512. *The Structure of* pseudo*Morphine.*

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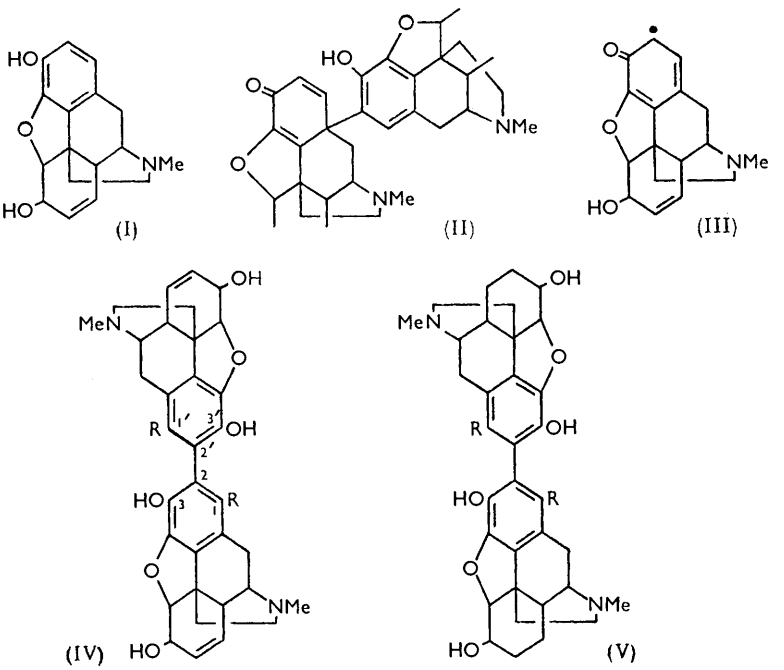
*pseudo*Morphine has been shown to be 2 : 2′-bimorphine. The chemistry and spectral properties of the base and its derivatives are discussed in the light of this finding.

The oxidation of morphine (I; R = H) by a variety of reagents affords *pseudo*morphine [1] which has been shown to be a bimolecular base, though the mode of union of the two morphine molecules has never been satisfactorily determined. The fact that the base gives a tetra-acetate [2] and a monomethyl ether triacetate and tribenzoate [3] indicates that it contains four hydroxyl groups and therefore the oxidative coupling of the two units



through oxygen can be discounted, as can a union of the type (II), or a variant of this; the latter type of union is also ruled out by the fact that the infrared spectrum of *pseudo*morphine shows no carbonyl absorption band. Serious consideration can therefore be given only to a 2 : 2′-union (IV; R = H) resulting from pairing of two radicals of the type (III) or a 1 : 2′-union (V; R = H) arising from the substitution of the radical (III) in the 1-position of the morphine molecule, a view supported by the ultraviolet spectrum of the base (Fig. 1) which shows that aromatic nuclei of the two morphine units are conjugated.

[1] See Bentley, " The Chemistry of the Morphine Alkaloids," The Clarendon Press, Oxford, 1954.
[2] Nadler, *Bull. Soc. chim. France*, 1874, **21**, 326; Danckwort, *Arch. Pharm.*, 1890, **228**, 572.
[3] Vongerichten, *Annalen*, 1896, **294**, 206.

Vongerichten [4] stated that bromomorphine cannot be oxidised to a bimolecular base of the *pseudo*morphine type, and this was held to indicate that *pseudo*morphine is 2 : 2′-bimorphine, as the bromine atom in bromomorphine was at that time believed to occupy position 2; it is now known [5] to occupy position 1, and oxidation of bromomorphine to a bimolecular base should be possible if *pseudo*morphine is 2 : 2′-bimorphine. Indeed, if the oxidation could be accomplished and shown to give a dibromo-bimolecular base this could only have the structure (IV; R = H), whether radical pairing or radical substitution was involved since a 1 : 2′-union could only give a monobromo-bimolecular base by the expulsion of a bromine atom.

We have successfully oxidised 1-bromodihydromorphine with alkaline potassium ferricyanide at 80° and shown that the product is identical with dibromotetrahydro*pseudo*morphine (V; R = Br), prepared by the bromination of tetrahydro*pseudo*morphine [VI;

FIG. 1. FIG. 2.

