192. *The Absolute Stereochemistry of Narcotine and Narcotoline.*

By A. R. Battersby and H. Spencer.

Natural α-narcotine (I; R = Me) and the isomeric β-narcotine (X) are transformed into the corresponding 13-hydroxytetrahydroprotoberberines (VII) and (VIII). Nuclear magnetic resonance spectra and chemical evidence are combined to establish the relative stereochemistry of these products and so of α-narcotine. The absolute configuration of the series of bases is determined by conversion of the hydroxy-base (VII) into the deoxy-base (IX). Narcotoline (I; R = H) is shown to have the same absolute stereochemistry as α-narcotine (I; R = Me).

Narcotine (I; R = Me) was among the first of the alkaloids to be isolated [1] and its gross structure was determined more than fifty years ago.[2] Yet the relative and absolute stereochemistry of its two asymmetric centres was not known; concurrent work on the biosynthesis of narcotine required a solution of this problem. The phthalideisoquinoline

[1] Derosne, *Ann. Chim.*, 1804, [1] **45**, 274; Robiquet, *ibid.*, 1817, [2] **5**, 275.
[2] Roser, *Annalen*, 1889, **254**, 334, 359; Perkin and Robinson, *J.*, 1911, **99**, 775.

alkaloids (skeleton as I), of which narcotine is a member, are considered on structural grounds to be related to the protoberberines [3] (skeleton as II). If the stereochemistry of narcotine could be determined, experiments in which optically active labelled precursors of narcotine (*e.g.*, derivatives of II) are fed to poppy plants should be more revealing than the earlier ones involving racemic precursors.[4]

Narcotine is isolated from opium, and some types can contain [5] as much as 10%. The interest of this alkaloid has recently been heightened by its emergence as a valuable agent for the suppression of cough.[6] The natural base is designated α-narcotine to distinguish it from the optically active isomer, β-narcotine, produced by vigorous treatment of the α-base with alkali.[7] Both α- and β-narcotine are converted by Hofmann degradation into narceine [8] (III); they are therefore diastereoisomers, the inversion in the conversion of α- into β-narcotine having occurred [7] at position 9. For simplicity, the stereochemistry established in the sequel will be shown on the structural formulæ.

We planned to convert the α- and β-narcotines into the corresponding tetrahydroprotoberberines (VII) and (VIII) which, having the asymmetric centres at positions 13 and 14 fixed relative to each other, are suitable for stereochemical study by nuclear magnetic resonance. Accordingly, α-narcotine (I; R = Me) was reduced by lithium aluminium hydride to the known α-narcotine diol (V).[9,10] Early experiments involved treatment of α-narcotine diol with toluene-*p*-sulphonyl chloride or methanesulphonyl chloride to afford a mixture of products in which the dihydroprotoberberine (IV) was detected by its characteristic ultraviolet absorption. This had been the outcome also of previous work with thionyl chloride as the reagent.[9] However, mild conditions were later found which permitted preferential attack of methanesulphonyl chloride on the primary alcoholic group of the α-diol and so led to the formation of the desired quaternary salt (VI); this was isolated as the crystalline chloride. Pyrolysis of this salt in a high vacuum [11] afforded the corresponding 13α-hydroxy-tertiary base * (VII) in 53% yield. This reacted with methyl iodide to give a quaternary salt which after conversion into the corresponding chloride was identical with the starting material (VI). Structural changes in the pyrolysis step are thus excluded.

