349. *Experiments on the Synthesis of Physostigmine (Eserine). Part IX. An Improvement in the Synthesis of* dl-*Eserethole.*

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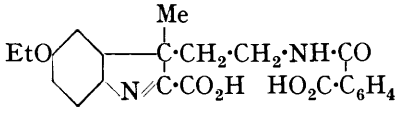
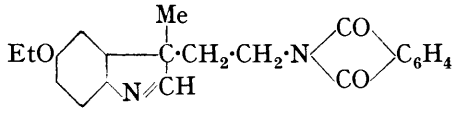
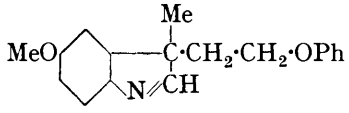
The synthesis of *dl*-eserethole described in Part II (Robinson and Suginome, J., 1932, 314) includes one unsatisfactory stage, namely, the decarboxylation and dehydration of the dicarboxylic acid (I) with formation of the indolenine (II).

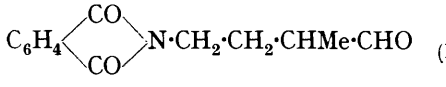
(I.) 

(II.) 

The subsequent hydrolysis and ring-closure to noreserethole proceed smoothly and we were desirous of improving the preparation of (II) in order to acquire sufficient material for resolution of the enantiomorphic bases.

As a preliminary the method of Part VII (King and Robinson, this vol., p. 270) was extended to the preparation of 5-*methoxy*-3-*methyl*-3-β-*phenoxyethylindolenine* (III), which was obtained by the action of boiling alcoholic hydrogen chloride on the *p*-methoxyphenyl-

(III.) 

(IV.) 

hydrazone of γ-phenoxy-α-methylbutaldehyde. The methochloride of this base could not be dephenoxylated by means of hot hydrobromic acid (or by other means) without extensive simultaneous decomposition. The method of protection by means of a phenoxy-group gives good results in the indolinone series (compare Part VI; King and Robinson, J., 1932, 1433), but evidently the indolenine nucleus is so sensitive to the action of hot mineral acids that the replacement of the phenoxy-group by a halogen atom is not feasible in this group of bases. Hence we returned to the device of employing the phthalimido-derivatives and have now obtained the aldehyde (IV) which is unquestionably the ideal intermediate for our purpose.

γ-Phthalimido-α-methylbutyric acid (compare Part II, *loc. cit.*) was converted into the acid chloride, the *amide*, and the *nitrile*, which on reduction by Stephen's method (J., 1925, **127**, 1874) furnished *γ-phthalimido-α-methylbutaldehyde* (IV). In conjunction with *p*-ethoxyphenylhydrazine the indolenine synthesis then afforded the base (II), the picrate and the methosulphate of which were shown by careful comparison to be identical with the specimens obtained by the method of Part II (*loc. cit.*). The stages leading to eserethole are described in a preliminary manner in the preceding communication, but all the indolenine base (II) used for those experiments was made by the method of Part II. The modification here described is a great advance on the older process and renders *dl*-eserethole a relatively easily accessible base.

Experimental.

γ-Phenoxy-α-methylbutaldehyde.—An improved yield of this aldehyde (compare Part VII, *loc. cit.*) was obtained under the following conditions. Hydrogen chloride was passed into a suspension of anhydrous stannous chloride (30 g.) in ether (300 c.c.) until separation into two liquid layers was complete. γ-Phenoxy-α-methylbutyronitrile (15 g. of b. p. 150—155°/12 mm.), dissolved in ether (50 c.c.), was introduced with vigorous shaking, and the mixture kept at room temperature for 12 hours and then refluxed for 10 hours, cooled, and saturated with hydrogen chloride. The white crystalline aldimine stannichloride (17 g.) was collected and hydrolysed by means of cold water (100 c.c.) during 5 hours; the aldehyde then separated as a nearly colourless, viscous oil (7·8 g.), which was collected by means of ether.

