Researches on the constitution of physostigmine. Pt. I[-II] / by Arthur H. Salway.

No. 142

24.

RESEARCHES

ON THE

CONSTITUTION OF PHYSOSTIGMINE

PART I.

BY

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES
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CI.—*Researches on the Constitution of Physostigmine. Part I.*

By Arthur Henry Salway.

The constitution of physostigmine (eserine), $C_{15}H_{21}O_2N_3$, is a subject of considerable interest on account of the valuable therapeutic properties which the alkaloid possesses. It has already been shown by Petit and Polonowsky (*Bull. Soc. chim.*, 1893, [iii], **9**, 1008) that physostigmine is a monacidic tertiary base, and that it also contains a CO·NHMe complex, since carbon dioxide and methylamine are eliminated on heating with aqueous potassium hydroxide. Ehrenberg (*Verh. Ges. deut. Naturforsch. Aerzte*, 1893, ii, 102) independently confirmed the conclusions of Petit and Polonowsky, and also obtained from the alkaloid by the action of potassium hydroxide in the absence of air a new base, $C_{13}H_{18}ON_2$, to which the name of eseroline was given. Physostigmine was therefore stated by him to be a substituted carbamide, represented by the formula $(C_{13}H_{16}ON)NH\cdot CO\cdot NHMe$, and the action of alkalis on the alkaloid was represented by the equation:

$$(C_{13}H_{16}ON)NH\cdot CO\cdot NHMe + H_2O = C_{13}H_{16}ON\cdot NH_2 + CO_2 + NH_2Me.$$

Eseroline is therefore, according to Ehrenberg, an amino-derivative of the complex $C_{13}H_{16}ON$, but it should be pointed out that the action of alkalis on physostigmine would be equally well explained by assuming that the alkaloid is a urethane of the formula $NHMe\cdot CO\cdot O\cdot C_{13}H_{17}N_2$, in which case eseroline would be an alcohol, $C_{13}H_{17}N_2\cdot OH$.

It is well known that physostigmine absorbs oxygen rapidly in the presence of alkalis, and is converted into oxidation products known as rubreserine, eserine brown, and eserine blue respectively. Ehrenberg (*loc. cit.*) has already shown that rubreserine possesses the formula $C_{13}H_{16}O_2N_2$, and that its formation from physostigmine depends on the primary conversion of the latter into eseroline according to the following scheme:

$$\underset{\text{Phyostigmine.}}{C_{15}H_{21}O_2N_3} \xrightarrow{KOH} \underset{\text{Eseroline.}}{C_{13}H_{18}ON_2} \xrightarrow{O_2} \underset{\text{Rubreserine.}}{C_{13}H_{16}O_2N_2}.$$

Little is otherwise known, however, regarding the chemical character of eseroline and rubreserine, whilst the so-called eserine blue and eserine brown have not previously been isolated in the pure condition. In view of these facts, it seemed evident that further information regarding the constitution of physostigmine would be obtained by a complete examination of eseroline and its

oxidation products, and accordingly these substances have now been investigated.

Eseroline was found to be a strong base, which yields salts with only one equivalent of an acid. It contains one methyl group attached to nitrogen, and forms an additive product with one molecule only of methyl iodide, being therefore a tertiary base. Eseroline also possesses acidic properties, since it dissolves in aqueous sodium hydroxide without change in the absence of air. The state of combination of the oxygen atom in eseroline could not be determined with certainty, since the base did not react with semicarbazide or diazomethane, whilst attempts to prove the presence of a hydroxyl group by means of acetic anhydride led to indefinite products. Eseroline, in the presence of alkalis, was found to absorb 5 atoms of oxygen per molecule of the base. The first product of the oxidation, rubreserine, is formed by the rapid absorption of two atoms of oxygen. This compound, the formula of which has now been definitely established as $C_{13}H_{16}O_2N_2$, possesses both basic and acidic properties, and, unlike eseroline, readily reacts with diazomethane. If the oxidation is allowed to proceed further with free access of air or oxygen, the red colour of the rubreserine changes to yellowish-brown, with the formation of an indefinite mixture of degradation products. When the oxidation, on the other hand, proceeds slowly with a limited supply of air, the red solution gradually changes to an intense blue. This blue colour is due to the presence of a compound termed eserine blue, which has now been isolated in a pure state. It is a base which has the formula $C_{17}H_{23}O_2N_3$, and yields salts with two equivalents of an acid. Its formation appears to be due to the condensation of eseroline with a degradation product of this base.

In order to obtain further information regarding the structure of physostigmine, many attempts were made to resolve it into products having a less carbon content than that of eseroline and rubreserine. Hofmann's method of degradation by exhaustive methylation was applied to eseroline, but found impracticable on account of the ease with which eseroline methiodide is oxidised in the presence of alkalis, whilst the vigorous oxidation of physostigmine and eseroline under varied conditions yielded no definite compound. On the other hand, distillation of physostigmine with zinc dust gave a product which consisted of 2-methylindole,

$$C_6H_4\begin{<}{CH \atop NH}\end{>}CMe,$$

together with a small proportion of the isomeric 1-methylindole, $C_6H_4\begin{<}{CH \atop NMe}\end{>}CH$. The formation of indole derivatives by the

zinc dust distillation of physostigmine cannot be accepted, however, as definite proof of the presence of the $C_6H_4<\overset{C}{\underset{N}{>}}C$ complex, since indole is produced by the dry distillation of a number of nitrogen compounds in which the above complex is absent. Nevertheless, in all such instances, there is present a benzene nucleus attached to a nitrogen atom, and therefore physostigmine must also contain this atomic grouping.

It has now been shown that physostigmine contains the groups CO·NHMe, NMe, and NPh. Further investigations are contemplated, by which it is hoped that it may be possible to determine the character of the remaining part of the molecule, and also the relations existing between eseroline, rubreserine, and eserine blue.

Experimental.

The Preparation and Properties of Eseroline.

The preliminary experiments, undertaken with the object of ascertaining the best conditions for the preparation of eseroline, led to the ultimate adoption of the following method: Twenty grams of physostigmine dissolved in a little alcohol were introduced into a flask, and the air displaced from the latter by a current of hydrogen. An excess of sodium hydroxide (100 c.c. of a 10 per cent. solution) which had been freed from dissolved air by boiling was then added by means of a dropping funnel, and the mixture kept at the ordinary temperature for four hours with a constant stream of hydrogen passing through it. At the expiration of this time, ether was added, the mixture well shaken, and the ethereal layer then syphoned off, care being taken to avoid contact of air with the alkaline liquid in the flask. The process of extraction with ether was repeated many times (six to ten extractions were necessary) until no further basic matter was removed by this treatment. The ethereal extracts were then washed with a little water, dried, and carefully concentrated, the last portions of solvent being removed in a vacuum desiccator over potassium hydroxide. The oily residue which was thus obtained slowly crystallised after keeping for some time. The crystals were collected, washed with a little ether, and recrystallised from a mixture of benzene and petroleum, when the base separated in colourless prisms melting at 128°. The yield of pure substance amounted to 70 per cent. of the physostigmine employed. It was analysed with the following result:

0·1164 gave 0·3062 CO_2 and 0·0914 H_2O. C = 71·7; H = 8·7.
0·1426 „ 15·9 N_2 at 16° and 744 mm. N = 12·8.