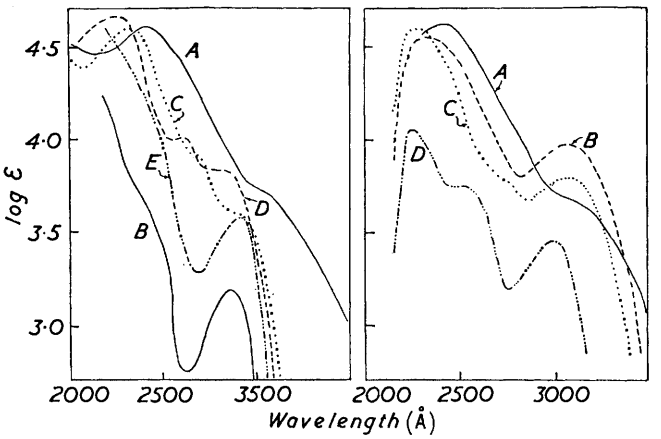


FIG. 1. *Absorption spectra of* (*A*) pseudo*morphine*, (*B*) *morphine*, (*C*) pseudo*morphine dimethyl ether*, (*D*) pseudo*morphine tetra-acetate, and* (*E*) *dibromotetrahydro*pseudo*morphine, all in* MeOH.

FIG. 2. *Absorption spectra of* (*A*) pseudo*morphine in* MeOH, (*B*) pseudo*morphine in* MeOH–KOH, (*C*) *tetrahydro*pseudo*morphine in* MeOH–KOH, *and* (*D*) *morphine in* MeOH–KOH.

R = H)] (obtained by the oxidation of dihydromorphine), the infrared spectra of the two bases in paraffin paste being identical over the range 4000—400 cm.$^{-1}$. Analytical data of both specimens establish the presence of the two bromine atoms. *pseudo*Morphine must therefore be 2 : 2′-bimorphine. The reduced compounds were selected for this investigation to avoid the complications that would arise from the bromination of the double bonds in *pseudo*morphine.

The assignment of the structure (V; R = Br) to dibromotetrahydro*pseudo*morphine is supported by the infrared spectra of this base and related compounds. All the *pseudo*morphine derivatives examined show a band in the region 870—890 cm.$^{-1}$ attributable to the out-of-plane aromatic C–H deformation, except dibromotetrahydro*pseudo*morphine which has no free nuclear position. A second band in the region 1714—694 cm.$^{-1}$ in the spectra of *pseudo*morphine, tetrahydro*pseudo*morphine, and 1-bromomorphine may also be due to aromatic C–H vibrations, and dibromotetrahydro*pseudo*morphine does not absorb in this region.

Earlier workers have failed to prepare a dimethyl ether of *pseudo*morphine and this led to some suspicion that the two phenolic hydroxyl groups differ in some way. This failure may be attributed, on the basis of structure (IV; R = H) for *pseudo*morphine, to strong

[4] Vongerichten, *Annalen*, 1897, **297**, 204.
[5] Small and Turnbull, *J. Amer. Chem. Soc.*, 1937, **59**, 1541.

hydrogen-bonding in the monomethyl ether. We have succeeded in preparing the dimethyl ether by use of nascent diazomethane, a procedure used with success in the *iso*thebaine series [6] where also complete methylation is very difficult.

The apparent difference in properties of the two nitrogen atoms has excited comment; both nitrogen atoms can be quaternised and the conversion of the dimethiodide into the methiodide methohydroxide by aqueous ammonia [3] is probably due only to the relative solubilities of the two substances. Potentiometric and electrometric titrations of the bimolecular derivatives gave only one end-point (quite sharp), presumably indicating that the environments of the two nitrogen atoms are alike.