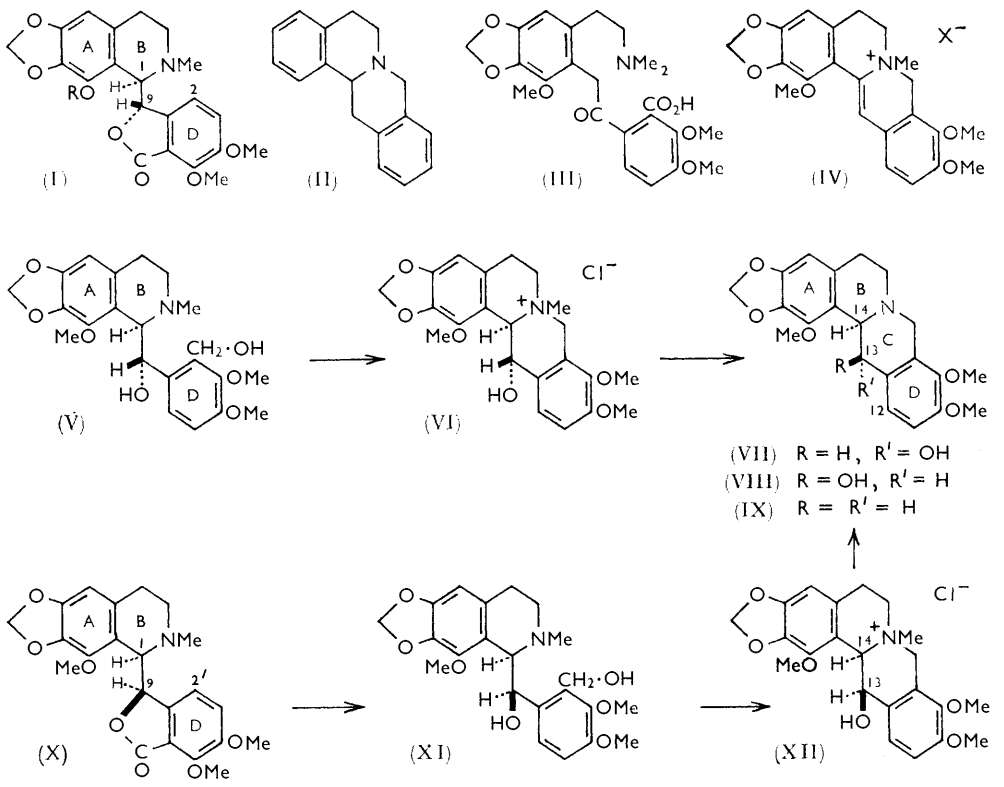
β-Narcotine (X), prepared by isomerisation of α-narcotine,[7] was isolated by the simplified procedure described on p. 1091. Reduction with lithium aluminium hydride then gave β-narcotine diol (XI) as a gum which was purified and characterised as its crystalline picrolonate. Ring-closure of the recovered pure base was carried out as above to give the corresponding quaternary salt (XII) and pyrolysis then yielded the 13β-hydroxytetrahydroprotoberberine (VIII).

The 13α- and 13β-hydroxytetrahydroprotoberberines (VII) and (VIII) both showed bands in their infrared spectra which are characteristic of *trans*-quinolizidine systems.[12] The framework of these molecules is thus of defined conformation and models of it (Courtauld) show that the dihedral angle between the protons at positions 13 and 14 of the 13α-base (VII) is *ca.* 160° whereas for the 13β-base (VIII) this angle is *ca.* 60°. From the Karplus equation,[13] spin–spin coupling between these two protons should be large in

* The standard steroid conventions used with α designating the group below the plane and β the one above. Fortuitiously, this accords with the established designation of α- and β-narcotine.

[3] Robinson, " The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, p. 88.
[4] Battersby and McCaldin, *Proc. Chem. Soc.*, 1962, 365.
[5] Jermstad, *Schweiz. Apoth. Ztg.*, 1922, **60**, 691.
[6] Segal, Goldstein, and Attinger, *Dis. Chest.*, 1957, **32**, 305; Winter and Flataker, *Toxicol. Appl. Pharmacol.*, 1961, **3**, 96.
[7] Marshall, Pyman, and Robinson, *J.*, 1934, 1315.
[8] Hope and Robinson, *J.*, 1914, **105**, 2085.
[9] Mirza and Robinson, *Nature*, 1950, **166**, 271.
[10] Bentley and Murray, *J.*, 1963, 2491.
[11] Karrer and Schmid, *Helv. Chim. Acta*, 1946, **29**, 1853.
[12] Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.
[13] Karplus, *J. Chem. Phys.*, 1959, **30**, 11; Jackman, " Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959, p. 84.

