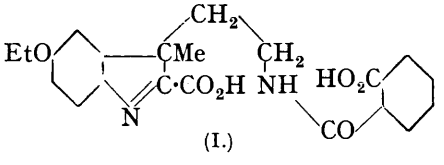
348. *Experiments on the Synthesis of Physostigmine (Eserine). Part VIII.*

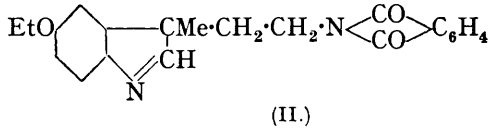
By F. E. King, Robert Robinson, and H. Suginome.

Following the appearance of the earlier parts of this narrative (J., 1932, 298—336, 1433), Hoshino and Tamura (*Proc. Imp. Acad. Japan*, 1932, **8**, 17; *Annalen*, 1933, **500**, 42) have described compounds containing the so-called eserine ring-system, and their contribution to the subject is of great interest. It might be gathered, however, from the introductory remarks of these authors that the present series of researches had failed to achieve the synthesis of the eserine nucleus.* Reference to the publications cited by the Japanese authors (Parts II and VI) will show that this supposition is erroneous, and, far from abandoning the methods already devised, we have confirmed that described in Part II and repeated it on a scale sufficient to enable the performance of preliminary experiments on the resolution of synthetic eserethole. An account of this work is appended, and it is anticipated that modifications in the earlier stages of the synthesis, which are described in part in the following communication, will adapt the process for the preparation of such quantities of *dl*-eserethole as may be required to bring the enterprise to a successful conclusion.

During the decarboxylation of the acid (I), which is an integral stage of the synthesis, in addition to the desired indolenine (II) and the by-product (III), the isolation of an



(I.)

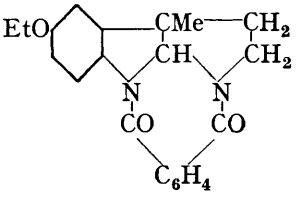


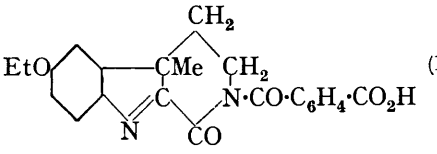
(II.)

unidentified acid, m. p. 170°, was recorded (*loc. cit.*, p. 312). This is now recognised to be 3-*keto*-4-o-*carboxybenzoyl*-10-*ethoxy*-7-*methyl*-3 : 4 : 5 : 6-*tetrahydro*-4-ψ-*carboline* (IV), and its formation in an amount approximately five times that of the indolenine (II) may be considered to be due to the more facile ring-closure to a 6-membered piperidone than to a 5-membered phthalimide derivative. Alternatively, and perhaps more acceptably, it may be regarded as a measure of the reactivities of the respective carboxyl groups, that attached to the indolenine nucleus being analogous to the carboxyls of picolinic or oxalic acids, and

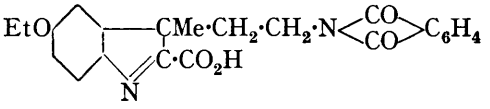
* Our reference is to the following remark quoted from the memoir of Hoshino and Tamura : " In jüngster Zeit haben R. Robinson und seine Mitarbeiter (besonders H. Suginome) Versuche Eserin zu synthetisieren, veröffentlicht. Aber die Synthese des Eserinringes ist noch nicht ganz gelungen."

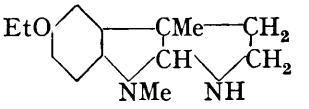
therefore exhibiting appreciably the greater kationoid reactivity. The relatively slower dehydration reaction may then afford the intermediate (V), which under the experimental conditions gives rise to the indolenine (II).

(III.) 


(IV.)

dl-Noreserethole (VI) and methyl *p*-toluenesulphonate gave an oil, shown by examination of its *picrate* to be substantially *dl*-eserethole. The salt which crystallised from a solution

(V.) 