The ultraviolet spectrum of *pseudo*morphine (Fig. 1) indicates that there is considerable conjugation between the two aromatic nuclei, and thus little restriction of rotation. Absorption occurs at somewhat lower wavelengths for the tetra-acetate and the dimethyl ether (Fig. 1), suggesting greater restriction of rotation in these substances. Introduction

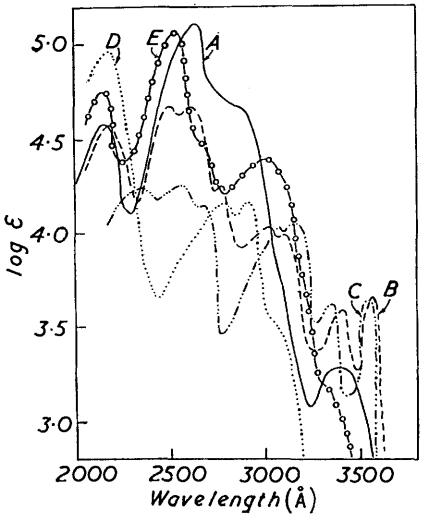


FIG. 3. *Absorption spectra of* (*A*) 3 : 4 : 3′ : 4′-*tetra-acetoxy*-2 : 2′-*biphenanthryl*, (*B*) 9-*ethoxy*-3-*methyl*-*phenanthrene*, (*C*) *methylmorphenol* (4 : 5-*epoxy*-3-*methoxyphenanthrene*), (*E*) 1 : 1′-*dihydroxy*-2 : 2′-*binaphthyl*, *and* (*D*) 2 : 2′-*dihydroxy*-1 : 1′-*binaphthyl*.

of the two bromine atoms in the 2 : 2′-positions of the diphenyl system in dibromotetrahydro*pseudo*morphine (V; R = Br), however, results in almost complete restriction of rotation, and the chromophore reverts to that of the isolated morphine system (Fig. 1). The spectra of *pseudo*morphine and tetrahydro*pseudo*morphine in alkaline solution show an increase in detail over those in neutral or acid media, the shoulder at 3100 Å becoming a distinct band (Fig. 2), indicating some decrease in conjugation of the two aromatic nuclei under such conditions. The product of acetolysis of *pseudo*morphine methiodide methohydroxide, 3 : 4 : 3′ : 4′-tetra-acetoxy-2 : 2′-biphenanthryl, has an ultraviolet spectrum (Fig. 3) similar in general to those of phenanthrenes, but showing appreciably less fine structure, presumably indicative of a moderate degree of conjugation between the two systems.

Bertrand and Meyer [7] have claimed that since *pseudo*morphine has a strong optical rotation the two morphine units cannot be linked 2 : 2′, *i.e.*, symmetrically, otherwise the base would be optically inactive by analogy with *meso*tartaric acid. This is clearly fallacious since the two " halves " of the *meso*tartaric acid molecule do not belong to the same stereochemical series, as do the two halves of *pseudo*morphine, which is thus analogous to (+)- or (−)-tartaric acid.

[6] Klee, *Arch. Pharm.*, 1914, **252**, 211.
[7] Bertrand and Meyer, *Compt. rend.*, 1909, **148**, 1681.

Experimental

pseudo*Morphine.*—Morphine (10 g.) was added to a hot solution of potassium hydroxide (2·0 g.) in water (1 l.), and the mixture cooled to room temperature. A solution of potassium ferricyanide (11·58 g.) in water (400 ml.) was then added to the solution during 50 min., with stirring, which was continued for an additional 30 min. The solid matter was collected and stirred with hot methanol, which removed morphine (1 g.). The methanol-insoluble material (8·4 g.) was dissolved in concentrated ammonia solution, and the mixture diluted to 700 ml. and boiled; 7·7 g. of *pseudo*morphine were deposited as almost colourless rods, decomp. *ca.* 330° (Found: C, 69·3; H, 6·4; N, 5·4. Calc. for $C_{34}H_{36}O_6N_2,H_2O$: C, 69·7; H, 6·4; N, 5·8%).

