

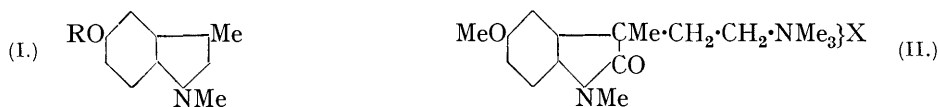
169. *Experiments on the Synthesis of Physostigmine (Eserine). Part XI.*
The Later Phases of the Synthetical Investigations.

By FREDERICK E. KING and ROBERT ROBINSON.

THE chief steps in the progress of the attack on physostigmine from the synthetical angle are the following :

(1) The synthesis by Stedman (J., 1924, **125**, 1373) of physostigmol ethyl ether (I, R = Et), and of the methyl ether (I, R = Me) by Späth (*Ber.*, 1925, **58**, 518), which established the presence of the indole nucleus and the orientation of certain substituents.

(2) The synthesis *and resolution* of dehydroesermetholemethine metho-salts (II) (King and Robinson, Part V, J., 1932, 326). The identity of the synthetic salts with those derived by degradation of the alkaloid established for the first time the existence of the angle methyl group and gave important support to the view of the constitution of eserine which is now generally accepted. As this fact does not seem to have been recognised by other workers in the field, we venture to draw attention to it.

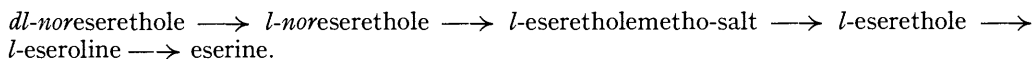


(3) Various syntheses of the eserine ring system, for example, that of *dl*-noreserethole (III), first accomplished by Robinson and Sugimoto (J., 1932, 304), and *dl*-noresermethole (King and Robinson, *ibid.*, p. 1433); and also improvements in the methods, due to King, Liguori, and Robinson (J., 1933, 1475), Hoshino and Tamura (*Proc. Imp. Acad. Japan*, 1932, **8**, 171; *Annalen*, 1933, **500**, 42), Hoshino and Kobayashi (*Proc. Imp. Acad. Japan*, 1934, **10**, 99, 564; *Annalen*, 1935, **516**, 81), Hoshino and Kotake (*ibid.*, p. 76), Julian, Pikel, and Boggess (*J. Amer. Chem. Soc.*, 1934, **56**, 1797), and Julian and Pikel (*ibid.*, 1935, **57**, 539, 563).

(4) The resolution of *dl*-noreserethole and its conversion into optically active eserethole metho-salts identical with those derived from eserine by successive hydrolysis, ethylation, and *N*-methylation (Hoshino and Kobayashi, *loc. cit.*).

(5) The final stage, chronologically the first to be accomplished, namely, the conversion of eseroline into eserine (Polonovski and Nitzberg, *Bull. Soc. chim.*, 1916, **19**, 33).

This is the position at the time of writing,* and the total synthesis of eserine may eventually be realised by way of several routes, of which the following is one of the more promising:

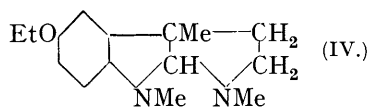
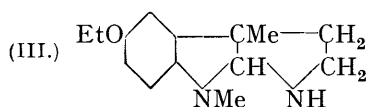


The necessary stage, eserethole \longrightarrow eseroline, has not been effected hitherto and, although the yields are not yet satisfactory, we have bridged this particular gap by experiments described in the present communication.

Unfortunately the eserethole metho-salts cannot be thermally decomposed without breaking of the ring system. Reference to this difficulty was made when the degradation of *l*-esermethole methochloride was described (J., 1933, 270), and we now find that the related eserethole salt behaves in a similar manner, affording only physostigmol ethyl ether. The methofluoride, on the other hand, distils partly unchanged (!) (at least the distillate gives the methopicrate on treatment with picric acid), and is partly decomposed with the formation of a base not yet identified, but which from the nature of its picrate is certainly not *l*-eserethole.

