisture, was kept at room temperature for 48 hours; a considerable quantity of crystalline material had then separated from the brown solution. The solvent and phosphorus oxychloride were removed by distillation on the water-bath under reduced pressure, and the yellow residue was dissolved in very dilute hydrochloric acid by heating on the water-bath. This solution was cooled in ice, treated with charcoal, filtered, and rendered just alkaline with sodium carbonate, any rise in temperature being carefully avoided. *2'-Nitro-3' : 6 : 7-trimethoxy-4'-ethylcarbonato-1-benzyl-3 : 4-dihydro*iso*quinoline* separated as a colourless precipitate, which was washed with water and crystallised twice from methyl alcohol. It formed faintly brown, sharp-ended prisms, m. p. 137° (Found : C, 59·7; H, 5·6. $C_{22}H_{24}O_8N_2$ requires C, 59·5; H, 5·4%). Hydrolysis of the carbethoxy-group took place rapidly when the base was shaken with dilute sodium hydroxide (2*N*), but slowly in presence of cold dilute aqueous ammonia or when warmed with dilute sodium carbonate solution.

The *methiodide* was obtained by boiling a solution of the base (1·8 g.) in methyl iodide (10 c.c.) on the water-bath. Crystals soon filled the clear solution, and after the excess of methyl iodide had been distilled, the methiodide was crystallised from methyl alcohol, from which it separated in stellate clusters of yellow needles, m. p. 160° (decomp.) (Found : C, 47·0; H, 4·8. $C_{22}H_{24}O_8N_2$,MeI requires C, 47·1; H, 4·6%).

2'-Nitro-3' : 4'-diethylcarbonatophenylaceto-β-3 : 4-dimethoxyphenylethylamide.—2-Nitro-3 : 4-diethylcarbonatophenylacetyl chloride was obtained as a red oil when solvent and excess of thionyl chloride were removed in a vacuum below 50° from a mixture of the acid (Part I; this vol., p. 2879), thionyl chloride, and chloroform which had been boiled under reflux for 30 minutes.

A solution of the chloride in dry benzene was added slowly to a cooled solution of homoveratrylamine (1·1 mols.) in the same solvent. A semi-crystalline precipitate formed, and, after 1 hour, ice-cold potassium bicarbonate solution was added. The precipitate dissolved, and the benzene and aqueous layers were separated as rapidly as possible. The aqueous layer was extracted once with benzene, and the mixed benzene solutions were washed with ice-cold bicarbonate, dilute hydrochloric acid, and finally with water. The solution was dried and freed from solvent, and the amide remained in good yield as a yellow resin.

2′-Nitro-6 : 7-*dimethoxy*-3′ : 4′-*diethylcarbonato*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline* (III).—The amide prepared as described above was dissolved in chloroform and mixed with a chloroform solution of phosphorus pentachloride (2 mols.). The solution, protected from moisture, was left at room temperature for 4 days, water added, and the chloroform distilled under diminished pressure. The residual dark tar was extracted repeatedly with water, and the mixed aqueous extracts were neutralised with cold bicarbonate solution. The base separated as a yellow amorphous precipitate which has not been obtained crystalline.

The picrate was obtained as an oil, which soon crystallised, from alcoholic solutions of the base and excess of picric acid. When recrystallised from alcohol, it formed shining plates, m. p. 178—179°.

The *methiodide* separated as yellow needles when a solution of the base in methyl iodide was boiled under reflux for 4 hours. It crystallised from methyl alcohol in the same form, m. p. 166·5° (decomp.) (Found: C, 46·5; H, 4·8. $C_{24}H_{26}O_{10}N_2$,MeI requires C, 46·6; H, 4·8%).

Action of Benzyl Chloride on Phenylacetic Acid.—A solution of phenylacetic acid (5 g.) in sodium carbonate (40 c.c. of 2*N*) and benzyl chloride (6 c.c.) were heated under reflux on the water-bath for 2 hours. The mixture was cooled and extracted thoroughly with ether. The aqueous layer, on acidification with hydrochloric acid and extraction with ether, gave an almost quantitative yield of phenylacetic acid. The ethereal extract was dried and distilled, and yielded only ether and benzyl chloride.

Benzyl p-*Nitrophenylacetate.*—A mixture of *p*-nitrophenylacetic acid (5 g.) in sodium carbonate solution (40 c.c. of 2*N*) and benzyl chloride (6 c.c.) was heated under reflux on the water-bath for 2 hours. The solution was cooled, and extracted twice with ether. The aqueous layer on acidification gave a precipitate of the unchanged acid. The ethereal solution was washed, dried, and evaporated, and the residual oil dissolved in light petroleum and left over-night. *Benzyl* p-*nitrophenylacetate* separated in colourless needles, m. p. 92° alone or mixed with the specimen prepared from benzyl alcohol and the acid chloride (below) (Found: C, 66·6; H, 4·9. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8%).

The experiment was repeated under various conditions with the following results.

Acid, g.	2*N*-Na_2CO_3, c.c.	Benzyl chloride, c.c.	Time, hrs.	Ester, g.
8	70	9	3	0·2
6	100	20	5	0·1
5	15	15	3	0·5
4	Nil; faintly acid	12	3	0·1

p-Nitrophenylacetic acid (10 g.) in chloroform (100 c.c.) was warmed gently for 1·5 hours on the water-bath with thionyl chloride (50 g.). The chloroform and excess of thionyl chloride were distilled under diminished pressure at 40°, and the residual acid chloride was added slowly to benzyl alcohol (10 g.) dissolved in pyridine (30 c.c.) and cooled in ice. After 6 hours, the solution was mixed with dilute sulphuric acid, and extracted with ether. The extract, when dried and distilled, left a pasty crystalline mass, which was pressed on porous tile and crystallised from alcohol. Benzyl *p*-nitrophenylacetate formed colourless, cross-twinned needles, m. p. 92°.

Benzyl 6-Nitro-3 : 4-dimethoxyphenylacetate.—6-Nitro-3 : 4-dimethoxyphenylacetic acid (4·8 g.) was treated with benzyl chloride (15 c.c.) and sodium carbonate (10 c.c.; 1 mol.) as in the previous experiments. The *ester* (1·9 g.) crystallised from ethyl alcohol in needles, m. p. 117° (Found : C, 61·9; H, 5·1. $C_{17}H_{17}O_6N$ requires C, 61·5; H, 5·1%).

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