309. *Experiments on the Synthesis of Physostigmine (Eserine). Part X.* dl-*Noresermethole and Crystalline* dl-*Eserethole.*

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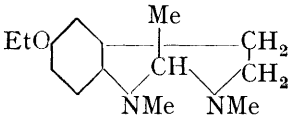
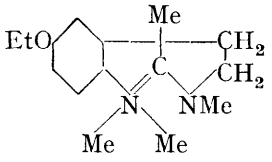
dl-Eserethole (I) synthesised by the method of the present authors (J., 1933, 1474) has now been obtained in crystalline form and fully characterised. Unfortunately, however, all attempts to effect its resolution into diastereoisomerides have been unsuccessful. In the meantime, Hoshino and Kobayashi have continued their parallel investigations and

(I.) 



(II.)

obtained several of the substances already described in this series of memoirs, *e.g.*, noreserethole and eserethole methopicrate (*Proc. Imp. Acad. Japan*, 1934, **10**, No. 2, 99). The m. p.'s ascribed are somewhat lower than ours, doubtless because the Japanese chemists rely on a methylation of dinoreserethole salts, and the methyl group may take one of two positions; for instance, Robinson and Suginome (J., 1932, 313) give *dl*-noreserethole picrate, m. p. 191—192° (Hoshino and Kobayashi, m. p. 180—181°); picrolonate, 227° (221°). The descriptions tally, however, and we consider that the monomethylation must proceed substantially as Hoshino and Kobayashi state.

These authors further claim that the direct action of methyl iodide on dinoreserethole furnishes a methiodide of a dimethyl derivative (introduction of 3Me), and by the action of alkali this yields a base, $C_{16}H_{24}ON_2$, to which they ascribe the formula (II). This is a highly improbable constitution and, if the composition has been correctly determined, we consider the extra methyl must be attached to a carbon atom, most plausibly that which connects the nitrogens. But the description of the base and its derivatives tallies with our findings in respect of *dl*-eserethole and corresponding derivatives; we are furthermore satisfied that the composition of our base is $C_{15}H_{22}ON_2$ and it certainly contains only two methyl groups attached to nitrogen. We anticipate that reinvestigation will show that the bases are identical and that the action of alkali on trimethyldinoreserethole iodide results in the loss of a methyl group.

As we experienced such difficulty in the resolution of *dl*-eserethole, we turned to the case of *dl*-esermethole and have greatly improved the details of the synthesis of *dl*-noresermethole (*loc. cit.*) so that it is now a reasonably convenient series of processes. Unfortunately, the monomethylation of *dl*-noresermethole could not be accomplished under the conditions that succeed with *dl*-noreserethole; only a minute amount of esermethole picrate could be isolated.

In the course of these methylation experiments we isolated an esermethole methopicrate crystallising in rhomboidal plates, m. p. 192—193°. Esermethole methopicrate (King and Robinson, J., 1932, 1433) usually occurs in hexagonal plates, m. p. 184—186°, and natural (active) esermethole methopicrate forms rhomboidal plates, m. p. 194°. It appears that the substance exists in two crystalline modifications, and it is of interest that one of them very closely resembles the derivative of natural origin. The alternative hopeful idea of spontaneous resolution did not survive the experimental test.

Experimental.

γ-Phthalimido-α-methylbutaldehyde.—Experience in the preparation of this substance (J., 1933, 1475) has enabled us to effect improvements in the yields at the various stages.

Phthalo-β-bromoethylimide. An intimate mixture of powdered phthalimide (147 g.), dried potassium carbonate (75 g.), and ethylene dibromide (470 g.) was gradually heated until reaction occurred. It was then refluxed for 5 hours (oil-bath kept rigorously at 150°), and the excess of ethylene dibromide recovered by steam distillation. The pale brown residue solidified and was

washed with water and dried. The crude product was extracted with light petroleum (b. p. 40—60°) in the known manner (yield, 140 g.; m. p. 80—81°)

Methyl-β-phthalimidoethylmalonic acid. Hydrochloric acid (160 c.c., *d* 1·17) was mixed with acetic anhydride (100 c.c.), and ethyl methyl-β-phthalimidoethylmalonate (20 g.) added; solution occurred at once. After 1 hour's boiling, the solvent was removed by heating on the steam-bath under diminished pressure, and the crystalline acid which separated was collected, washed with a little water, and dried; yield 14·5 g., m. p. 170—173° (decomp.).