$C_{13}H_{18}ON_2$ requires C = 71·6; H = 8·3; N = 12·8 per cent.

The empirical formula assigned to eseroline by Ehrenberg (*loc. cit.*) is thus confirmed.

The molecular weight of eseroline was next determined by the cryoscopic method in benzene:

0·2058 in 22·53 benzene gave Δt −0·116°. M.W. = 394.
0·1792 „ 24·40 „ „ Δt −0·093°. M.W. = 395.
$(C_{13}H_{18}ON_2)_2$ requires M.W. = 436.

It appears from these results that eseroline either possesses twice the molecular weight previously assigned to it, or is associated in benzene solution. A determination of the molecular weight of the base in nitrobenzene gave the following results:

0·1251 in 31·25 nitrobenzene gave Δt −0·094°. M.W. = 298.
0·2459 „ 31·25 „ „ Δt −0·164°. M.W. = 336.
$C_{13}H_{18}ON_2$ requires M.W. = 218.

It is to be inferred from these determinations that the simplest molecular formula of eseroline is $C_{13}H_{18}ON_2$, but that the base is associated in benzene solution and to a less extent also in nitrobenzene. Physostigmine, on the other hand, was found to give normal results, both in benzene and nitrobenzene.

A determination of the specific rotatory power of eseroline resulted as follows:

0·2736, made up to 20 c.c. with methyl alcohol, gave, in a 2-dcm. tube, α_D −2°56′, whence $[\alpha]_D$ −107·2°.

Eseroline is readily soluble in alcohol, ether, chloroform, or benzene, but only sparingly so in light petroleum. The free base is quite stable when pure, and can be kept for a long time exposed to the air without change. In neutral or acid solutions it is slowly oxidised, whilst in the presence of alkalis the oxidation is extremely rapid. On account of the ease with which it oxidises, eseroline possesses strong reducing properties, silver nitrate, gold chloride, and platinic chloride being reduced by it to the metallic state. Eseroline possesses a strongly alkaline reaction. Its basicity was ascertained by dissolving it in *N*/10-sulphuric acid, and titrating the excess of acid with barium hydroxide in the presence of ether, using iodeosin as indicator:

0·1791 required for neutralisation 8·15 c.c. *N*/10-H_2SO_4, whereas a monacidic base, $C_{13}H_{18}ON_2$, requires 8·2 c.c.

It is evident from this result that eseroline contains only one basic nitrogen atom.

Eseroline Hydrochloride.—This salt was prepared by passing dry hydrogen chloride into an ethereal solution of the base. The colourless precipitate which formed was collected and purified by crystallisation from a mixture of alcohol and ethyl acetate, when

it was obtained in stellate clusters of colourless needles melting at 212°:

0·2772, heated at 110°, lost 0·0189 H_2O. $H_2O = 6·8$.

$C_{13}H_{19}ON_2Cl,H_2O$ requires $H_2O = 6·6$ per cent.

0·1071 gave 0·2406 CO_2 and 0·0756 H_2O. $C = 61·3$; $H = 7·8$.

0·0983* ,, 0·0564 AgCl. $Cl = 14·2$.

$C_{13}H_{19}ON_2Cl$ requires $C = 61·3$; $H = 7·5$; $Cl = 14·0$ per cent.

Eseroline picrate crystallises from alcohol in stellate clusters of yellow needles melting at 195°:

Eseroline possesses feeble acidic properties, since it is readily soluble in alkali hydroxides, and can be recovered from the alkaline solution unchanged in the absence of air. It contains one methylimide group, NMe, the presence of which was proved by the method of Herzig and Meyer (*Monatsh.*, 1895, **18**, 379):

0·1208 gave 0·0986 AgI. $NMe = 11·4$.

$C_{12}H_{15}ON(NMe)$ requires $NMe = 13·3$ per cent.

In order to obtain if possible some knowledge of the state of combination of the oxygen atom of eseroline, the latter was treated with semicarbazide hydrochloride in dilute alcohol and the mixture kept for some time, but no reaction took place. Diazomethane in ethereal solution was likewise without action on eseroline. Acetic anhydride, on the other hand, appears to produce some change, but no definite product could be isolated from the reaction mixture. It would appear from these results that eseroline does not contain a carbonyl group, whilst the presence of a hydroxyl group is doubtful.

Eseroline Methiodide.—When methyl iodide is added to a solution of eseroline in chloroform, reaction takes place with evolution of heat, and a crystalline precipitate immediately separates. This substance crystallises from water in thin, colourless needles melting at 196°:

0·1208 gave 0·2079 CO_2 and 0·0652 H_2O. $C = 46·9$; $H = 6·0$.

$C_{14}H_{21}ON_2I$ requires $C = 46·7$; $H = 5·8$ per cent.

It is evident that the above compound is formed by the combination of one molecule of methyl iodide with one molecule of eseroline. The same compound is produced when an excess of methyl iodide is employed in the reaction; eseroline must therefore be a tertiary base.

* The amount of chlorine in eseroline hydrochloride cannot be determined by simple precipitation with aqueous silver nitrate, since the latter is reduced by eseroline in the absence of nitric acid, whilst, in the presence of this acid, eseroline is decomposed with the formation of hydrocyanic acid, which forms, with the silver nitrate, a precipitate of silver cyanide. The result recorded above was obtained by the Carius method.

Eseroline methiodide is readily soluble in alcohol, but only sparingly so in chloroform and acetone. The quaternary ammonium base produced from it by the addition of alkalis is very unstable, being readily oxidised in the presence of air with the formation of a deep red solution. On account of this property it was found impractical to obtain information regarding its structure by means of Hofmann's method for the degradation of quaternary ammonium bases.

The Oxidation Products of Physostigmine and Eseroline.