the former case and small for the latter. The nuclear magnetic resonance spectrum of the 13-hydroxytetrahydroprotoberberine base derived originally from α-narcotine showed, after exchange of the hydroxylic proton for deuterium, a doublet at 5·25 τ with a large coupling (J = 9 c./sec.). This signal appeared as a quartet before deuterium exchange because of additional coupling to the hydroxylic proton, a result which allows this signal



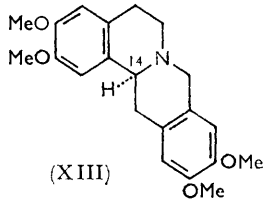
to be assigned with certainty. The base from α-narcotine therefore possesses the relative stereochemistry as in structure (VII); the relative configurations shown for the bases (I) and (V)—(VII) in the α-series are now established.

Interlocking evidence comes from the spectrum of the hydroxytetrahydroprotoberberine derived from β-narcotine. After exchange with deuterium oxide, the relevant signal at 4·9 τ appeard as a partly resolved doublet (J *ca.* 1·5 c./sec.). The small coupling is in accord with a 60° dihedral angle [13] for the protons at C-13 and C-14 and this base is thereby shown to possess the relative stereochemistry as in structure (VIII).

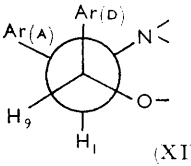
Molecular models of the two bases (VII) and (VIII) show two further features. First, the proton at position 13 in the base (VIII) should be more affected by deshielding from the aromatic rings than the corresponding proton in the base (VII), and the observed signal positions accord with this. Secondly, the hydroxyl group in the 13α-hydroxy-base (VII) is strongly compressed by the methoxyl group of ring A and by the hydrogen atom at position 12 of ring D whereas it is relatively free in the isomeric 13β-base (VIII). The α-base (VII) was accordingly treated under equilibrating conditions with hot methanolic sodium methoxide and a catalytic amount of acetone.[14] Almost complete conversion into the β-base (VIII) occurred; under the same conditions, the β-base (VIII) was recovered unchanged. These results give chemical support to the relative configurations deduced above from spectroscopic evidence.

[14] von Doering, Coates, and Knox, *J. Amer. Chem. Soc.*, 1947, **60**, 1700.

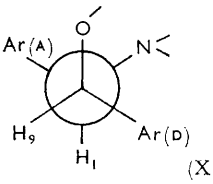
Reductive removal of the hydroxyl group from the α-base (VII) was achieved in ethanolic perchloric acid over palladium; the tetrahydroprotoberberine (IX) so obtained showed a strong negative rotation ($[\alpha]_D$ −261°). Corrodi and Hardegger [15] determined the absolute configuration of bases of this type by chemical correlation of (−)-norcoralydine (XIII) with primary standards. Bases having an α-hydrogen at position 14 have rotations of *ca.* −300° in chloroform or ethanol, and those with a 14β-hydrogen atom, *ca.* +300°. The product (IX) clearly has the 14α-configuration. It follows that the absolute configurations shown in formulæ (V)—(XII) correctly represent the corresponding molecules, and the complete stereochemistry of α-narcotine is as shown in formula (I), that is 1*R*,9*S*.[16]



(XIII)



(XIV)



(XV)

Narcotoline has the structure (I; R = H) since by *O*-methylation it yields narcotine (I; R = Me) though it is not clear from the original Paper [17] whether the product had the same optical rotation as natural α-narcotine. This point has been clarified, and the structure (I; R = H) correctly represents narcotoline.