γ-Phthalimido-α-methylbutyric acid. The foregoing acid (15·5 g.) was decarboxylated by heating at 170—180° until evolution of carbon dioxide ceased. The oily residue was dissolved in boiling benzene (100 c.c.), filtered, and an equal volume of light petroleum (b.p. 40—60°) added. After being kept for 12 hours, the crystals were collected and dried (14 g., m. p. 109—110°); twice recrystallised from benzene–light petroleum, they melted at 113—114°.

γ-Phthalimido-α-methylbutyramide. The preceding acid (18 g.) was converted into its chloride by refluxing for ½ hour with thionyl chloride (27 g.). The excess of the reagent was then evaporated under diminished pressure, the oily residue dissolved in anhydrous ether (200 c.c.), and the solution saturated at 0° with dry ammonia. The thick white paste containing amide and ammonium chloride was filtered off, and the white powder shaken with water (50 c.c.). The crude amide was collected, dried, and crystallised from alcohol (150 c.c.) (yield, 14 g., m. p. 161—162°, representing a considerable improvement).

γ-Phthalimido-α-methylbutyronitrile. The amide (28 g.) was refluxed with thionyl chloride (45 g.) for ½ hour. The excess of thionyl chloride was then removed, and the residue crystallised from alcohol (100 c.c.) (yield 24 g., m. p. 101—102°).

The preparation of γ-phthalimido-α-methylbutaldehyde was carried out as previously described (*loc. cit.*), but on a larger scale (8 g. of the nitrile gave 5 g. of the nearly pure aldehyde).

5-Methoxy-3-methyl-3-(β-phthalimidoethyl)indolenine.—A solution of γ-phthalimido-α-methylbutaldehyde (5 g.) and *p*-methoxyphenylhydrazine (3 g.) in alcohol (100 c.c.), when refluxed for ½ hour, became nearly colourless. It was cooled in ice–salt, saturated alcoholic hydrogen chloride (40 c.c.) slowly added, and the whole kept for 12 hours at room temperature. The acid solvent was evaporated as far as possible in a vacuum over sodium hydroxide, the residue was diluted with water, and the base then liberated by means of sodium carbonate and collected by means of ether, the solvent being removed in the cold under diminished pressure. The brown syrupy residue was dissolved in alcohol (20 c.c.) and mixed with a solution of picric acid (5 g.) in boiling alcohol (30 c.c.). The *picrate* separated in yellow prisms (7·2 g.), m. p. 158—159°; recrystallised from alcohol, m. p. 159—160° (Found: C, 55·4; H, 3·9; N, 12·6. $C_{26}H_{21}O_{10}N_5$ requires C, 55·4; H, 3·7; N, 12·4%).

A suspension of the picrate (7 g.) in ether (200 c.c.) was repeatedly shaken with aqueous sodium bicarbonate until the aqueous layer was colourless. After being dried over anhydrous sodium sulphate, the ether was distilled, and the residue dried in a vacuum desiccator over phosphoric oxide. The free base was a clear thick syrup (4 g.) which could not be crystallised. The *methosulphate* was prepared by heating a mixture of the crude base (4 g.), pure methyl sulphate (3 g.), and dry benzene (20 c.c.) for 5 minutes on the steam-bath. On cooling, the viscous oil which had separated solidified; it was collected, washed with ether, and recrystallised from alcohol–ether, forming colourless prisms, m. p. 170° (4·8 g.) (Found: N, 6·0. $C_{22}H_{24}O_7N_2S$ requires N, 6·1%).

