727. *Chemical Constitution and Amœbicidal Action. Part V.* Stereochemistry of Emetine.*

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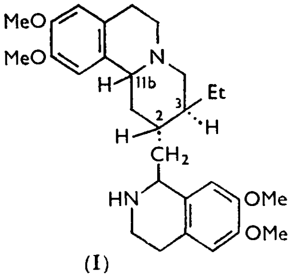
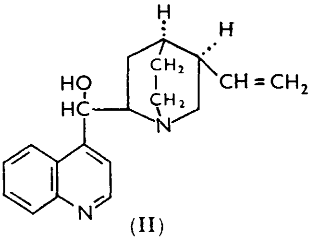
An investigation of the stereochemistry of emetine has led to formula (I). The 2- and the 3-substituent are in a *trans*-relation and the 11b-hydrogen atom is *cis* to the 2-hydrogen atom.

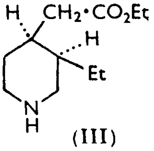
Recent preliminary communications[1-6] have described the relative configurations at the four asymmetric centres (2, 3, 11*b*, and 1′) of emetine. The synthesis of emetine and three stereoisomers described in Part IV * forms the basis of the present investigation. These compounds were derived from the two acetic acids (VI; A and B). The former led to (±)-emetine and (±)-isoemetine; therefore determination of the configuration of one of these acids would reveal that of emetine at $C_{(2)}$ and $C_{(3)}$. The possible biogenetic link between the cinchona and ipecacuanha alkaloids[7] led us to degrade cinchonine (II) by known methods[8,9] to ethyl cincholoiponate (III), which is known[8] to have *cis*-substituents at positions 3 and 4, in order to link the latter compound with one of the acids (VI).



(I)



(II)



(III)

Condensing the ester (III) with 3,4-dimethoxyphenethyl iodide gave the *cis*-4-piperidylacetate (IV) which was reduced with lithium aluminium hydride to the *cis*-(+)-alcohol (V), m. p. 49·5—51°, $[\alpha]_D$ +9°. Esters of the synthetic acids (VI; A and B) were reduced similarly to the (±)-alcohols (V; A), m. p. 64·5—65·5°, and (B), m. p. 76·5—79·5°. The (±)-alcohol (V; A) was characterised by a crystalline hydrobromide and hydrogen oxalate; the same salts of the (±)-alcohol (V; B) and *cis*-(+)-alcohol (V), however, did not crystallise. Infrared spectroscopy of the three bases in solution showed that the *cis*-(+)-alcohol V (from cinchonine) and (±)-alcohol (V; B) were identical whereas the spectrum of the alcohol (V; A) showed several differences. Emetine, which we had located in the A series (Part IV), therefore has the *trans*-configuration at $C_{(2)}$ and $C_{(3)}$, in

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* Part IV, *J.*, 1959, 3530.

[1] Battersby, Binks, Davidson, Davidson, and Edwards, *Chem. and Ind.*, 1957, 982; Battersby and Garratt, *Proc. Chem. Soc.*, 1959, 86.

[2] Battersby and Cox, *Chem. and Ind.*, 1957, 983.

[3] (*a*) van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1957, **79**, 4817; (*b*) van Tamelen and Hester, *ibid.*, 1959, **81**, 507.

[4] (*a*) Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *Chem. and Ind.*, 1958, 491; (*b*) Osbond, *ibid.*, 1959, 257.

[5] Battersby, *ibid.*, 1958, 1324.

[6] Battersby and Turner, *ibid.*, p. 1324.

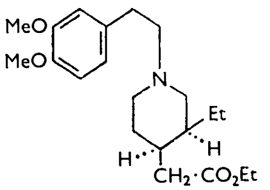
[7] Turner and Woodward in " The Alkaloids," Manske and Holmes, 1953, **3**, 54.

[8] Prelog and Zalan, *Helv. Chim. Acta*, 1944, **27**, 535.