As a preliminary experiment the amounts of oxygen absorbed by both physostigmine and eseroline were quantitatively determined by the following method: A quantity of oxygen was collected in a graduated burette over an aqueous solution of sodium hydroxide, and the volume, temperature, and pressure of the gas observed. The base to be examined (about 0·05 gram) was then introduced in a small glass capsule, the burette tightly corked, and the contents were agitated vigorously. By opening the burette from time to time under an aqueous solution of sodium hydroxide, the decrease in volume of the oxygen could be determined. The agitation of the mixture was continued until no further appreciable decrease in volume at constant temperature and pressure took place. The results of a number of concordant determinations obtained by this method are embodied in the following table:

	Atoms of oxygen absorbed per molecule.	
Time.	Physostigmine.	Eseroline.
10 minutes	—	1·37
1 hour	1·19	3·80
2 hours	2·46	4·41
3 ,,	3·49	4·68
5 ,,	4·51	4·80
7 ,,	4·70	4·98
20 ,,	5·03	5·02

When physostigmine and eseroline were oxidised in the manner described above, the alkaline solution immediately became red at the commencement of the oxidation, and the intensity of this colour continued to increase until approximately 2 atoms of oxygen had been absorbed. The colour then gradually changed from red to brown, and after 5 atoms of oxygen had been absorbed, became brownish-yellow. No trace of eserine blue was formed by this method of oxidation.

Preparation and Properties of Rubreserine.

It would appear from the above results that the preparation of rubreserine would be best effected by arresting the oxidation of eseroline after two atoms of oxygen had been absorbed. In order to achieve this object, 30 c.c. of a 1 per cent. solution of potassium hydroxide were introduced in a flask full of oxygen, and the latter connected with a small oxygen gasometer, by means of which any absorption of gas could be measured. A weighed quantity of eseroline (1 gram at each oxidation) was then quickly added, and the contents of the flask vigorously shaken. After the requisite volume of oxygen had been absorbed as indicated by the gasometer, sulphuric acid was added in an amount just sufficient to neutralise the potassium hydroxide, and the mixture then thoroughly extracted with chloroform. The chloroform solution was washed with a little water, dried, and the solvent removed, when a deep red residue, which rapidly solidified, was obtained. The substance was purified by crystallisation, first from a mixture of petroleum and chloroform, and finally from water:

0·0932 lost 0·0067 H_2O. $H_2O = 7·2$.

$C_{13}H_{16}O_2N_2,H_2O$ requires $H_2O = 7·2$ per cent.

0·0865 gave 0·2142 CO_2 and 0·0560 H_2O. $C = 67·5$; $H = 7·2$.

0·0631 „ 6·8 c.c. N_2 at 24° and 750 mm. $N = 12·1$.

$C_{13}H_{16}O_2N_2$ requires $C = 67·2$; $H = 6·9$; $N = 12·1$ per cent.

The molecular weight of rubreserine was determined* by Barger's microscopic method, which gave the following result:

0·0648 in 0·8422 alcohol was between 0·275 mol. and 0·300 mol.

Mean M.W. = 268. $C_{13}H_{16}O_2N_2$ requires M.W. = 232.

These results confirm the formula originally assigned to rubreserine by Ehrenberg.

Rubreserine crystallises from water in deep red needles, containing 1 molecule of water of crystallisation. It is stated by Eber (*Pharm. Zeit.*, 1888, **33**, 611) to melt at 138°, but the present author has not been able to confirm this melting point. The air-dried substance was found to melt indefinitely at 113—125°, but when the water of crystallisation was removed in a vacuum desiccator over potassium hydroxide the substance then melted at 152°. Rubreserine is insoluble in light petroleum or ether, but readily soluble in water, alcohol, or chloroform, giving blood-red solutions. It is moderately soluble in hot benzene, and crystallises from this solvent in red needles, which melt at 100° and contain

* The author wishes to express his thanks to Mr. A. J. Ewins, who has kindly conducted this determination.

benzene of crystallisation. It dissolves in concentrated sulphuric acid with a yellow colour, which becomes red on the addition of water. The aqueous solution of rubreserine is readily decolorised by reducing agents such as hydrogen sulphide, but the red colour reappears on removing the latter by a current of air. When anhydrous rubreserine is heated for a few hours at 115°, the colour changes from red to brown, and finally becomes quite black without alteration in weight. The product does not melt below 300°, and is undoubtedly a polymerised form of rubreserine. Rubreserine is neutral in reaction towards litmus, but it possesses both basic and acidic properties. Its basic properties were proved by the formation of a hydrochloride, picrate, and aurichloride respectively.

Rubreserine Hydrochloride.—This substance was prepared by passing dry hydrogen chloride into a solution of rubreserine in ethyl acetate containing a little alcohol. A dull red, crystalline precipitate was thus obtained, which melted and decomposed at 185°:

0·0992, heated at 110°, lost 0·0070 H_2O. $H_2O = 7·1$.

$C_{13}H_{17}O_2N_2Cl,H_2O$ requires $H_2O = 6·3$ per cent.

0·0912 * gave 0·1942 CO_2 and 0·0558 H_2O. $C = 58·1$; $H = 6·8$.

$C_{13}H_{17}O_2N_2Cl$ requires $C = 58·1$; $H = 6·3$ per cent.

Rubreserine picrate crystallises from dilute alcohol in brick-red leaflets, which begin to change at 186°, and completely decompose at 198°.

Rubreserine Aurichloride.—This substance separates from a solution of rubreserine in hydrochloric acid, to which gold chloride had been added, in bright red needles, which decompose at 190—195°:

0·1710 gave 0·1705 CO_2, 0·0442 H_2O, and 0·0595 Au. $C = 27·2$; $H = 2·9$; $Au = 34·8$.

$C_{13}H_{17}O_2N_2,AuCl_4$ requires $C = 27·3$; $H = 3·0$; $Au = 34·4$ per cent.

It is evident from the examination of the above salts that rubreserine, like physostigmine and eseroline, contains only one basic nitrogen atom.

The acidic properties of rubreserine were indicated by the formation of a silver salt; thus, when silver nitrate was added to an aqueous solution of rubreserine, the silver salt of rubreserine nitrate separated in dull red needles, which possess a bronze-like lustre:

0·0819 gave 0·1170 CO_2, 0·0316 H_2O, and 0·0221 Ag. $C = 39·0$; $H = 4·3$; $Ag = 27·0$.

$C_{13}H_{16}O_2N_2,AgNO_3$ requires $C = 38·8$; $H = 4·0$; $Ag = 26·9$ per cent.

Further evidence of the acidic character of rubreserine was

* Anhydrous substance.

afforded by its behaviour towards diazomethane. An ethereal solution of this reagent rapidly changed rubreserine dissolved in a little alcohol from red to yellow with evolution of nitrogen. From the reaction mixture, however, only a very small quantity of a homogeneous substance could be isolated. This was a base obtained in the form of a hydrochloride, which crystallised in stellar clusters of colourless needles decomposing at 185°. It is evident from the method of preparation of this compound that it is the hydrochloride of a methyl derivative of rubreserine, but the yield was too small for further examination.

Rubreserine is unstable in the presence of alkali hydroxides; when agitated with sodium hydroxide in the presence of air or oxygen the red colour of the rubreserine is changed first to brown and then to brownish-yellow. In this reaction a mixture of products is formed, from which no definite substance could be separated. It is evident, therefore, that the so-called eserine brown is not a homogeneous compound.