dl-*Noresermethole.*—A solution of the above methosulphate (4·5 g.) and hydrazine hydrate (4·5 g.) in alcohol (40 c.c.) was boiled for 5 minutes, then cooled, acidified with hydrochloric acid, left for 1 hour, and filtered. The filtrate was concentrated in a vacuum desiccator over sulphuric acid, the crystalline residue dissolved in water, and the base liberated by means of potassium hydroxide, and isolated, by means of ether, as a pale yellow oil (1·8 g.). The *picrate*, prepared in alcoholic solution, crystallised from alcohol in well-formed, reddish-orange, rhomboidal prisms, m. p. 162—163° (Found: C, 51·2; H, 4·6. $C_{19}H_{21}O_8N_5$ requires C, 51·0; H, 4·7%).

Methylation of dl-*Noresermethole.*—The base obtained as described above was purified through the picrate, which, after recrystallisation, was decomposed by means of 1% aqueous sodium hydroxide, and the regenerated base was isolated by means of ether.

(1) Pure *dl*-noresermethole (0·7 g.) in dry benzene (2 c.c.) was mixed with a solution of methyl *p*-toluenesulphonate (0·6 g., 1 mol.) in ethyl acetate (2 c.c.). The whole was kept for 24 hours at the room temperature and then heated for 20 minutes on a steam-bath. Light petroleum precipitated a viscous syrup, from which the solvent was decanted, and the residue, after stirring with a little ether, was mixed with water (50 c.c.). The solution was basified with sodium hydroxide and extracted with ether, the solvent separated and distilled, and the oily residue

dissolved in alcohol (2 c.c.) and mixed with a boiling solution of picric acid (0·8 g.) in alcohol (5 c.c.). After cooling, the picrate separated as a thick reddish syrup; it was obtained in a crystalline condition from alcohol, but proved to be a mixture and was therefore resolved by fractional crystallisation from alcohol. The first fraction was a mixture of a crystalline powder (0·5 g.), m. p. *ca.* 180°, and well-formed, reddish-orange, rhomboidal prisms (0·3 g.), m. p. 161—162°; these were separated mechanically. From the mother-liquors after several days, a third compound, m. p. *ca.* 150°, separated.

The product of m. p. *ca.* 180°, after several recrystallisations from alcohol, was obtained in well-formed hexagonal plates, m. p. 190° (A) (Found: C, 53·0, 53·2; H, 5·4, 5·4; N, 15·0. Calc. for *dl*-esermethole methopicrate, $C_{21}H_{25}O_8N_5$: C, 53·1; H, 5·3; N, 14·7%); mixed with the specimen of *dl*-esermethole methopicrate obtained by King and Robinson (*loc. cit.*), m. p. 183—184°, it melted at 184—185°.

The product of m. p. 161—162°, once recrystallised from alcohol, had m. p. 162—163° (B), and was identified as *dl*-noresermethole picrate.

The third product of m. p. *ca.* 150°, isolated from the mother-liquors, after several recrystallisations from alcohol was obtained in small yellow prisms, m. p. 180—181° (C). A mixture of the latter with (A) had m. p. *ca.* 160° (Found: C, 52·2; H, 5·2. $C_{20}H_{23}O_8N_5$ requires C, 52·1; H, 5·0%). It is therefore probable that (C) is dl-*esermethole picrate.*

(2) *dl*-Noresermethole (0·25 g.) and methyl *p*-toluenesulphonate (0·2 g., slightly less than 1 mol.) were dissolved in absolute ether (5 c.c.), and separation of a thick syrup soon occurred. After 2 days the solvent was decanted, the syrupy residue washed with ether, shaken with aqueous sodium hydroxide, and the base thus liberated was taken up in ether. The solvent was evaporated, and the residual bases converted into the picrates, which were fractionally crystallised from alcohol. The same products (A), (B), and (C) were isolated as in the previous experiment, (A) and (B) in the same proportions, but (C) only in traces.