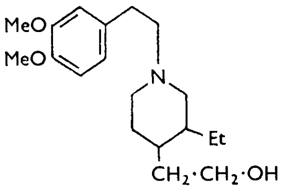
[9] Kaufmann, Rothlin, and Brunnschweiler, *Ber.*, 1916, **49**, 2299.

agreement with conclusions by Battersby and Cox[2] and van Tamelen, Aldrich, and Hester.[3]

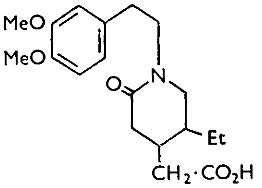
The 11b-hydrogen atom has been given the configuration shown in (I) by Battersby *et al.*[1] and van Tamelen *et al.*,[3] and later Battersby[5] advanced further evidence and arguments supported by a synthesis of emetine[6] which would be expected to give an axial attachment of the 11b-hydrogen atom. At first our results were not in agreement with this conclusion[4a] but after Battersby's further preliminary communications[5,6] our evidence was re-examined and a correction was made.[4b]



(IV)



(V)



(VI) A, m.p. 154—156°
B, m.p. 152—153°

Battersby *et al.*[1] have also determined the absolute configuration at position 1′, and van Tamelen and Hester[3b] have determined the relative configuration. We observed[4a] that the rate of dehydrogenation, by mercuric acetate,[10] of isoemetine (Ab_2) to the rubremetinium ion is *ca.* twice as fast as that of emetine (the 1′-epimer).

EXPERIMENTAL

Ethyl Cincholoiponate (III).—This ester was prepared from cinchonine by the method of Kaufmann, Rothlin, and Brunnschweiler.[9] Hydrolysis of the benzoylcincholoiponitrile with barium hydroxide gave a mixture of the corresponding free amino-nitrile and -acid and unchanged benzoyl-nitrile. However, hydrolysis with concentrated hydrochloric acid for 7 hr. gave cincholoiponic acid which without isolation was esterified with ethanol saturated with hydrogen chloride. Ethyl cincholoiponate, b. p. 134—138°/14 mm., n_D^{20} 1·4680 was obtained, in 70% yield (for the two steps) (Prelog and Zalan[8] give b. p. 137—138°/11 mm., n_D^{20} 1·4675). The hydrochloride, after crystallisation from acetone, had m. p. 160—161·5°, $[\alpha]_D^{21}$ $-11{\cdot}07°$ (*c* 2·981 in EtOH) [lit.,[8] m. p. 159—160°, $[\alpha]_D^{23}$ $-9{\cdot}3° \pm 1°$ (*c* 2·576 in EtOH)].

cis-1-(3,4-*Dimethoxyphenethyl*)-4-*ethoxycarbonylmethyl*-3-*ethylpiperidine Hydrochloride* (cf. IV).—Ethyl cincholoiponate (3·99 g.), 3,4-dimethoxyphenethyl iodide (5·84 g.), and anhydrous potassium carbonate (5·0 g.) were refluxed in dry benzene (50 c.c.) for 3·5 hr. After addition of water, the benzene extracts were washed with 2N-hydrochloric acid (3 × 25 c.c.). The base liberated from the acid extracts was extracted with ether (3 × 25 c.c.) and dried (Na_2SO_4). Treatment of the resulting basic oil (5·8 g.) in ether with hydrogen chloride gave the *hydrochloride* which crystallised from acetone or methanol–ether as needles, m. p. 126—129° (3·30 g., 41%) (Found: C, 62·1; H, 8·7; N, 3·4; Cl, 8·7. $C_{21}H_{33}O_4N,HCl,0{\cdot}5H_2O$ requires C, 61·7; H, 8·6; N, 3·4; Cl, 8·7%). The infrared spectrum confirmed the structure and showed a hydroxyl band due to hydration of the salt. The neutral benzene extract gave unchanged iodide (2·39 g.) on evaporation.