Isolation of Eserine Blue, $C_{17}H_{23}O_2N_3$.

In the course of the preliminary experiments on the oxidation of physostigmine it was observed that the blue coloration was only produced when oxidation proceeded slowly with a limited supply of air or oxygen. In view of this fact, the method adopted for the preparation of the blue compound was as follows: A quantity of physostigmine (1 gram) dissolved in a little alcohol was added to an aqueous solution of barium hydroxide in a small flask, so that the latter contained about three parts of liquid to one part of air. The flask was then closed, and kept for some time. The oxygen in the flask was soon absorbed, and the solution became red with the formation of rubreserine, but after keeping a few hours the red colour changed to green and then to blue, when more air was admitted and the vessel again closed. The mixture was thus supplied at intervals with oxygen, care being taken, however, that the solution never became red by too rapid oxidation. This process was continued for several days until a test portion, when freely exposed to the air, did not change its blue colour. The blue solutions obtained from several such oxidations were united and thoroughly extracted with chloroform. The chloroform extract, which was intensely blue, was washed with a little water, and then agitated with successive small portions of $N/10$-hydrochloric acid until the solution became acid to litmus.* The first few extracts

* The chloroform solution remaining after this treatment contained a small quantity of rubreserine.

were deep blue by transmitted light, but purple-red by reflected light; from these no pure substance could be isolated, and they evidently contained a mixture of bases. The final extracts, however, were deep blue, both by transmitted and reflected light. They were united, then evaporated to dryness under diminished pressure, and the residue dissolved in a little hot alcohol, when, on cooling, a crystalline hydrochloride separated in deep blue needles. The yield of this compound was equivalent to about 8 per cent. of the physostigmine employed in the reaction:

0·0708 gave 0·1419 CO_2 and 0·0465 H_2O. C = 54·7; H = 7·3.
0·0913 „ 8·7 N_2 at 18° and 764 mm. N = 11·2.
0·0888 „ 0·0686 AgCl. Cl = 19·1.

Another preparation of the blue hydrochloride gave the following numbers:

0·1120 gave 0·2247 CO_2 and 0·0694 H_2O. C = 54·7; H = 6·9.
$C_{17}H_{25}O_2N_3Cl_2$ requires C = 54·5; H = 6·7; N = 11·2; Cl = 19·1 per cent.

The free base corresponding with this hydrochloride was prepared by treating the latter with dilute sodium hydroxide, and extracting the alkaline liquid with chloroform. On the addition of light petroleum to the dry chloroform solution the base separated as a dark blue powder, which was not obtained in the crystalline condition:

0·0310 gave 0·0766 CO_2 and 0·0222 H_2O. C = 67·4; H = 8·0.
$C_{17}H_{23}O_2N_3$ requires C = 67·8; H = 7·6 per cent.

An attempt was made to determine the molecular weight of the above base by the microscopic method, but owing to the intensity of the blue colour a satisfactory determination was not possible. It is evident, however, from the above analyses, that the simplest formula for the compound is $C_{17}H_{23}O_2N_3$.

Eserine blue is a dark blue powder, which is readily soluble in water, chloroform, or alcohol with the formation of intensely blue solutions. When the aqueous solution is heated with alkali hydroxides, an insoluble black powder separates. Eserine blue is a strong base, which forms salts with two equivalents of an acid.

The *hydrochloride*, $C_{17}H_{23}O_2N_3,2HCl$, prepared as described above, crystallises in blue needles, which by reflected light have a bronze-like lustre. It is readily soluble in water, yielding a deep blue solution, but on the addition of a little acid a beautiful carmine-red fluorescence is produced.

The *aurichloride* was prepared by the addition of gold chloride to a solution of the base in hydrochloric acid. The violet precipitate thus obtained crystallised from hot alcohol containing a little

hydrochloric acid in minute, violet prisms, which began to decompose at 165°:

0·1671 gave 0·0666 Au. Au = 39·9.

$C_{17}H_{25}O_2N_3(AuCl_4)_2$ requires Au = 40·2 per cent.

Eserine blue can also be prepared by the slow oxidation of eseroline in the presence of alkalis, but it does not appear to be formed when pure rubreserine is oxidised. In view of these facts it seems probable that the formation of eserine blue is due to the condensation of eseroline with a degradation product of this base. An attempt was therefore made to obtain from physostigmine products having a carbon content lower than that of eseroline and rubreserine, but although experiments were conducted with various oxidising agents under diverse conditions, no definite compound was obtained.

Formation of Indole Derivatives from Physostigmine.

Fifteen grams of physostigmine were intimately mixed with ten times its weight of zinc dust, and the mixture strongly heated, in convenient portions, in a combustion tube in a current of hydrogen. The products of the distillation were first conducted over red-hot pumice, which had been impregnated with zinc dust, and then condensed in a receiver immersed in a freezing mixture, when a quantity of an ammoniacal liquid, together with a brown, viscid, oily substance, collected in the receiver. The oily substance was separated from the ammoniacal liquid, and then distilled in a current of steam. A pale yellow, volatile oil passed over in the steam distillate, whilst a small amount of a non-volatile, brown, resinous substance remained in the flask. The volatile oil was dissolved in ether, the ethereal solution washed with a little dilute hydrochloric acid, then dried, and the solvent removed. The yellow oil thus obtained amounted to 5—10 per cent. of the physostigmine employed in the distillation. It possessed the characteristic odour of indole compounds, and yielded a cherry-red coloration with a pine shaving which had been moistened with hydrochloric acid. It was insoluble in dilute acids, but dissolved in concentrated hydrochloric acid with the formation of a yellow solution, from which a resinous substance separated on heating. It gave a red coloration with sodium nitrite and glacial acetic acid, whilst with a trace of bromine water an evanescent, blue coloration was produced. The boiling point of the compound was determined by Schleiermacher's method (*Ber.*, 1891, **24**, 944) applicable to small quantities of substance, and found to be 268°. The substance after

redistillation was analysed. (Found, C=82·0; H=7·3; N=10·5. C_9H_9N requires C=82·4; H=6·9; N=10·7 per cent.)

The above analyses and the properties of the substance indicate that it is a methyl derivative of indole. It is not identical with 3-methylindole, $C_6H_4\langle^{CMe}_{NH}\rangle CH$, since the latter dissolves in concentrated hydrochloric acid with a violet colour. The properties of the substance, as described above, are identical with those of 2-methylindole, $C_6H_4\langle^{CH}_{NH}\rangle CMe$. The latter compound, however, melts at 59°, whilst the above product did not solidify in the cold. This behaviour was found to be due to the presence of the isomeric 1-methylindole, since on heating the substance with hydriodic acid at 200—300° methyl iodide was liberated. The amount of 1-methylindole was ascertained by a quantitative determination of the methylimido-group, when the result indicated the presence of 15 per cent. of this compound. It is evident, therefore, that physostigmine, when distilled with zinc dust, yields 2-methylindole with a small quantity of 1-methylindole.