(VI.)

of this base and one equivalent of *d*-tartaric acid in alcohol could not be purified, and furthermore it appeared probable (compare also Hoshino and Tamura, *loc. cit.*) that, of the mixed salts derived from the *dl*-base, the *d*-base-*d*-acid would separate first. Conversely, of the two salts to be obtained by combination of inactive eserethole with *l*-tartaric acid, the *l*-base-*l*-acid might be the less soluble. With a view to examining the properties of the latter, l-*eserethole hydrogen racemate* was prepared, but no separation into optical antipodes could be effected. l-*Eserethole hydrogen* l-*tartrate* is slightly less soluble than the *l*-base-*d*-acid and crystallises in a highly characteristic manner, but an attempt to resolve the synthetic base by means of *l*-tartaric acid was inconclusive. The recovered basic residues from these trials were converted into dl-*eserethole methopicrate*, which closely resembles the corresponding l-*base methopicrate*.

Preliminary experiments on the formation of δ-phenoxy-*sec*.-butyl bromide (v. Braun and Deutsch, *Ber.*, 1911, **44**, 3706) from αγ-dibromobutane, for which a convenient preparation is given, suggest that the phenoxy-indolenines of Part VII (this vol., p. 27) might be derived by a synthesis analogous to that of Part II. The constitution of the phenoxy-bromide (compare v. Braun and Deutsch, *loc. cit.*) depends on its conversion through the nitrile into γ-phenoxy-α-methylbutyric acid. The bromide condenses with ethyl methylmalonate to give what is apparently *ethyl ε-phenoxy-γ-methylpentane-ββ-dicarboxylate*.

Experimental.

3-*Keto*-4-*o*-*carboxybenzoyl*-10-*ethoxy*-7-*methyl*-3 : 4 : 5 : 6-*tetrahydro*-4-ψ-*carboline* (IV).—Following decomposition of the dicarboxylic acid (I) (15 g.) by heating in xylene (320 c.c.) as described in Part II (*loc. cit.*), a non-basic material began to separate, and after the accumulation of 5—6 g. of the indolenine (II) this by-product (50 g.) was shaken with aqueous sodium carbonate, leaving a residue of the very stable *NN'*-phthaloyldinoreserethole (III). The acidic fraction was crystallised from alcohol, affording the *acid* (31 g.) of m. p. *ca.* 170°, with effervescence, which varied slightly with the rate of heating. When recrystallised, it very slowly separated from acetic acid or from alcohol in hard nodules of minute colourless prisms (Found : C, 64·5; H, 5·5; N, 7·0; loss at 145°, 5·0. $C_{22}H_{20}O_5N_2,H_2O$ requires C, 64·4; H, 5·4; N, 6·8; H_2O, 4·4%. Found in dried material : C, 66·2; H, 5·1. $C_{22}H_{20}O_5N_2$ requires C, 67·3; H, 5·1%). The substance dissolves in concentrated sulphuric acid to a bright lemon-yellow solution.

The acid (2 g.) did not readily dissolve in 20% aqueous sodium hydroxide (25 c.c.), and when heated a heavy oily layer separated which vanished on cooling. Hydrolysis was completed by boiling under reflux for 1 hour, and the plastic solid precipitated by hydrochloric acid was dissolved in a little alcohol and treated with a slight excess of potassium hydroxide. On standing, a crystalline precipitate appeared, and this separated from a large volume of 95% alcohol in colourless prisms, m. p. 275—285°, evidently identical with the dipotassium salt of 5-ethoxy-3-methyl-3-(β-*o*-carboxybenzamidoethyl)indolenine-2-carboxylic acid (I) (Part II, *loc. cit.*, p. 311).

