CXXV.—*The Morphine Group. Part III. The Constitution of Neopine.*

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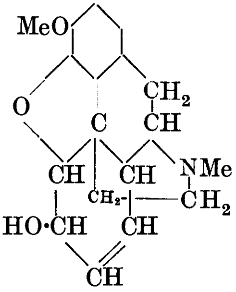
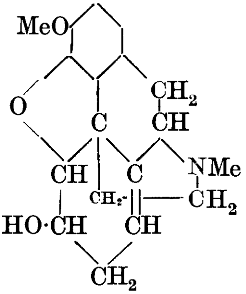
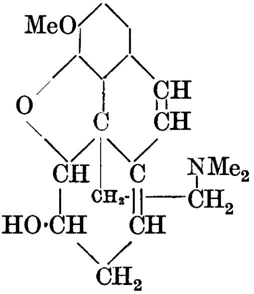
THE rare opium alkaloid which is the subject of this communication was discovered by Messrs. T. and H. Smith of Edinburgh in the final mother-liquors from the isolation of opium alkaloids and separated in the form of its readily crystallisable hydrobromide. Dobbie and Lauder (J., 1911, **99**, 34) investigated this salt and the amorphous base which could be obtained from it and concluded that neopine is a hydroxycodeine. We found that neopine hydrobromide, for a supply of which we are greatly indebted to Messrs. T. and H. Smith, possessed the properties described by Dobbie and Lauder. The analysis, however, gave the formula $C_{18}H_{22}O_3NBr$ instead of $C_{18}H_{22}O_4NBr$ required for a hydroxycodeine hydrobromide. The free base was obtained in a crystalline condition, m. p. 127·5° (corr.), and was found to have the formula $C_{18}H_{21}O_3N$. It appeared to be an isomeride of codeine and this was confirmed by the examination of several derivatives. Moreover, like codeine, neopine contains one methoxyl group, one alcoholic hydroxyl group, and one methyl group attached to nitrogen. The close relation of the base to codeine is brought out in a very clear light by the fact that catalytic hydrogenation of neopine leads to the formation of dihydrocodeine. It will be recalled that the decomposition of codeine methohydroxide leads to the formation of α-methylmorphimethine, which is changed to an isomeric β-methylmorphimethine by means of boiling alcoholic potassium hydroxide. The decomposition of neopine methohydroxide gives at once pure β-methylmorphimethine. Neopine is thus to be regarded as β-codeine; it stands to codeine in the same relationship that β-methylmorphimethine bears to α-methylmorphimethine. In Parts I and II of this series (J., 1923, **123**, 980, 998) Gulland and Robinson suggested a new formula for codeine, but they modified this expression in a subsequent paper * (*Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10), in that they returned to the view that codeine is an unsaturated substance and put forward the formula (I) as the best representation of the constitution of the base. The corresponding expressions for neopine and β-methylmorphimethine (unchanged from Part I) are (II) and (III), respectively.



(I.)



(II.) *Neopine.*



(III.)

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* This paper was read at a meeting of the Manchester Literary and Philosophical Society on February 7th, 1925, and a statement of the proposed change in the morphine formula was given in an abstract in *Nature* (1925, **115**, 625). The memoir could be purchased in a separate form in July, 1925. About the same time, Wieland and Kotake (*Annalen*, 1925, **444**, 69) emphasised the unsaturated nature of codeine and located the double bond in the new position also adopted by Gulland and Robinson. The above particulars are contributed in order to prove that the suggestions of Gulland and Robinson and of Wieland and Kotake were independent and contemporaneous.

The existence of a β-codeine might be anticipated on the basis of many codeine formulæ, but it should be noted that neopine is less readily oxidised by permanganate and also less readily catalytically hydrogenated than codeine. Any hypothesis, therefore, of the relation of codeine to neopine or of α- to β-methylmorphimethine which suggests that codeine has a bridge ring that becomes an ethylene linking in neopine is definitely opposed to the facts. The only possible conclusion that can be drawn from the circumstance that neopine is more stable than codeine towards reagents for the ethylene linking is that the latter contains a double bond which moves, in the transformation of α-methylmorphimethine to the β-isomeride, to a more sheltered position or at least to a position in which it exhibits a smaller degree of reactivity.

EXPERIMENTAL.