Eserethole metho-salts are much more smoothly de-ethylated by means of hydrobromic acid than eserethole itself, and in this way hitherto unknown eseroline metho-salts have been obtained which were identified in the form of *eseroline methopicrate*.

The completion of the synthesis of eserine along the lines of the present series of memoirs, therefore, requires yet a further stage, which might be one of the following: (a) the resolution of *dl*-eserethole, (b) the *N*-demethylation of an eserethole metho-salt, or (c) the *N*-demethylation of an eseroline metho-salt.

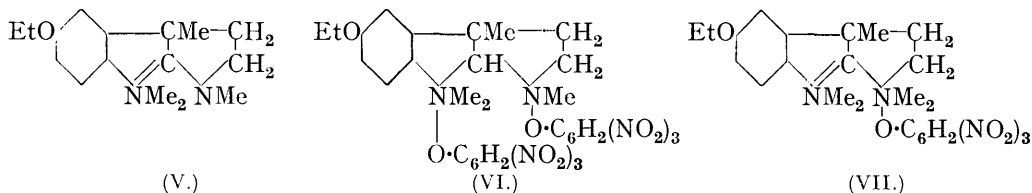


The important intermediate *dl*-noreserethole (III) is a rallying point, because the description of its derivatives shows that the same substance has been obtained both in the course of this series of investigations and by the Japanese and American chemists. On controlled methylation with methyl *p*-toluenesulphonate we found that it yielded a crystalline *dl*-eserethole (IV), m. p. 79–80° (J., 1934, 1416), and we then surmised that this substance would prove to be identical with a base, m. p. 80–81°, obtained by Hoshino and Kobayashi (*Proc. Imp. Acad. Japan*, 1934, 10, 99). Through the kindness of these authors we have been able to confirm this view by a direct comparison of the specimens. Hoshino and Kobayashi, however, described their base as having the composition C₁₆H₂₄ON₂ and have recently reaffirmed this view (*ibid.*, p. 564). We can only reply that three separate sets of estimations (that originally published, which was by Schoeller, and five more by Weiler and by Roth) of carbon and hydrogen support our view that the base is C₁₅H₂₂ON₂, and we can also confirm the statement already made (*loc. cit.*, 1934, 1416) that there are only two methyl groups attached to nitrogen. In our opinion the base is structurally identical with eserethole, and it may be a stereoisomeride of this base. We accept the evidence of Hoshino and Kobayashi (*loc. cit.*) that the substance is not *dl*-eserethole, although the facts leading to this conclusion have not fallen within our experience. It is relevant to note that Linstead and Meade (J., 1934, 935) have isolated *cis-cis*- and *cis-trans*-isomerides of fused dicyclooctanes (two five-membered rings), and we provisionally regard the isomerism of *dl*-eserethole-*a*, m. p. 38° (synthesised by Julian and Pikel, *loc. cit.*), and our *dl*-eserethole-*b*, m. p. 80°, as another case of the same kind. The fact that the behaviour of *dl*-eserethole-*a* and *dl*-eserethole-*b* towards methyl iodide is different is not surprising, because the stereochemical hypothesis closely concerns the configuration of the nitrogen atoms.

* The completion of the synthesis of eserine has meanwhile been announced by Julian and Pikel (*J. Amer. Chem. Soc.*, 1935, 57, 755), but, as this paper arrived in England after the present MS. had been submitted to the Society, we must reserve our comment.

The formula (V) formerly attributed by Hoshino and Kobayashi to their base of the supposed formula $C_{16}H_{24}ON_2$ has not been abandoned by these authors, but they do not print it in their recent publication in the *Annalen*.