The ammoniacal bases formed in the distillation were carefully examined, and found to consist almost entirely of ammonia. Petit and Polonowsky (*loc. cit.*) state to have obtained a phenolic substance, melting at 108°, by the distillation of physostigmine with zinc dust, but no trace of this compound could be isolated in the above experiment.

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RESEARCHES
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PART II

BY

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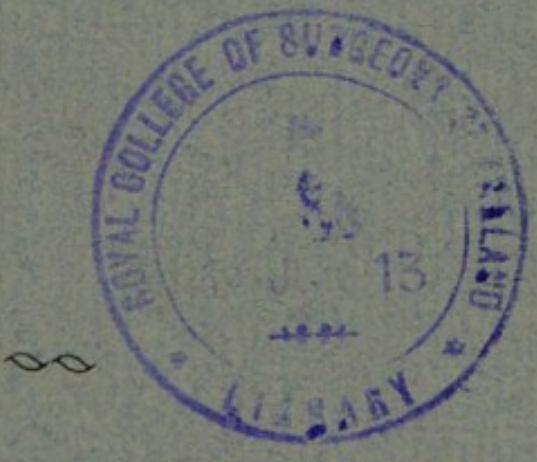

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XLIII.—*Researches on the Constitution of Physostigmine. Part II. The Synthesis of 3-Dimethylaminoacetyl-2-methylindole and 2-α-Dimethylamino-γ-hydroxypropylindole.*

By Arthur Henry Salway.

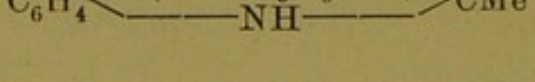
Previous investigations on the constitution of physostigmine (eserine), $C_{15}H_{21}O_2N_3$, have shown that the principal degradation product of the alkaloid is eseroline, $C_{13}H_{18}ON_2$, this substance being derived from the parent compound by alkaline hydrolysis with

elimination of carbon dioxide and methylamine, according to the equation:

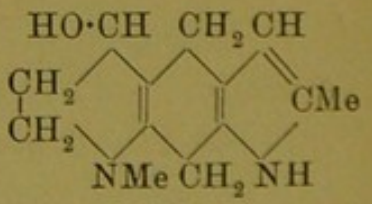
$$C_{13}H_{17}ON_2\cdot CO\cdot NHMe + H_2O = C_{13}H_{18}ON_2 + CO_2 + NH_2Me.$$

The solution of the problem of the constitution of physostigmine thus depends on the determination of the constitution of eseroline. The investigation of the latter was recently undertaken by the present author (T., 1912, **101**, 978), who showed that this substance is in all probability an indole derivative, since it yields 2-methylindole when distilled with zinc dust in a current of hydrogen. Moreover, it was also shown that eseroline is a tertiary monacid base containing a methyl group attached to nitrogen, that it possesses weakly acid properties, and that it rapidly absorbs oxygen in the presence of alkalis with the formation of rubreserine, eserine-blue, and other oxidation products. Whilst this knowledge concerning the properties of eseroline and its degradation products is insufficient to enable the author to propose a constitution for the alkaloid with a reasonable degree of certainty, it nevertheless seemed desirable for the purpose of the present investigation to construct a hypothetical formula which would serve as a basis for some synthetical experiments.

In the construction of such a formula it is evident that the methylindole complex, which eseroline presumably contains, will account for the group of atoms C_9H_9N, the nitrogen atom of which will correspond with the non-basic nitrogen atom of eseroline. The remaining part of the molecule, C_4H_9ON, will contain a tertiary basic nitrogen atom attached to a methyl group, and also, in all probability, a hydroxyl group,* and may therefore be further resolved into the group $C_3H_5(OH)(NMe)$. The nature of the union between the indole complex and the group $C_3H_5(OH)(NMe)$ now remains to be considered. In the first place, the latter might be in combination with the indole nucleus as an aliphatic side-chain, in which case eseroline would be represented by a formula of the type I:



(I.)



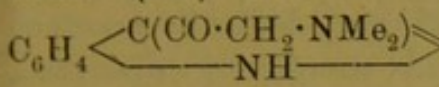
(II.)

On the other hand, there exists the possibility that the group, $C_3H_5(OH)(NMe)$, forms a closed chain with the indolic part of the molecule. In this case the simplest formula which can be con-

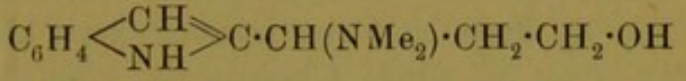
* The presence of a hydroxyl group in eseroline is probable, but has not been established beyond question.

structed in agreement with the known properties of eseroline is of the type II.

The author has now undertaken the synthesis of compounds belonging to the types I and II in the hope of obtaining more definite knowledge regarding the constitution of eseroline. In the present investigation two derivatives of indole containing a basic and oxygenated side-chain, namely, *3-dimethylaminoacetyl-2-methylindole* (III) and *2-α-dimethylamino-γ-hydroxypropylindole* (IV),



(III.)



(IV.)

have been prepared, and their properties compared with those of eseroline. It has been found that these synthetic compounds possess properties which differ greatly from those of eseroline, and it may therefore be concluded that the latter is not a simple substituted indole of the type represented by formula I.

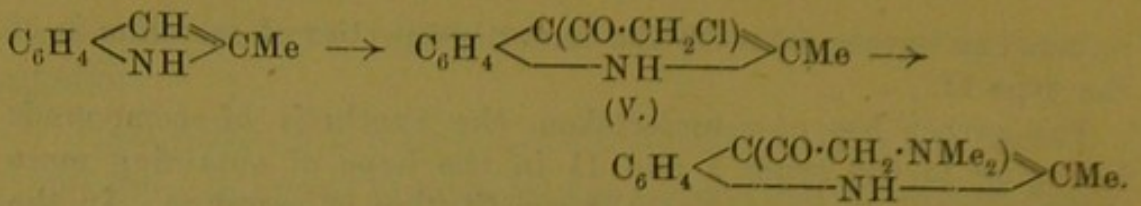
It is proposed in subsequent investigations to attempt the synthesis of compounds of the kind represented by formula II.

A number of general methods are known for the synthesis of substituted indoles, but whilst a few of these can be applied with good results in the preparation of the simpler indole derivatives, none of them appears to be of much service in the preparation of indoles with an extended side-chain. Recently, however, Oddo (*Gazzetta*, 1911, **41**, i, 234) has indicated the possibility of preparing indoles, substituted in the 3-position, by the aid of the Grignard reaction, whilst Madelung (*Ber.*, 1912, **45**, 1128, 3541) has found that *o*-toluidides may be converted into substituted indoles by heating with sodium ethoxide at a high temperature. These methods have now been used by the author for the preparation of the indole compounds described in the present investigation.