Neopine Hydrobromide.—The substance provided by Messrs. T. and H. Smith was anhydrous and remarkably homogeneous. It darkened from about 240°, became very dark at 279°, blackened at 281°, and melted with decomposition at 282—283° (Found: Br, by titration, 21·1. $C_{18}H_{22}O_3NBr$ requires Br, 21·0%). The salt was dried at 100° for 5 hours (Found: Br, 21·1%); it was then recrystallised and dried at 100° for 5 hours (Found: Br, 21·1%). The identity of the material with that examined by Dobbie and Lauder (*loc. cit.*) is evident from the determination of the rotatory power. The salt supplied by Messrs. T. and H. Smith dried at 100° for 5 hours had $[\alpha]_D^{24^\circ}$ + 17·08° in aqueous solution ($c = 5{\cdot}152$). After recrystallisation and drying at 100°, we found $[\alpha]_D^{23^\circ}$ + 17·32° ($c = 3{\cdot}696$). Dobbie and Lauder found $[\alpha]_D^{20^\circ}$ + 17·07° ($c = 5{\cdot}1884$) and $[\alpha]_D^{20^\circ}$ 17·4° ($c = 5{\cdot}0741$).

Neopine.—The hydrobromide was dissolved in water, decomposed by the addition of sufficient concentrated aqueous potassium hydroxide to produce an emulsion (the base is rather readily soluble in water), and the neopine thrice extracted with benzene. The benzene solutions were dried with potassium carbonate and evaporated, leaving a soft varnish. This was dried at about 80° and after some hours a crystal nucleus was noticed. On cooling and scratching, the whole varnish crystallised and the crude product had m. p. 125°. The base is best recrystallised from light petroleum (b. p. 80—100°) and separates in long, glistening, brittle, colourless needles, m. p. 127—127·5° (corr.) (Found in material heated at 80°: C, 72·4; H, 7·1; N, 4·6, 4·7*, 4·7*; MeO, 10·5*, 10·4*; NMe*, 5·2; *M* in camphor, 288. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0; N, 4·7; MeO, 10·4; NMe, 5·0%; *M*, 299).

* By micro-methods.

In aqueous solution ($c = 5{\cdot}1084$) the base is apparently optically inactive (D line at 20°), but on the addition of hydrochloric acid (Neop., HCl in 0·397*N*-HCl) the value $[\alpha]_D^{25^\circ} + 18{\cdot}85^\circ$ was observed. In dry chloroform ($c = 7{\cdot}4740$), we found $[\alpha]_D^{23^\circ} - 28{\cdot}10^\circ$ for the base. With the Froehde and Mandelin reagent, codeine and neopine give yellow colorations changing to blue; this change appears to be slower in the case of neopine. The alkaloid dissolves in water, and a very dilute solution does not immediately decolorise a drop of dilute aqueous potassium permanganate which is added to it. Under similar conditions, codeine rapidly reduces the oxidising agent.

Acetylneopine.—A hydroxycodeine has the same state of oxidation as thebaine, and before we were aware of the true composition of neopine an attempt to degrade it was made under the conditions of the preparation of diacetylthebaol from thebaine, but the result was negative. Neopine (4 g.) was acetylated in 2 hours with boiling acetic anhydride (15 c.c.) in presence of anhydrous sodium acetate (2 g.), and the resulting solution added to water and rendered alkaline by means of sodium carbonate. The base, isolated by means of ether, was obtained as a pale yellow varnish which has not yet been crystallised [Found: $CH_3{\cdot}CO$, 12·7 (by A. G. Perkin's method; J., 1905, **87**, 107). $C_{18}H_{20}O_3N{\cdot}CO{\cdot}CH_3$ requires $CH_3{\cdot}CO$, 12·6%]. Acetylneopine combines very readily with methyl iodide in methyl-alcoholic solution; the product crystallises from methyl alcohol in long, glistening needles which probably contain solvent of crystallisation, since they lose their lustre on heating. *Acetylneopine methiodide* darkens at 250° and has m.p. 256—257° (decomp.; corr.) (Found in material dried at 95—100° to constant weight: C, 52·4; H, 5·5; I, by titration, 26·15. $C_{21}H_{26}O_4NI$ requires C, 52·2; H, 5·4; I, 26·3%).