After the submission of the preliminary account of this work,[18] there appeared three independent reports from other laboratories all of which agree with the results described above. Ohta and his co-workers [19] deduced the absolute stereochemistry of α-narcotine largely by measurements of optical rotatory dispersion, Šantavý and his colleagues [20] reached the same conclusion on the basis of various physical methods, whilst Safe and Moir [21] deduced the *relative* stereochemistry of α-narcotine from its n.m.r. spectrum. We agree with the assignment of signals given by the last authors, in particular with the explanation that the high-field position (3·92 τ) of the resonance corresponding to the proton at position 2′ of narcotine results from its being in the shielding area over ring A in the only favoured conformation (XIV) as viewed along the C-9–C-1 bond. The conformation (XV) is the preferred one for β-narcotine which takes the 2′-proton well away from ring A and the corresponding signal in the n.m.r. spectrum appears at 2·8 τ, *ca.* 1·1 p.p.m. to lower field than for α-narcotine. Cleavage of the lactone ring of α-narcotine to form the corresponding diol (V) renders the molecule much more flexible, and the preferred conformation should now be one having ring D turned away from ring A with the primary alcohol hydrogen-bonded to the nitrogen atom. As expected for this conformation, the signal corresponding to the 2′-proton appears at the normal position of 2·66 τ (cf. α-narcotine above).

Experiments in which resolved precursors, suitably labelled and of known absolute configuration, are fed to poppy plants are in progress.

Experimental

For general directions, see Battersby and Harper.[22] The m. p.s below were determined on a Kofler hot-stage apparatus.

[15] Corrodi and Hardegger, *Helv. Chim. Acta*, 1956, **39**, 889.
[16] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[17] Wrede, *Arch. Exp. Path. Pharmakol.*, 1937, **184**, 331.
[18] Battersby and Spencer, *Tetrahedron Letters*, 1964, 11.
[19] Ohta, Tani, Morozumi, Kodaira, and Kuriyama. *Tetrahedron Letters*, 1963, 1857.
[20] Bláha, Hrbek, Kouář, Pijevska, and Šantavý, *Coll. Czech. Chem. Comm.*, 1964, **29**, 2428; we thank Professor F. Šantavý for sending us an advance copy of this Paper.
[21] Safe and Moir, *Canad. J. Chem.*, 1964, **42**, 160.
[22] Battersby and Harper, *J.*, 1962, 3526.

(−)-13α-*Hydroxy*-2,3-*methylenedioxy*-1,9,10-*trimethoxytetrahydroprotoberberine Methochloride* (VI).—A solution of α-narcotine diol (V) [9,10] (4·67 g.) in anhydrous pyridine (25 ml.) was treated with methanesulphonyl chloride (0·72 ml., 1·01 mol.) and the solution was shaken at room temperature in the dark for 40 hr. Evaporation of the pyridine at 30° left a residue which was dissolved in water (25 ml.), and the solution, after basification, was extracted thrice with ether. The aqueous solution was percolated through a column of Amberlite IRA-400 resin (chloride phase) and then evaporated to dryness. The ethanol-soluble part of the residue was chromatographed in chloroform over alumina, and elution with this solvent removed a fast running fraction which showed ultraviolet absorption consistent with its being largely dehydrated material (IV). Chloroform with 5% (by vol.) of ethanol eluted a second fraction and the separation was controlled by thin-layer chromatography on alumina using 12% (by vol.) ethanol in chloroform as the solvent. The second fraction was further purified by chromatography over powdered cellulose (Whatman No. 1) in n-butanol saturated with water, to yield, from the appropriate fractions, the α-*hydroxytetrahydroprotoberberine methochloride* (VI) as rods (2·3 g.) (from n-butanol–ether), m. p. 220—222° (Found: C, 60·6; H, 6·2; Cl, 8·0; N, 3·1. $C_{22}H_{26}ClNO_6$ requires C, 60·6; H, 6·1; Cl, 8·1; N, 3·2%), $\lambda_{max.}$ 282 mμ (log ε 3·49) (in 1 : 1 aqueous ethanol), $[\alpha]_D^{20}$ −208 ± 4° (*c* 0·26 in $CHCl_3$).