l-*Eserethole Hydrogen* d-*Tartrate*.—By the method of Polonovski (*Bull. Soc. chim.*, 1915, **17**, 235), *l*-eserethole of b. p. 174°/12 mm. was obtained in 75% yield. A solution of the base (0·78 g.) and *d*-tartaric acid (0·5 g.) in methyl alcohol after 12 hours gave the *acid tartrate* (0·9 g.) in prisms, m. p. 164—166° (Found in material dried at 100° in a vacuum : C, 57·4; H, 7·2; N, 7·4. $C_{19}H_{28}O_7N_2$ requires C, 57·6; H, 7·1; N, 7·1%). This salt dissolves readily in alcohol, but is much less soluble in acetone or in ethyl acetate.

dl-*Eserethole* (compare Part II, *loc. cit.*, p. 314).—*dl*-Noreserethole (1·1 g.) in dry benzene (3 c.c.) was mixed with a solution of methyl *p*-toluenesulphonate (0·88 g., 1 mol.) in ethyl acetate (3 c.c.). The whole was left for 24 hours at room temperature and heated for 20 minutes under reflux on a steam-bath; light petroleum was then added, whereupon a viscous syrup separated, from which the solvents were decanted. The residue was stirred with a little ether and shaken with water (20 c.c.) and after separation from the small quantity of ether-insoluble matter the solution was basified and extracted with ether. Distillation of the extract from an oil-bath at 165—170° gave a straw-coloured oil (0·6 g.), b. p. 130—135°/1 mm. It was dissolved in alcohol (3 c.c.) containing *d*-tartaric acid (0·38 g.) and the minute crystals (0·45 g.) which separated after 6 hours at 0° were repeatedly crystallised. Determinations of m. p. suggested that the salt was contaminated with a persistent impurity; with a specimen of the final product fusion began at 133°, but was not complete until *ca.* 155°. The base which was regenerated from material derived from the alcoholic residues yielded a *picrate*, eventually obtained in voluminous clusters of fine yellow needles, m. p. 138—140° (Found : N, 15·1. $C_{21}H_{25}O_8N_5$ requires N, 14·7%). Noreserethole picrate (Part II, *loc. cit.*, p. 314), $C_{20}H_{23}O_8N_5$ (N, 15·2%), crystallises in orange-red prisms, m. p. 180—181°.

l-*Eserethole Hydrogen* d-*Racemate*.—Racemic acid dried at 110° (0·61 g., 1 mol.) was dissolved in an alcoholic solution (8 c.c.) of the natural base (1 g.). Clusters of rectangular plates (1·5 g.) rapidly separated, m. p. 157—158°, identical with a further small amount obtained by concentration of the mother-liquor. Recrystallisation from alcohol (15 c.c.) gave the pure *racemate* (1·1 g.), m. p. 159°, unaffected by further crystallisation (Found : C, 57·6; H, 6·9; N, 7·2. $C_{19}H_{28}O_7N_2$ requires C, 57·6; H, 7·1; N, 7·1%).

l-*Eserethole Hydrogen* l-*Tartrate*.—A solution of *l*-tartaric acid (0·35 g.) and *l*-eserethole (0·56 g.) in alcohol (4 c.c.) deposited the *acid tartrate* in sheaf-like clusters of large prisms (0·81 g.), which on recrystallisation had m. p. 172—173° (Found : C, 57·6; H, 7·2; N, 7·3. $C_{19}H_{28}O_7N_2$ requires C, 57·6; H, 7·1; N, 7·1%). It is slightly less soluble in organic solvents than the isomeric *l*-base-*d*-acid but it resembles all other tartrates in this series in being freely soluble in water.