A similar, highly improbable constitution is attributed by Julian and Pikl to a monopicrate (VII) made from eserethole dimethiodipicrate (VI) by loss of picric acid on crystallisation from alcohol.



Julian and Pikl also support the formula (V) as an expression for our base, m. p. 80° , but without any new evidence other than the synthesis of an isomeride. As they imply violations of fundamental theory, the expressions (V) and (VII) cannot be accepted, and furthermore, a dipicrate that loses picric acid on recrystallisation can hardly be a diquaternary picrate. It is probably a tertiary-quaternary picrate with a methyl group less than Julian and Pikl suppose.

EXPERIMENTAL.

Comparison of Specimens by Melting Point Determinations.—The following observations are made concerning the three specimens supplied by Hoshino and Kobayashi :

(1) The *dl*-noreserethole picrate of m. p. 180 — 181° was indistinguishable from the material of Robinson and Suginome (J., 1932, 314), who recorded m. p. 180 — 181° , not 191 — 192° as recently quoted in error (J., 1934, 1416).

(2) *dl*-Eserethole-*b*, for which the Japanese chemists claim m. p. 80 — 81° , when mixed with our substance of m. p. 79 — 80° , melted at 77 — 79° . It was then found that their specimen actually had m. p. 77° .

(3) *dl*-Eserethole-*b* picrate. For this substance the m. p.'s 138 — 140° (King, Robinson, and Suginome, J., 1933, 1474), 139 — 140° (King, Liguori, and Robinson, J., 1934, 1418), and 140 — 141° (Hoshino and Kobayashi, *Proc. Imp. Acad. Japan*, 1934, 10, 99) have been recorded. The m. p. has since been stated as 150 — 151° (Hoshino and Kobayashi, *Annalen*, 1935, 516, 87), which we have verified for the sample received. On admixture with either of the two specimens, m. p. 138 — 140° and 139 — 140° , no depression was observable, and it was then discovered that both of these now have m. p. 150 — 151° ! It is therefore supposed that the picrate of the base m. p. 80° is dimorphic, the two modifications having m. p. *ca.* 140° and 150 — 151° respectively.

Analyses of dl-Eserethole-b, m. p. 80° .—As this matter has to some extent become one in which the reliability of analytical technique is involved, we append the actual figures in order that those who carried out the determinations may be able to identify the experiments (weights in mg.).

R.W. 347.	Substance.	CO ₂ .	%C.	H ₂ O.	%H.
	3·562	9·590	73·43	2·810	8·83
	3·657	9·870	73·61	2·925	8·95
	3·820	10·250	73·18	3·040	8·90

These analyses were carried out with different apparatus by three different analysts. The blank tests showed an error of C, — 0·04, 0·01; H, 0·16, — 0·07. G. Weiler.

R.R. 49.	Substance.	CO ₂ .	%C.	H ₂ O.	%H.
	4·329	11·59	73·02	3·52	9·10
	3·673	9·84	73·07	2·95	8·99
		<i>p.</i>	<i>t</i> °.	<i>v</i> (c.c.).	%N
	4·167	746	21	0·408	11·16
	3·867	746	20	0·371	10·97
		AgI.			%C ₂ H ₅ O.
	4·536	4·440			18·77
	4·166	4·085			18·81
		AgI (total).	AgI (less OEt).		%NMe.
	4·169	10·740	6·656		19·70
	4·778	12·335	7·654		19·77 H. Roth.

Calc. for $C_{15}H_{22}ON_2$: C, 73.2; H, 8.9; N, 11.4; OEt, 18.3; 2NMe, 23.6%.

Calc. for $C_{16}H_{24}ON_2$: C, 73.8; H, 9.2; N, 10.8; OEt, 17.5; 2NMe, 22.7%.