The 2 : 4-*dinitrophenylhydrazone* separated as a yellow crystalline powder (1·1 g.) when a solution of the aldehyde (0·8 g.) in methyl alcohol (5 c.c.) was added to a boiling one of dinitrophenylhydrazine (0·9 g.) in acetic acid (25 c.c.). The derivative crystallised from acetic acid in yellow prisms, m. p. 109—110° (Found: N, 15·8. $C_{17}H_{18}O_5N_4$ requires N, 15·6%).

5-*Methoxy*-3-*methyl*-3-β-*phenoxyethylindolenine* (III).—A solution of phenoxymethylbutaldehyde (3·5 g.) and *p*-methoxyphenylhydrazine (2·7 g.) (Altschul, *Ber.*, 1892, **25**, 1849; Blaikie and Perkin, J., 1924, **125**, 313) in alcohol (20 c.c.) was refluxed for ½ hour, the reddish-yellow liquid then becoming almost colourless. It was cooled in a freezing mixture, saturated alcoholic hydrogen chloride (20 c.c.) slowly added, and the mixture kept till next day at room temperature. Ammonium chloride was deposited and was separated and the filtrate was concentrated under diminished pressure. The base was then liberated by means of sodium carbonate and collected in ether, the solvent being finally completely removed by exposure in a vacuum over phosphoric oxide. The brown syrupy base (4·8 g.) was converted in hot alcoholic solution into the *picrate*, which separated as a yellow crystalline powder (5·4 g., m. p. 156—157°). It crystallised from ethyl acetate in clusters of yellow prisms, m. p. 157° (Found in material dried at 80° in a high vacuum over phosphoric oxide: C, 56·5; H, 4·4; N, 11·0. $C_{18}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 56·5; H, 4·3; N, 11·0%). The free base, liberated from the picrate (5 g.) and collected by means of pure ether, formed a thick syrup (2·4 g.) which would not crystallise. It was redissolved in ether (10 c.c.) and after the addition of methyl iodide (5 g.) the solution was refluxed for 3 hours. The *methiodide* separated gradually in slender needles (3·2 g.), which, recrystallised from alcohol, formed golden-yellow needles, m. p. 180—181° (Found: N, 3·4. $C_{19}H_{22}O_2NI$ requires N, 3·3%).

The corresponding methochloride was obtained as a greyish-coloured gum by interaction of the methiodide and silver chloride in hot aqueous suspension and subsequent evaporation of the filtered solution. A large number of fruitless experiments were made on the decomposition of this salt by means of hydrobromic acid under various conditions. In some cases the product was not directly worked up but was treated with methylamine and some evidence of esermethole formation was noted. The yields were, however, hopelessly low and this method of synthesis was abandoned.

Phthalo-β-bromoethylimide and Methyl-β-phthalimidoethylmalonic Acid.—An improved yield was obtained under the following conditions. An intimate mixture of powdered phthalimide (147 g.), dried potassium carbonate (75 g.), and ethylene dibromide (470 g.) was carefully heated in an oil-bath until it became nearly solid and then liquefied; it was then refluxed for 5 hours, and ethylene dibromide (320 g.) recovered by distillation in steam. The residue in the flask (dried, 245 g.) was separated into its constituents by extraction with light petroleum (yield, 118 g. of phthalobromoethylimide, m. p. 80—81°). Two crystallisations from 3 parts of methyl alcohol raised the m. p. to 83—84°. The preparation of ethyl methyl-β-phthalimidoethylmalonate was carried out exactly as described in Part II (*loc. cit.*, p. 316), but the crude product

(105 g. from ethyl methylmalonate, 83 g.) was purified by distillation, b. p. 225—230°/3 mm. The fraction (47 g.) crystallised (m. p. 67—68°) and after two recrystallisations from an equal volume of alcohol or from light petroleum had m. p. 72·5—73°. The hydrolysis of this ester by the method described in Part II is dependent on some elusive condition and we found that consistent results were obtainable by the use of the following modified process.

Hydrochloric acid (120 g., *d* 1·17) was carefully mixed with acetic anhydride (80 c.c.), and ethyl methylphthalimidoethylmalonate (10 g.) added; solution then occurred at once. After boiling for 1 hour, the solvent was removed at or below 100° under diminished pressure and the desired acid then crystallised (yield, 6—6·5 g., m. p. 171—173° with decomp.).