(−)-13α-*Hydroxy*-2,3-*methylenedioxy*-1,9,10-*trimethoxytetrahydroprotoberberine* (VII).—The foreoing methochloride (1·10 g.) was spread from methanol as very thin films over 36 glass pyrolysis bulbs (*ca.* 34 mg. per bulb). Each bulb was evacuated to 2 × 10^{-4} mm. and dipped for 8 sec. into a metal bath at 300 ± 10°, when the tertiary base distilled rapidly on to the cooler parts of the bulb. The contents of the bulbs were collected in methanol and the residue obtained by evaporation was dissolved in 2N-hydrochloric acid (50 ml.). Basification with sodium carbonate and extraction with 4 : 1 ether–chloroform yielded a gum which in aqueous methanol yielded the α-*hydroxytetrahydroprotoberberine* (VII) as needles (521 mg.), m. p. 161° (Found: C, 65·7; H, 6·1; N, 3·6. $C_{21}H_{23}NO_6$ requires C, 65·4; H, 6·0; N, 3·6%), $\lambda_{max.}$ 282 mμ (log ε 3·60) (in 1 : 1 aqueous ethanol), $[\alpha]_D^{22}$ −191 ± 4° (*c* 0·15 in chloroform).

Quaternisation of the Base (VII).—A solution of the above base (21·3 mg.) in methanol (1 ml.) was heated under reflux for 2 hr. with methyl iodide (2 ml.). The residue from evaporation was percolated in aqueous methanol (5 ml.) through Amberlite IRA-400 resin (chloride phase). The resultant methochloride crystallised from n-butanol–ether as above (20·3 mg.), and was identical (m. p., mixed m. p., and infrared spectra) with the methochloride (VI), $[\alpha]_D^{21}$ = −206 ± 4° (*c* 0·22 in chloroform).

(−)-2,3-*Methylenedioxy*-1,9,10-*trimethoxytetrahydroprotoberberine* (IX).—The 13α-hydroxytetrahydroprotoberberine (VII) (196 mg.) was shaken in ethanol (10 ml.) and 72% w/w aqueous perchloric acid (0·1 ml.) with hydrogen and 10% palladised charcoal (240 mg.). Uptake ceased after *ca.* 0·35 mol. had been absorbed. The catalyst was filtered off, the methanol evaporated, and the basified solution extracted with 4 : 1 ether–chloroform to afford a gum. This was fractionated on alumina in 4 : 1 (by vol.) benzene–chloroform, to yield 2,3-*methylenedioxy*-1,9,10-*trimethoxytetrahydroprotoberberine* as needles (57 mg.) (from aqueous ethanol), m. p. 145° (Found: C, 68·5; H, 6·5. $C_{21}H_{23}NO_5$ requires C, 68·3; H, 6·3%), $\lambda_{max.}$ 282 mμ (log ε 3·52) (in 1 : 1 aqueous ethanol), $[\alpha]_D^{21}$ −261 ± 4° (*c* 0·052 in chloroform).

(−)-β-*Narcotine* (X).—The natural alkaloid (α-narcotine) (15 g.) was equilibrated [7] with base, and the further steps carried to the point where the crude mixture of bases is precipitated. A solution of these in chloroform was run on to a column of alumina, and elution was continued with 1 : 1 (by vol.) benzene–chloroform which removed α-narcotine. Chloroform then eluted β-narcotine, m. p. 178° (from ethanol), $[\alpha]_D^{23}$ −88° (*c* 0·22 in chloroform) {lit.,[7] m. p. 178°, $[\alpha]_{546}^{18}$ −101° (*c* 1·2 in chloroform)}.

Reduction of β-*Narcotine.*—A solution of β-narcotine (1·41 g.) in dry tetrahydrofuran (300 ml.) was treated with a slurry of lithium aluminium hydride (2·8 g.) in tetrahydrofuran, and the mixture was heated under reflux for 5 hr. More hydride (2·0 g.) was then added and the heating was continued for a further 15 hr. Saturated aqueous sodium potassium tartrate (100 ml.) was added to the mixture, the tetrahydrofuran was evaporated, and the aqueous solution was extracted thrice with ether, to afford a gum (0·85 g.), $\lambda_{max.}$ 283 mμ (log ε 3·54) (in 1 : 1 aqueous ethanol). This was converted into the picrolonate in ethanol and recrystallised from the same solvent to yield β-*narcotinediol picrolonate*, m. p. 199° (decomp.) (Found: C, 56·2; H, 5·4; N, 10·1. $C_{32}H_{36}N_5O_{12}$ requires C, 56·3; H, 5·3; N, 10·0%).