Experimental.

I.—*Synthesis of 3-Dimethylaminoacetyl-2-methylindole* (III).

Oddo has shown (*loc. cit.*) that indole reacts with magnesium methyl iodide with the formation of magnesium indolyl iodide, which by subsequent treatment with acetyl chloride yields 3-acetylindole. In the present experiments a similar process has been employed for the conversion of 2-methylindole into 3-chloroacetyl-2-methylindole, which then yielded 3-dimethylaminoacetyl-2-methylindole on treatment with dimethylamine. These changes are represented in the following scheme:



3-Chloroacetyl-2-methylindole (V).

For the preparation of this compound two parts of magnesium powder were mixed with nine parts of ethyl bromide in the presence of dry ether. After the magnesium had completely dissolved, eleven parts of 2-methylindole, dissolved in dry ether, were added drop by drop, and the mixture kept at the ordinary temperature for about an hour. Chloroacetyl chloride (nine parts), dissolved in ether, was then slowly added in the cold. At first the addition of the latter caused the precipitation of a viscid, yellow solid, which finally became cherry-red. After all the chloroacetyl chloride had been added, the upper layer of ethereal liquid was decanted, and the viscid solid which remained was agitated vigorously with an aqueous solution of sodium hydrogen carbonate, when an almost colourless solid, insoluble in the alkaline liquid, was obtained. This was collected, dried, and crystallised several times from ethyl acetate, from which it was deposited in slender, colourless needles, melting at 220°:

0·0830 gave 0·1946 CO_2 and 0·0380 H_2O. C = 63·9; H = 5·1.

0·1286 „ 0·0876 AgCl. Cl = 16·9.

$C_{11}H_{10}ONCl$ requires C = 63·6; H = 4·8; Cl = 17·1 per cent.

3-Chloroacetyl-2-methylindole is sparingly soluble in ether, benzene, or chloroform, but more readily so in alcohol or ethyl acetate. Its chlorine atom is very reactive, being quickly removed when heated with alkalis, and also to some extent when heated with alcohol.

In one experiment for the preparation of the above compound magnesium methyl iodide was employed in the place of magnesium ethyl bromide with a somewhat unexpected result. The product of the reaction in this case was a mixture of two compounds in approximately equal proportions. One of these compounds was the desired 3-chloroacetyl-2-methylindole melting at 220°, whilst the other melted at 197°, and did not contain chlorine. The latter substance on analysis gave the following figures:

0·1075 gave 0·3011 CO_2 and 0·0642 H_2O. C = 76·4; H = 6·6.

$C_{11}H_{11}ON$ requires C = 76·3; H = 6·4 per cent.

It appeared probable from this result that the compound melting at 197° possessed the constitution $C_6H_4\langle^{CAc}_{NH}\rangle CMe$, and had been

formed in the above reaction by the reducing action of the liberated hydriodic acid on the 3-chloroacetyl-2-methylindole. If this supposition regarding the constitution of the compound melting at 197° were correct, then the same substance should be obtained by the action of acetyl chloride on magnesium 2-methylindolyl iodide. This experiment, conducted in a manner similar to that employed in the preparation of 3-chloroacetyl-2-methylindole, yielded a product identical with the above-mentioned substance melting at 197°. The latter is therefore 3-acetyl-2-methylindole.

3-*Acetyl-2-methylindole* is moderately soluble in chloroform or alcohol, but only sparingly so in benzene or ether. It crystallises from hot alcohol in slender, colourless needles, and from chloroform in thin, colourless plates, melting at 197°. It does not give the pine-shaving colour reaction of indole. It yields an *oxime*, which crystallises from dilute alcohol in glistening leaflets, melting and decomposing at 199°:

0·0972 gave 0·2502 CO_2 and 0·0568 H_2O. C = 70·2; H = 6·5.

$C_{11}H_{12}ON_2$ requires C = 70·2; H = 6·4 per cent.

3-*Dimethylaminoacetyl-2-methylindole* (III).

A quantity of 3-chloroacetyl-2-methylindole was heated for four hours at 100° in a sealed tube with an excess of dimethylamine dissolved in alcohol. The solvent and the excess of dimethylamine were first removed in a current of steam, and the mixture then acidified with dilute hydrochloric acid, when a quantity of non-basic material remained undissolved, the latter being collected and set aside for subsequent examination. The acid liquid was now made alkaline with sodium carbonate, and the precipitated base collected, washed with water, and purified by crystallisation from alcohol. It was obtained in colourless, rhombohedral prisms, which melted at 201°. The yield of pure substance amounted to 62 per cent. of the theoretical:

0·0958 gave 0·2540 CO_2 and 0·0640 H_2O. C = 72·3; H = 7·4.

$C_{13}H_{16}ON_2$ requires C = 72·2; H = 7·4 per cent.

The non-basic by-product in the above reaction was very sparingly soluble in the usual organic solvents. It was crystallised, however, from much hot acetic acid, and then obtained in small, colourless, square prisms, which melted and decomposed at 270°:

0·1304 gave 0·3243 CO_2 and 0·0760 H_2O. C = 67·8; H = 6·5.

0·1980 „ 0·0640 AgCl. Cl = 8·0.

0·1718 „ 14·4 c.c. N_2 at 12° and 775 mm. N = 10·2.

$C_{24}H_{25}O_2N_3Cl$ requires C = 68·0; H = 6·1; N = 9·9; Cl = 8·4 per cent.

It appears from these results and the properties of the compound

that the latter is a quaternary ammonium salt formed by the union of one molecule of 3-dimethylaminoacetyl-2-methylindole and one of 3-chloroacetyl-2-methylindole, and therefore has the constitution:

$$\left(C_6H_4\!<\!\begin{matrix}C(CO\cdot CH_2\cdot)\\ NH\end{matrix}\!>\!CMe\right)_2NMe_2Cl.$$

3-*Dimethylaminoacetyl-2-methylindole* is sparingly soluble in ether, chloroform, or benzene, and moderately so in alcohol. It is a stable base, showing no tendency to absorb oxygen in the presence of alkalis. It does not respond to the pine-shaving test for indoles. Its *hydrochloride*, prepared by dissolving the base in dilute hydrochloric acid, evaporating the solution to dryness and crystallising the residue from alcohol, was obtained in colourless, rhombohedral crystals, melting at 258°.

Many attempts were made to reduce the above base in order to obtain from it by the addition of two atoms of hydrogen a substance of the same empirical formula as eseroline, but reduction could not be effected; thus, when the base was heated with tin and hydrochloric acid, or with sodium in amyl alcohol, no change occurred, whilst treatment with hydriodic acid and red phosphorus at 120° caused disruption of the molecule with formation of 2-methylindole.