Resolution Experiments with dl-*Eserethole Hydrogen* l-*Tartrate*.—The yield of distillable product derived from *dl*-noreserethole was not affected by employment of slightly more (1·3 mols.) than the theoretical amount of methyl *p*-toluenesulphonate. The salt (0·2—0·3 g.) which separated from a solution of the base (0·6 g.) and *l*-tartaric acid (0·38 g.) in alcohol (4 c.c.) was recrystallised, and afforded small clusters of microcrystalline prisms, m. p. 125—140° (Found : C, 54·3; H, 7·1; N, 7·0. $C_{19}H_{28}O_7N_2,H_2O$ requires C, 55·1; H, 7·2; N, 6·8%. $C_{18}H_{26}O_7N_2,H_2O$ requires C, 54·0; H, 7·0; N, 7·0%). The residues were recovered, decomposed by aqueous sodium hydroxide, and converted by the successive action of methyl iodide and alcoholic picric acid into the quaternary picrate. The alcoholic solution first deposited a trifling amount of yellow crystalline solid, which was separated from the bright red methopicrate by hand. One crystallisation gave yellow hexagonal tablets, melting at 150—152° to a red liquid. The bulk of the product was dl-*eserethole methopicrate*, which crystallised from alcohol in orange-red hexagonal plates, m. p. 184—186°, followed by decomposition (Found : C, 53·8; H, 5·4; N, 14·3. $C_{16}H_{25}ON_2,C_6H_2O_7N_3$ requires C, 54·0; H, 5·5; N, 14·3%). The related salt from physostigmine, l-*eserethole methopicrate*, was likewise prepared. It formed splendid orange-red rhombic leaflets, m. p. 190° with rapid decomposition (Found : C, 53·9; H, 5·5; N, 14·6. $C_{16}H_{25}ON_2,C_6H_2O_7N_3$ requires C, 54·0; H, 5·5; N, 14·3%).

αγ-Dibromobutane.—To a solution containing hydrobromic acid (1250 c.c. of *d* 1·5), concentrated sulphuric acid (375 g.), and αγ-dihydroxybutane (270 g.), a further quantity of sulphuric acid (600 g.) was cautiously added. Following 3 hours' boiling under reflux, the mixture was distilled for 1 hour. Appreciable charring was then apparent (the use of an external source of steam for isolation of the product should improve the yield). The heavy oil was separated, dried over calcium chloride, and distilled under reduced pressure, the main fraction (440 g. or 68%) having b. p. 73—78°/22 mm.

Condensation of αγ-Dibromobutane with Phenol.—A stirred mixture of the dibromide (440 g.), phenol (160 g.), and water (530 c.c.) was heated to boiling and treated dropwise during 30—40

minutes with sodium hydroxide (70 g.) in water (220 c.c.). Heating was continued for 6 hours and the non-aqueous material was then roughly separated and distilled. The fraction (133 g.), b. p. 131—141°/13 mm. (v. Braun and Deutsch, *loc. cit.*, give 130—131°/9 mm. as the b. p. of δ-phenoxy-*sec.*-butyl bromide), was collected in two parts (90 g. and 43 g.). Equal quantities (25 g.) of the two portions and potassium cyanide (25 g.) in water (45 c.c.) and alcohol (125 c.c.) were heated under reflux on a steam-bath for 20 hours. The product, isolated in the usual manner, was distilled under reduced pressure, the fraction (12—13 g.), b. p. above 145°/14 mm. (γ-phenoxy-α-methylbutyronitrile has b. p. 165°/18—20 mm.), being reserved for hydrolysis, which was effected by boiling for 10 hours with aqueous potassium hydroxide (75 c.c. of 40%). The alkali-soluble material was precipitated by acid as a brown oil, which became turbid with crystals. When isolated by pressing on a porous tile and once crystallised from light petroleum, the colourless solid (2·6—3·7 g.) had m. p. 78—80° undepressed by the authentic γ-phenoxy-α-methylbutyric acid.

Ethyl ε-Phenoxy-γ-methylpentane-ββ-dicarboxylate.—A solution of sodium (1 g.) in alcohol (40 c.c.) was heated under reflux on a steam-bath for several hours with ethyl methylmalonate (11·5 g.) and the phenoxy-bromide (15 g.). After neutralisation with acetic acid, the product was isolated and distilled as a colourless oil (10—11 g.), b. p. 211—212°/17 mm., consisting of the *ester* (Found : C, 67·2; H, 7·8. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·0%), but neither the related acid nor the acid amide could be crystallised.

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