(−)-13β-*Hydroxy*-2,3-*methylenedioxy*-1,9,10-*trimethoxytetrahydroprotoberberine* (VIII).—

β-Narcotinediol (909 mg.) was treated with methanesulphonyl chloride (258 mg.) as described for the α-isomer, and the products were worked up as before save that only chromatography on alumina was necessary using chloroform followed by 8% (by vol.) ethanol in chloroform. The latter solvent eluted the β-hydroxytetrahydroprotoberberine methochloride (XII) which crystallised from a mixture of chloroform, ethanol, and ether as needles (382 mg.), m. p. 178°. Part (194 mg.) was pyrolysed as for the α-isomer, to yield, after the same work-up, the *β-hydroxytetrahydroprotoberberine* as cubes (75 mg.) (from ethanol), m. p. 185° (Found: C, 65·2; H, 5·9. $C_{21}H_{23}NO_6$ requires C, 65·4; H, 6·0%), $\lambda_{max.}$ 280 mμ (log ε 3·48) (in 1 : 1 aqueous ethanol), $[\alpha]_D^{21}$ −298 ± 4° (*c* 0·17 in chloroform).

Equilibration of the α- and β-Hydroxytetrahydroprotoberberines (VII) *and* (VIII) *with Base.*—The α-base (67 mg.) and the β-base (64 mg.) were dissolved separately in methanol (30 ml.), and to each solution was added sodium (45 mg.) and acetone (0·1 ml.). The solutions were heated (reflux) under the same conditions for 48 hr. After acidification of the solutions, they were freed from methanol by evaporation, basified, and extracted thrice with ether, to afford two gums. These were examined by thin-layer chromatography on alumina with 1 : 1 chloroform–benzene as solvent to show that the α-base had been converted almost entirely into the β-base whereas the latter had been largely unaffected. The unchanged β-base was recrystallised twice, and the product (28 mg.) had m. p. and mixed m. p. 185°, $[\alpha]_D^{21}$ −298 ± 4° (*c* 0·125 in chloroform).

A solution of the product from the α-base in 1 : 1 benzene–chloroform was run on to a column of alumina and eluted with 4 : 1 benzene–chloroform. The appropriate fractions yielded the β-base which crystallised from ethanol (23 mg.), m. p. and mixed m. p. 185°, infrared spectrum identical with authentic material, $[\alpha]_D^{21}$ −298 ± 4° (*c* 0·167 in chloroform).

Methylation of Narcotoline (I; R = H).—A solution of narcotoline (33·4 mg.) in methanol (5 ml.) was treated with ethereal diazomethane (85 mg. in 10 ml.). After the solution had been kept overnight, it was evaporated to near dryness and the residue was partitioned between ether and 2N-hydrochloric acid. The acidic solution was basified and extracted with ether, to afford a gum which crystallised from aqueous ethanol (Found: C, 64·2; H, 5·8; N, 3·3. Calc. for $C_{22}H_{23}NO_7$: C, 63·9; H, 5·6; N, 3·4%). The product was identified as α-narcotine by m. p., mixed m. p., and infrared spectrum, $[\alpha]_D^{22·5}$ −206° (*c* 0·197 in chloroform) and $[\alpha]_D^{22·5}$ +53° (*c* 0·19 in 1% aqueous hydrochloric acid). Natural α-narcotine showed $[\alpha]_D^{22·5}$ −205° (*c* 0·165 in chloroform) and $[\alpha]_D^{22·5}$ +53° (*c* 0·33 in 1% aqueous hydrochloric acid).

Grateful acknowledgment is made to Professor S. Pfeifer (Berlin) and Professor E. Hardegger (Zürich) for generous samples of narcotoline and norcoralydine, respectively, to Dr. F. R. Smith and Edinburgh Pharmaceutical Industries Ltd. for valuable gifts of narcotine, and to the D.S.I.R. for a Research Studentship (H. S.).

THE ROBERT ROBINSON LABORATORIES,
UNIVERSITY OF LIVERPOOL.

[*Received, June 23rd,* 1964.]