Tetra-acetyl*pseudo*morphine was obtained as prisms, m. p. 294—296°, from methanol (Found: C, 68·4; H, 5·9; N, 3·7. Calc. for $C_{42}H_{44}O_{10}N_2$: C, 68·4; H, 6·0; N, 3·8%).

pseudo*Morphine Dimethyl Ether.*—The potassium salt of *pseudo*morphine (0·5 g.) was dissolved in water (100 ml.), and potassium hydroxide (3 g.) was added. The solution was covered with ether (25 ml.), and *N*-nitrosomethylurea (5 g.) was added in portions with shaking, while the mixture was cooled in ice. The pale yellow solution was then left at 0° for 18 hr., after which the ether was removed on the steam-bath. The white solid was then collected (0·24 g.) and recrystallised from 1 : 1 ether–light petroleum (b. p. 50—60°), *pseudo*morphine dimethyl ether being obtained as needles, m. p. 155—156° (Found: C, 70·1; H, 7·0; OMe, 10·7. $C_{36}H_{40}O_6N_2,H_2O$ requires C, 70·3; H, 6·8; OMe, 10·1%).

1-*Bromodihydromorphine.*—Bromine (1·725 g.) in glacial acetic acid (17·25 ml.) was slowly added to a stirred solution of diacetyldihydromorphine (4 g.) in acetic acid (100 ml.) at <15°. The resultant yellow solution was evaporated *in vacuo*, and the residual syrup dissolved in water, basified with potassium hydrogen carbonate and exhaustively extracted with chloroform. The residue after removal of the chloroform crystallised from methanol (3·0 g.) and on recrystallisation from methanol gave *diacetyl*-1-*bromodihydromorphine* as rectangular plates, m. p. 259—260° (Found: C, 56·1; H, 5·5; Br, 17·7. $C_{21}H_{24}O_5NBr$ requires C, 56·1; H, 5·3; Br, 17·8%). Hydrolysis with hot methanolic sodium hydroxide afforded 1-*bromodihydromorphine*, needles, m. p. 248—250° (from methanol) (Found: C, 52·9; H, 5·7; N, 3·6; Br, 20·7. $C_{17}H_{20}O_3NBr,H_2O$ requires C, 53·2; H, 5·7; N, 3·6; Br, 20·8%).

The identity of this product was demonstrated by conversion into 1-bromodihydrocodeine by diazomethane, the product being identical with material prepared by bromination of dihydrocodeine. 1-*Bromodihydrocodeine methiodide* was obtained as needles, m. p. 243—245° (from methanol) (Found: C, 43·4; H, 4·8. $C_{19}H_{25}O_3NBrI$ requires C, 43·7; H, 4·8%).

Oxidation of 1-*Bromodihydromorphine.*—A solution of potassium ferricyanide (0·292 g.) in water (150 ml.) was added in 30 min. to a stirred suspension of 1-bromodihydromorphine (1·9 g.) in a solution of potassium hydroxide (0·29 g.) in water (150 ml.) at 70—80°. The mixture was stirred at 80° for a further 4 hr., during which the pH fell to about 8. The solid was collected, dried, and recrystallised from methanol (200 ml.), *dibromotetrahydro*pseudo*morphine* (0·15 g.) being obtained as square plates, m. p. >350°, $[\alpha]_D^{18}$ −47° (*c* 0·518 in N-HCl) (Found: C, 51·9, 51·9; H, 5·4, 5·6; Br, 20·8. $C_{34}H_{38}O_6N_2Br_2,3H_2O$ requires C, 52·0; H, 5·6; Br, 20·4%). The water was not completely lost on prolonged drying at 155° *in vacuo*.

*Bromination of Tetrahydro*pseudo*morphine.*—A solution of bromine (1·12 g.) in glacial acetic acid (11·2 ml.) was slowly added in 30 min. to a solution of tetrahydro*pseudo*morphine (2 g.) in acetic acid (60 ml.) at 15°. An immediate yellow precipitate was formed, and after a further 30 min. this was collected, but attempts to recrystallise it failed. The acetic acid solution was evaporated *in vacuo* and the resulting syrup together with the yellow precipitate was dissolved in water. The yellow solution obtained was basified with ammonia to pH 9, a yellow-brown precipitate being formed. This crystallised from methanol, giving dibromotetrahydro*pseudo*morphine (0·9 g.) as square plates, m. p. >350°, $[\alpha]_D^{18}$ −50° (*c* 0·627 in N-HCl) (Found: C, 52·3; 52·3; H, 5·5, 5·6; Br, 21·0%).

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