Catalytic Hydrogenation of Neopine with Formation of Dihydrocodeine.—The reductions were carried out at the ordinary temperature in a vessel filled with hydrogen and provided with a stirrer. Codeine (5 g.) dissolved in water (50 c.c.) and acetic acid (2 c.c.) absorbed in 25 minutes 385 c.c. of hydrogen in presence of colloidal palladium (from 10 c.c. of 0·5% palladous chloride *). This was equivalent to 370 c.c. at *N.T.P.* The volume theoretically required for the saturation of one double bond is 375 c.c. The isolated product had at first m. p. 55° and was dried at 110°. It then melted at 112—113° (corr.) after crystallisation from water containing a few drops of methyl alcohol. This was the highest value that could be obtained. Skita and Frank (*Ber.*, 1911, **44**, 2865) gave the m. p.

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* The solution employed in both reductions contained also 0·5% of gum arabic.

of dihydrocodeine as 65°, whilst Freund (*J. pr. Chem.*, 1920, **101**, 12) gave 86—88°. Oldenburg (D.R.-P. 260,233) also quoted the value 62—63°. Mannich and Löwenheim (*Arch. Pharm.*, 1920, **258**, 304) showed that dihydrocodeine with $2H_2O$ melts at 55° or 88°, whilst the anhydrous substance has m. p. 111—112°. Wieland and Koralek (*Annalen*, 1923, **433**, 269) crystallised the base from 80% methyl alcohol, a process which we cannot repeat, and gave the m. p. 112—114°.

A solution of neopine (2·5 g.) in water (25 c.c.) and acetic acid (1 c.c.) containing colloidal palladium (5 c.c. of 0·5% palladous chloride) was stirred in hydrogen, when the palladium was at once flocculated. More palladous chloride solution (10 c.c.) was added, but flocculation again occurred. In about 15 hours, 180 c.c. of hydrogen were absorbed (equiv. to 176 c.c. at *N.T.P.*; calc., 185 c.c.). The base was rendered to chloroform from the filtered solution and, after removal of the solvent, the residual oil crystallised when inoculated with dihydrocodeine (variety, m. p. 55°). This material melted at 51—53°, but after resolidification it had m. p. 81—84° and after drying at 80° for 1 hour the m. p. was 110—111°. After crystallisation from water containing a few drops of methyl alcohol, the substance dried at 80° had m. p. 112—113° (corr.) (Found: C, 71·5; H, 7·9. Calc. for $C_{18}H_{23}O_3N$: C, 71·7; H, 7·7%). Approximately equal quantities of dihydrocodeine, m. p. 112—113°, and dihydroneopine, m. p. 112—113°, were melted together on a watch glass. The mixture rapidly crystallised on cooling and had m. p. 112—113°.

Conversion of Neopine into β-Methylmorphimethine.—Neopine combined rapidly with methyl sulphate in benzene solution to a *methosulphate*, which separated in a resinous condition. It was very deliquescent and readily soluble in water and on the addition of potassium hydroxide to the solution no precipitation occurred. On boiling, the methine suddenly made its appearance as oily drops, and these crystallised at once even in the hot liquid on the introduction of a crystal of β-methylmorphimethine. We are greatly indebted to Dr. R. S. Cahn for a specimen of pure β-methylmorphimethine. The neopinemethine crystallised from alcohol in large, twinned, rhombohedral prisms, m. p. 135°, and at the same temperature when mixed with β-methylmorphimethine. It dissolved in sulphuric acid to a deep crimson solution, which became royal blue on heating and on dilution with water, green and then yellow with an intense green fluorescence. This reaction is characteristic of β-methylmorphimethine.

Neopinemethine methiodide was prepared from the methine before the latter had been crystallised. The substance crystallised from water in glistening needles, m. p. 291° (decomp.) after darkening from 260° (Found : I, 27·8. Calc., I, 27·9%). Knorr and Smiles (*Ber.*, 1902, **35**, 3010) and Knorr and Hawthorne (*Ber.*, 1902, **35**, 3012) found that β-methylmorphimethine methiodide had $[\alpha]_D^{17^\circ}$ + 233° (c = 0·6) in 97% and 90% alcohol. Solutions of neopinemethine methiodide having a similar concentration crystallised on cooling, but we now know that neopinemethine is β-methylmorphimethine in an exceptionally pure condition. We found that neopinemethine methiodide had $[\alpha]_D^{21^\circ}$ + 241·1° (c = 0·506) in absolute methyl alcohol and $[\alpha]_D^{21^\circ}$ + 262·0° (c = 0·3) in 90% ethyl alcohol.

We desire to thank the Ramsay Memorial Trust for a Fellowship (Netherlands) which enabled one of us to take part in this investigation, and for a similar reason we are also grateful to the Royal Commissioners of the Exhibition of 1851 for a Scholarship.

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