De-ethylation of l-Eserethole and of l-Eserethole Methiodide.—(i) *Experiments with hydriodic acid.* A solution of *l*-eserethole (0.9 g.) in colourless redistilled hydriodic acid (12 c.c., *d* 1.7) was heated in a stream of pure carbon dioxide by an oil-bath at 140—150°. Evolution of ethyl iodide appeared to be complete within 15 minutes, but much iodine had been liberated, and dilution with water precipitated a tarry material. After being cleared with ether, the acid solution was neutralised with sodium bicarbonate and immediately extracted both with ether and with chloroform, but no pure substance could be isolated.

When *l*-eserethole methiodide (0.7 g.), m. p. 171°, dissolved in the pure acid (10 c.c.), was heated under the above conditions for 12 minutes, the amount of iodine liberated was considerably diminished. On evaporation to dryness at 50° under reduced pressure, the residue was a dark red gum, which was washed with ethyl acetate, dissolved in alcohol, and treated with alcoholic picric acid. The charcoaled solution when quite cold was decanted from a resinous deposit, and the yellow woolly aggregates of needles (0.2 g., softening *ca.* 160° and decomposing at 190°) which had separated after 48 hours were collected and thrice crystallised from alcohol. Stout irregular orange-yellow prisms, m. p. 193—195° (decomp.), were thus obtained, later identified as *l*-eseroline methopicate (Found: C, 52.3; H, 5.1; N, 14.9. $C_{20}H_{23}O_8N_5$ requires C, 52.1; H, 5.0; N, 15.2%).

(ii) *Experiments with hydrobromic acid.* A solution of *l*-eserethole (0.9 g.) in colourless redistilled hydrobromic acid (12 c.c., *d* 1.5) was heated, as already described, in a carbon dioxide atmosphere at 145—150° for 50 minutes, and then evaporated at 50° under diminished pressure. The pale olive-green residue was dissolved in hot alcohol (18 c.c.) containing picric acid (1 g.), and after 24 hours the precipitated salt was collected and once recrystallised. The product (0.45 g.) then decomposed above 160—170°, but after further recrystallisation compact rosettes of deep yellow prisms were obtained, m. p. 195° (decomp.) after slight sintering at 160—165° (Found: C, 50.8; H, 4.7; N, 15.5. Calc. for *l*-eseroline picrate, $C_{19}H_{21}O_8N_5$: C, 51.0; H, 4.7; N, 15.7%).

The experiment was then repeated with the methiodide (1 g.), and the pale green gum remaining after evaporation of the hydrobromic acid was dissolved in hot alcoholic picric acid (0.65 g. in 22 c.c.). By decanting the cold solution from a small quantity of resin, then boiling with charcoal and filtering, a voluminous mass of yellow needles was obtained, softening at 160—170° and decomposing above 190°. The yield of *l*-eseroline methopicate reached 0.7 g. or 59%, but was considerably reduced by recrystallisation, since relatively large volumes of alcohol (20—25 c.c.) were required to render the specimen of analytical purity (orange-yellow prisms, m. p. 194—195°, decomp.) (Found: C, 52.0; H, 5.1; N, 15.0%).

l-Eseroline Picrate and l-Eseroline Methopicate.—The eseroline salts required for the identification of the foregoing products were obtained from a sample of the base prepared by the method of Polonovski (*Bull. Soc. chim.*, 1915, 17, 239). The product, which was more conveniently extracted with chloroform, when washed with a little ether and once crystallised from chloroform-light petroleum, had m. p. 125—127° (literature, 128°, 129°): yield, 78%.

The picrate, which was obtained by mixing equivalent amounts of base and acid in alcoholic solution, after several crystallisations from alcohol, separated in clusters of orange-yellow prismatic crystals, m. p. 195° (decomp.), with softening at 160—165° (Found: C, 50.9; H, 4.9; N, 15.4. Calc. for $C_{19}H_{21}O_8N_5$: C, 51.0; H, 4.7; N, 15.7%). This is in agreement with Salway's description (J., 1912, 101, 982), who gives m. p. 195°, but it remains to be ascertained whether softening at 160—165° is characteristic of the salt derived from highly purified eseroline. It is perhaps significant that the specimen of this picrate having its origin in eserethole (*vide supra*) also has this feature. Other authorities give m. p. 190° (Polonovski, *loc. cit.*) and 167° (Strauss, *Annalen*, 1913, 401, 350), but the latter is thought to refer to a dimorphic form.