The ethereal solution decanted from the mixed *p*-toluenesulphonates, as above, after standing for 5 days longer deposited a further oily precipitate. This was washed with ether, shaken with aqueous sodium hydroxide, and the oily residue obtained by extraction with ether and evaporation of the solvent was converted into the picrate, which separated at once in well-formed rhomboidal plates, m. p. 189—190°, raised by two crystallisations from alcohol to 192—193° (D) (Found: C, 51·1; H, 5·4. Calc. for $C_{21}H_{25}O_8N_5$: C, 53·1; H, 5·3%). The composition is that of esermethole methopicrate, and a mixture of this compound with esermethole methopicrate of natural origin (rhomboidal plates, m. p. 194°) melted at 191—192°. A mixture with the product (A) melted at 191—192°, and one with a specimen of *dl*-esermethole methopicrate (hexagonal plates, m. p. 183—184°) obtained by King and Robinson (*loc. cit.*) melted at 185—186°.

The rotatory power of the natural esermethole methopicrate of m. p. 194°, measured in 1% acetone solution with a ½-dm. micro-tube, was $[\alpha]_D^{18°}$ — 12·00°. Similar examination of the synthetic products (A) and (B) showed them to be optically inactive.

Crystalline dl-*Eserethole. Further Resolution Experiments.*—Picric acid (2·5 g.) and *dl*-eserethole (2·5 g.) (J., 1933, 1474), which had been distilled under 1 mm., were dissolved in hot alcohol (25 c.c.); on cooling, a red oil separated which after several hours became semi-solid. The material was recrystallised from not too much alcohol, and at the fourth crystallisation appeared as clusters of lemon-yellow needles mixed with large red-brown leaflets. Specimens of the two forms were separated by hand; with rapid heating, the latter softened at 80—90°, but on slowly raising the temperature the m. p. of both substances, alone or mixed, and also mixed with the specimen of *dl*-eserethole picrate already described (*loc. cit.*), was 139—140° (yield, 1·4 g.) (Found, after drying at 100°: C, 53·3; H, 5·3; N, 14·9. Calc. for $C_{21}H_{25}O_8N_5$: C, 53·1; H, 5·3; N, 14·7%. Calc. for $C_{20}H_{23}O_8N_5$: C, 52·1; H, 5·0; N, 15·2%).

The pure picrate, m. p. 139—140° (2 g.), was mixed with aqueous sodium hydroxide (40—50 c.c. of 1%), twice extracted with ether, and the extract dried over powdered sodium hydroxide and evaporated; the residue then suddenly solidified, m. p. 76—79°. It was dissolved in absolute alcohol (8—10 c.c.) and combined with *l*-tartaric acid (0·7 g., slightly more than 1 mol.). The solution was inoculated with a trace of the *l*-tartrate derived from the natural material, and set aside to evaporate in the air, but only a viscous syrup was obtained. Unsuccessful results were also obtained from acetone–alcohol, and from propyl alcohol, in which the syrup was much less soluble.

The propyl alcohol was evaporated at room temperature in a vacuum over sulphuric acid, and the base was recovered by shaking with benzene (12 c.c.) and aqueous sodium hydroxide. The benzene layer, twice washed with alkali, was dried over solid sodium hydroxide and evaporated;

the solid residue was distilled at 12 mm. from an oil-bath at 190°. The distillate (0·71 g.) immediately solidified to colourless aggregates of thick, rectangular plates, m. p. 79—80° (Found : C, 73·1; H, 9·1; N, 11·8; OEt, 17·4; NMe, 20·3. Calc. for $C_{15}H_{22}ON_2$: C, 73·2; H, 8·9; N, 11·4; OEt, 18·3; 2NMe, 23·6%). An aqueous solution (6 c.c.) of the distilled *dl*-eserethole (0·65 g.) and *l*-tartaric acid (0·49 g., 1 mol.) was very slowly concentrated over sulphuric acid at atmospheric pressure, but the product was a brittle resin, and the same result was obtained when the process was repeated with ethyl alcohol as the solvent.

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