γ-Phthalimido-α-methylbutyramide.—γ-Phthalimido-α-methylbutyric acid (13·5 g.) was converted into its chloride by refluxing with thionyl chloride (21 g.), and the product distilled as a colourless oil, b. p. 190—195°/5 mm. (yield, 13 g.). The whole quantity was then added to aqueous ammonia (45 c.c. of *d* 0·88 together with 30 c.c. of water) and vigorously shaken. The white precipitate was collected after ½ hour (6·3 g., m. p. 159—160°) and twice recrystallised from alcohol–benzene; m. p. 162—163° (Found: N, 11·6. $C_{13}H_{13}O_4N$ requires N, 11·4%).

γ-Phthalimido-α-methylbutyronitrile (V).—The amide (6 g.) was refluxed with thionyl chloride (12 g.) for ½ hour, and the product distilled as a thick oil, b. p. 200—205°/1 mm. (yield, 5·65 g.). The substance quickly solidified and after two recrystallisations from alcohol it melted at 102° (Found: N, 12·3. $C_{13}H_{12}O_2N_2$ requires N, 12·3%).

γ-Phthalimido-α-methylbutaldehyde (IV).—Hydrogen chloride was led into a suspension of anhydrous stannous chloride in absolute ether (50 c.c.) until layering occurred; phthalimidomethylbutyronitrile (2 g., m. p. 101—102°), dissolved in chloroform (5 c.c.), was then added with shaking and the mixture kept for 12 hours at room temperature. The liquid was then refluxed for 4 hours (separation of crystals), cooled, and again saturated with hydrogen chloride. The aldimine stannichloride (2·9 g.) was collected and hydrolysed by contact with water (10 c.c.) and hydrochloric acid (2 c.c., *d* 1·16) for 3 hours at room temperature. The aldehyde (1·1 g.) was isolated by means of ether as a clear, nearly colourless, viscous oil.

The 2 : 4-*dinitrophenylhydrazone*, prepared in hot methyl-alcoholic acetic acid solution, crystallised from acetic acid in small yellow needles, m. p. 191° (Found: N, 17·2. $C_{19}H_{17}O_6N_5$ requires N, 17·0%).

5-*Ethoxy*-3-*methyl*-3-(β-*phthalimidoethyl*)*indolenine* (II).—A mixture of crude γ-phthalimido-α-methylbutaldehyde (0·7 g.), *p*-ethoxyphenylhydrazine (0·46 g.) (Stolz, *Ber.*, 1892, **25**, 1663), and alcohol (20 c.c.) was intensely yellow, but became almost colourless after ½ hour's refluxing. The solution was cooled in a mixture of ice and salt, and saturated alcoholic hydrogen chloride (5 c.c.) gradually added. After 8 hours the filtrate from ammonium chloride was concentrated, and the base liberated and isolated by means of ether (yield, 0·8 g.). The picrate, prepared in hot alcoholic solution, had m. p. 154—155° and crystallised from alcohol in orange-yellow clusters of needles, m. p. 156—157°, and at the same temperature when mixed with the specimen obtained as described in Part II (*loc. cit.*, p. 312). The methosulphate crystallised from alcohol–ether in stellate clusters of colourless needles, m. p. 153—154°, as stated by Robinson and Suginome (*loc. cit.*).

The hydrolysis of this methosulphate followed precisely the previous description and the *dl*-noreserethole was converted into the picrate, which crystallised from alcohol in reddish-orange prisms, m. p. 180—181°, alone or mixed with the specimen described in Part II (*loc. cit.*).

The 5-methoxy-series has been prepared. The methods are the same throughout and γ-phthalimidoethyl-α-methylbutaldehyde (0·7 g.) with *p*-methoxyphenylhydrazine (0·42 g.) gave crude indolenine (0·85 g.); picrate, m. p. 157—159°; methosulphate, m. p. 168—169°, from alcohol–ether.

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