The addition of an equivalent of methyl iodide to an acetone solution of eseroline (m. p. 125—127°) precipitated the methiodide in colourless hexagonal plates, m. p. 192—194° (literature, 196°). An alcoholic solution of the requisite quantity of picric acid gave a mass of yellow needles, which on recrystallisation yielded the methopicate, m. p. 194—195° (decomp.), identical in form and analysis with the specimens described above (Found: C, 52.0; H, 5.0; N, 15.1%).

Thermal Decomposition of l-Eserethole Quaternary Salts.—(i) *Eserethole methochloride.* A solution of the methiodide (2.5 g.) in alcohol (6 c.c.) and water (25 c.c.) was digested for a few minutes at 100° with freshly prepared silver chloride (7.5 g.). After filtration, the solution was

evaporated at 55° (reduced pressure), and the solid product dissolved in acetone (*ca.* 15 c.c.). When diluted with an equal volume of ethyl acetate, the solution yielded colourless stout prisms (1.7 g.), softening at 126—127°, m. p. *ca.* 175°.

When the salt was heated in a vacuum (0.01 mm.), no indication of melting or decomposition was obtained until the temperature reached 200—210°. Rapid decomposition then ensued, the pressure fell to *ca.* 1—2 mm., and a white solid collected. This had m. p. 86°, gave a characteristic Ehrlich reaction (deep violet, turning to blue), and was identical with physostigmol ethyl ether (Stedman, *loc. cit.*).

(ii) *Eserethole methofluoride*. To the methiodide, dissolved in alcohol (6 c.c.) and water (30 c.c.), an aqueous solution of silver fluoride was added, potassium chromate being used as an external indicator. At the end-point the solution was filtered from silver iodide and evaporated to dryness under reduced pressure, leaving a colourless gum (1.4 g.) which later solidified. It was easily soluble in acetone, but was precipitated therefrom (*e.g.*, by light petroleum) as a gum, and was clearly deliquescent.

When heated in a high vacuum (0.001 mm.) the methofluoride (1.05 g.) melted at a bath temperature of 100—105°, and above 120—130° the pressure rose to 0.2—0.4 mm. The temperature was then very slowly increased, and at 140° a distillate began to collect consisting of a colourless liquid mixed with a white solid. Heating was discontinued at 180°, and the product (0.35 g.) divided into two portions. The first (0.2 g.) was dissolved in a boiling alcoholic solution of picric acid (0.16 g.), thus yielding a solid which after three crystallisations gave *l*-eserethole methopicrate (J., 1933, 1474) in glistening red rhombic plates (0.08 g.), m. p. 191° (decomp.). From the mother-liquors a more soluble salt was isolated which ultimately appeared as glistening bronze-yellow leaflets (0.07 g.), m. p. 197—198°. *l*-Eserethole picrate is stated by Polonovski (*loc. cit.*) to have m. p. 133°, whereas Hoshino and Kobayashi (*loc. cit.*, 1935) find 141—142°.

To the remainder of the distillate, after solution in ether and filtration from solid material, methyl iodide was added. A colourless methiodide, m. p. 95—100° (hydrate?), separated, which was converted into a yellow methopicrate (0.11 g.), m. p. 163—166°. This and the yellow picrate, m. p. 197—198°, above, are being investigated.

Ehrlich's test applied to the distillate remaining in the side-arm of the flask gave a red solution reflecting an olive-green colour.

Except where otherwise stated, the analyses are micro-determinations by Dr. G. Weiler.

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