II.—*Synthesis of 2-α-Dimethylamino-γ-hydroxypropylindole* (IV).

As already indicated, Madelung (*loc. cit.*) has shown that *o*-toluidides may be converted into substituted indole derivatives by heating with sodium ethoxide. Although this reaction has hitherto only been applied to the *o*-toluidides of acetic, benzoic, and oxalic acids, it appeared probable that the method might be extended to the preparation of any indole derivative, $C_6H_4\!<\!\begin{matrix}CH\\ NH\end{matrix}\!>\!CR$, provided that the acid $R\cdot CO_2H$ could be obtained. For the purpose of the present synthesis the radicle R was required to consist of an oxygenated acyl group containing a tertiary basic nitrogen atom, and the corresponding acid, $R\cdot CO_2H$, chosen as best fitted to meet these requirements, was α-dimethylamino-γ-hydroxybutyric acid,

$$HO\cdot CH_2\cdot CH_2\cdot CH(NMe_2)\cdot CO_2H.$$

The steps which were necessary for the preparation of this compound and for its conversion into the desired indole derivative are as follows:

$$CH_2Br\cdot CH_2Br \longrightarrow \underset{\text{(VI.)}}{PhO\cdot CH_2\cdot CH_2Br} \longrightarrow \underset{\text{(VII.)}}{PhO\cdot CH_2\cdot CH_2\cdot CH(CO_2H)_2}$$

$$\longrightarrow \underset{\text{(VIII.)}}{PhO\cdot CH_2\cdot CH_2\cdot CBr(CO_2H)_2} \longrightarrow \underset{\text{(IX.)}}{PhO\cdot CH_2\cdot CH_2\cdot CHBr\cdot CO_2H} \longrightarrow$$

$$\underset{\text{(X.)}}{PhO\cdot CH_2\cdot CH_2\cdot CH(NMe_2)\cdot CO_2H} \text{ and}$$

$$PhO\cdot CH_2\cdot CH_2\cdot CHBr\cdot CO\cdot NH\cdot C_6H_4Me \longrightarrow$$
(XI.)
$$PhO\cdot CH_2\cdot CH_2\cdot CH(NMe_2)\cdot CO\cdot NH\cdot C_6H_4Me \longrightarrow$$
(XII.)
$$PhO\cdot CH_2\cdot CH_2\cdot CH(NMe_2)\cdot C\begin{matrix}CH\\ \diagup\!\!\diagdown\\ NH\end{matrix}>C_6H_4 \longrightarrow$$
(XIII.)
$$HO\cdot CH_2\cdot CH_2\cdot CH(NMe_2)\cdot C\begin{matrix}CH\\ \diagup\!\!\diagdown\\ NH\end{matrix}>C_6H_4$$
(XIV.)

The compounds represented by the formulæ (VI) and (VII) in the above scheme have already been described by Perkin, Bentley, and Haworth (T., 1896, **69**, 169), whilst the compounds (VIII) and (IX) have been synthesised by Fischer (*Ber.*, 1907, **40**, 106).

α-Dimethylamino-γ-phenoxybutyric Acid (X).

For the preparation of this compound one part of α-bromo-γ-phenoxybutyric acid, obtained from ethylene dibromide as described by the above-mentioned investigators (*loc. cit.*), was heated in a sealed tube for six hours at 100° with two parts of an aqueous solution (33 per cent.) of dimethylamine. The product was then distilled in a current of steam with a known amount of sodium hydroxide until the excess of dimethylamine had been removed. A quantity of hydrobromic acid equivalent in amount to the sodium hydroxide employed was then added, and the liquid concentrated to dryness under diminished pressure. The residue was then digested with absolute alcohol, the alcoholic liquid filtered to remove the sodium bromide, and the filtrate evaporated. The amino-acid was thus obtained as a viscid oil, which did not crystallise on keeping. When agitated with a little aqueous hydrobromic acid, however, it immediately solidified, with the formation of a crystalline hydrobromide. This was purified by recrystallisation from water, and was then obtained in colourless, thin plates, melting at 86°:

0·1183 (air-dried), heated at 110°, lost 0·0124 H_2O. $H_2O = 10·5$.
0·1445 „ gave 0·0784 AgBr. Br = 23·1.

$C_{12}H_{18}O_3NBr,2H_2O$ requires $H_2O = 10·6$; Br = 23·5 per cent.

0·1059 * gave 0·1824 CO_2 and 0·0562 H_2O. C = 47·0; H = 5·9.

$C_{12}H_{18}O_3NBr$ requires C = 47·4; H = 5·9 per cent.

In order to obtain the free base, the above-described hydrobromide was dissolved in water, and an amount of sodium carbonate added just sufficient to combine with the hydrobromic acid. The mixture was then evaporated to dryness under diminished pressure,

* Anhydrous substance.

and the amino-acid extracted from the residue by means of absolute alcohol. After evaporating the alcoholic extract, the amino-acid was obtained as a very hygroscopic, amorphous solid, which could not be obtained crystalline.

α-Dimethylamino-γ-phenoxybutyric acid (X) is readily soluble in alcohol or water, insoluble in ether, benzene, or chloroform. It yields a *hydrochloride*, which crystallises from water in prismatic needles melting at 83°. The *methyl* ester of the latter,

$$PhO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Me){\cdot}NMe_2,HCl,$$

crystallises from hot ethyl acetate in colourless aggregates of flat plates, which melt at 130°:

0·1000 gave 0·2086 CO_2 and 0·0666 H_2O. C = 56·9; H = 7·4.

$C_{13}H_{19}O_3N,HCl$ requires C = 57·0; H = 7·3 per cent.

For the next stage in the synthesis it was necessary to prepare the *o*-toluidide of the above-described amino-acid (XII). Attempts were first made to obtain this compound from the acid chloride, $PhO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(NMe_2){\cdot}COCl$, but the latter could not be prepared. Ultimately the difficulty was overcome by first preparing the *o*-toluidide of α-bromo-γ-phenoxybutyric acid (XI), and subsequently displacing the bromine in this compound by the dimethylamino-group.

α-Bromo-γ-phenoxybutyro-o-toluidide (XI).

Seven parts of α-bromo-γ-phenoxybutyric acid were dissolved in ether, and six parts of phosphorus pentachloride added. After the reaction had subsided, the ether, together with the phosphoryl chloride which had been formed, was removed on the water-bath under diminished pressure, and the residual crude acid chloride then added to an excess of *o*-toluidine dissolved in ether. A voluminous precipitate of the *o*-toluidide was thus formed, which was collected, washed with water, and recrystallised from hot alcohol, when it separated in colourless, prismatic needles, melting at 147°:

0·1000 gave 0·2145 CO_2 and 0·0478 H_2O. C = 58·5; H = 5·3.

$C_{17}H_{18}O_2NBr$ requires C = 58·6; H = 5·2 per cent.

α-Bromo-γ-phenoxybutyro-o-toluidide is only moderately soluble in ether, but more readily so in chloroform, ethyl acetate, or alcohol.

α-Dimethylamino-γ-phenoxybutyro-o-toluidide (XII).

This substance was prepared by heating the foregoing compound in a sealed tube at 100° for two hours with an excess of dimethylamine dissolved in alcohol. The alcohol and excess of dimethylamine were then removed in a current of steam, when the required

base was precipitated as a colourless oil. This was dissolved in ether, the ethereal solution dried, and the solvent removed. The residual oil slowly solidified, and was then purified by crystallisation from light petroleum, when it separated in radiating clusters of colourless, prismatic needles, melting at 54°:

0·1265 gave 0·3376 CO_2 and 0·0898 H_2O. C = 72·8; H = 7·9.

$C_{19}H_{24}O_2N_2$ requires C = 73·1; H = 7·7 per cent.

α-Dimethylamino-γ-phenoxybutyro-o-toluidide is very readily soluble in the usual organic solvents, and can only be crystallised with difficulty. It is a weak base, forming salts which are acid towards litmus, and also possess an extremely bitter taste. The *hydrochloride*, prepared by passing a current of dry hydrogen chloride into an ethereal solution of the base, crystallises from a mixture of alcohol and ethyl acetate in slender, colourless needles, melting at 169°:

0·1010 gave 0·2410 CO_2 and 0·0646 H_2O. C = 65·1; H = 7·1.

$C_{19}H_{24}O_2N_2$,HCl requires C = 65·4; H = 7·2 per cent.

The *platinichloride* of the above base crystallises from alcohol, containing a little hydrochloric acid, in small, brown prisms, melting at 215°.

2-α-*Dimethylamino-γ-hydroxypropylindole.*

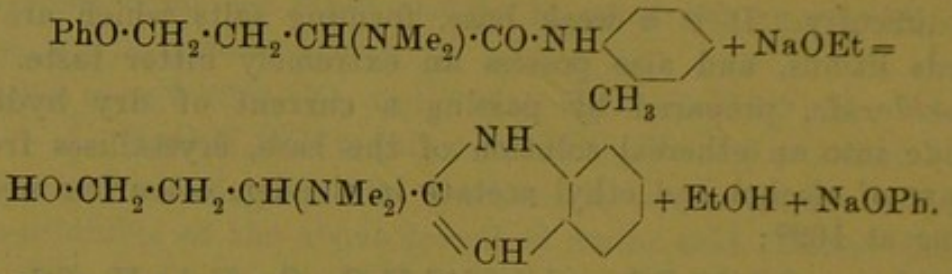
In order to prepare this compound 0·3 gram of sodium was dissolved in absolute alcohol in a capacious flask, and the alcohol removed under diminished pressure; to the sodium ethoxide thus obtained, 2 grams of α-dimethylamino-γ-phenoxybutyro-*o*-toluidide were added, and the mixture heated in a metal bath to a temperature of 250—300° in a current of hydrogen. At this temperature reaction took place with effervescence and a considerable darkening in colour, and the process was soon complete. The entire operation was repeated four times with the same quantities of material, and the products from the several reactions were then united and acidified with dilute hydrochloric acid. The acid liquid was next shaken with ether, which removed a considerable quantity of phenol, identified by means of its tribromo-derivative, then made alkaline with sodium carbonate, and the mixture repeatedly extracted with chloroform. The chloroform extracts were washed, dried, and the solvent removed, when an oily, basic residue was obtained, which did not crystallise on keeping. For its purification it was dissolved in dilute hydrochloric acid, the solution evaporated to dryness under diminished pressure, and the solid residue thus obtained crystallised from a mixture of alcohol and ethyl acetate. The hydrochloride of the base then separated in colourless, prismatic

needles, melting at 218°. The amount of pure hydrochloride obtained from 10 grams of the *o*-toluidide was 3·3 grams:

0·0962 gave 0·2166 CO_2 and 0·0646 H_2O. C = 61·4; H = 7·5.

$C_{13}H_{18}ON_2$,HCl requires C = 61·3; H = 7·5 per cent.

It is evident from this result that the sodium ethoxide in the above reaction has not only effected the expected indolic condensation, but has also simultaneously removed the phenyl group with the formation of 2-α-dimethylamino-γ-hydroxypropylindole, as represented by the following equation:



2-α-Dimethylamino-γ-hydroxypropylindole.—The pure base was prepared from the above-described hydrochloride by treating the latter with aqueous sodium carbonate, and extracting the alkaline liquid with chloroform; after the removal of the chloroform, the base was obtained as a colourless, volatile oil, which did not solidify in a freezing mixture. It was miscible with ether, chloroform, ethyl acetate, alcohol, or water:

0·0910 gave 0·2375 CO_2 and 0·0698 H_2O. C = 71·2; H = 8·5.

$C_{13}H_{18}ON_2$ requires C = 71·6; H = 8·3 per cent.

The *aurichloride* of the above base crystallises from dilute alcohol in yellow prisms, which melt at 133° and are anhydrous:

0·1140 gave 0·1174 CO_2, 0·0353 H_2O, and 0·0400 Au. C = 28·1; H = 3·4; Au = 35·1.

$C_{13}H_{18}ON_2$,$HAuCl_4$ requires C = 28·0; H = 3·4; Au = 35·3 per cent.

The *picrate* crystallises from dilute alcohol in spherical aggregates of bright yellow rhombs, which melt at 140°.

The base, 2-α-dimethylamino-γ-hydroxypropylindole, which has now been synthesised, is isomeric with the alkaloid eseroline. The properties of these two compounds are, however, very dissimilar, as a comparison shows: thus, eseroline in the presence of alkalis readily absorbs oxygen with the production of intensely coloured solutions, whilst the synthetic base is quite stable under similar conditions. Moreover, eseroline readily reduces gold and silver salts, and is also a strong base, which yields neutral salts. The synthetic base, on the other hand, possesses no reducing properties, and is a weak base yielding salts with a strongly acid reaction. The synthetic base, furthermore, differs considerably from eseroline in physiological action, as shown by some experiments kindly conducted by Dr.

H. H. Dale, director of the Wellcome Physiological Research Laboratories, to whom the author here wishes to express his best thanks: thus, on the one hand, eseroline was found to produce the characteristic myotic action of physostigmine (but in a diminished degree) when injected into the eye, and also to effect a slowing of the heart-beat after intravenous injection. The synthetic base, 2-α-dimethylamino-γ-hydroxypropylindole, on the other hand, possessed none of these physiological properties.

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