cis-(+)-1-(3,4-*Dimethoxyphenethyl*)-4-2′-*hydroxyethyl*-3-*ethylpiperidine* (V).—The free base from the above ester hydrochloride (3·99 g.) was added in ether (20 c.c.) to a solution of lithium aluminium hydride (0·38 g.) in ether (10 c.c.) during 0·25 hr. with stirring. After refluxing for 2·5 hr., the solution was cooled and treated with ethyl acetate (1 c.c.), water, and dilute acid. The acid layer was extracted once with ether, made alkaline with 2N-sodium hydroxide, extracted with ether (3 × 30 c.c.), and dried (Na_2SO_4). Removal of the ether gave the basic alcohol (3·24 g.) which, however, did not give a crystalline hydrobromide even when seeded

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[10] Battersby and Openshaw, *J.*, 1949, S67.

with the hydrobromide of the (±)-alcohol (V; A) (see below). When the base was seeded with the (±)-base (V; B) (see below) it immediately crystallised. Crystallisation from light petroleum (b. p. 40—60°) gave the pure *alcohol*, m. p. 49·5—51°, $[\alpha]_D^{22}$ +9·0° ±1·26° (*c* 2·399 in EtOH) (Found: C, 71·6; H, 9·8; N, 4·4. $C_{19}H_{31}O_3N$ requires C, 71·0; H, 9·7; N, 4·4%).

The acid (VI; A), m. p. 154—156°, was converted into the ethyl ester which (4·0 g.) was added in dry tetrahydrofuran (20 c.c.) to lithium aluminium hydride (1·2 g.) in dry tetrahydrofuran (50 c.c.) during 0·25 hr. The solution was then refluxed for 4 hr., cooled, and decomposed with ethyl acetate, water, 2N-sulphuric acid, and ether. The ether layer was extracted twice with sulphuric acid, the acid extracts were combined and made alkaline with 25% potassium hydroxide solution, and the basic alcohol was extracted with ether and dried (Na_2SO_4). The ether was removed and the *hydrobromide* was prepared; this crystallised from ethanol–ether as prisms (2·67 g.), m. p. 174—176·5° (Found: C, 57·0; H, 8·0; N, 3·5; Br, 19·45. $C_{19}H_{31}O_3N,HBr$ requires C, 56·7; H, 8·0; N, 3·5; Br, 20·1%). The hydrogen oxalate crystallised from ethanol–ether as prisms, m. p. 141—144° (Found: C, 60·4; H, 8·3; N, 3·4. $C_{19}H_{31}O_3N,H_2C_2O_4,0{\cdot}5H_2O$ requires C, 60·0; H, 8·1; N, 3·3%). Conversion of the hydrobromide into the base and crystallisation from light petroleum (b. p. 60—80°) gave the pure (±)-*alcohol* as prisms, m. p. 64·5—65·5° (Found: C, 71·1; H, 9·8; N, 4·5%).

The corresponding acid (VI; B) (2·0 g.), m. p. 152—153°, was similarly converted into the ethyl ester and reduced in tetrahydrofuran (50 c.c.) with lithium aluminium hydride (0·7 g.). After 4 hours' refluxing, the (±)-alcohol (V; B) was obtained as described above, as prisms (1·2 g.), m. p. 76·5—79·5° (Found: C, 71·6; H, 9·8; N, 4·3%). The base failed to give a crystalline hydrobromide, hydrogen oxalate, or hydriodide.

Mixed m. p.s between these bases were unsatisfactory; thus between (±)-A and (±)-B the mixed m. p. was 62·5—68°; between (±)-A and *cis*-(+)-(V), 46—55°; between (±)-B + *cis*-(+)-(V), 48—70°. Paper-chromatographic separation was also attempted. Several solvent systems were used but although each isomer gave only one spot they could not be separated from each other. The infrared spectra of the three bases in carbon disulphide, however, showed that the *cis*-(+)-base and (±)-B-isomer were identical. Comparison of the infrared spectra of the *cis*-(+)-base and (±)-A-isomer showed them to be very similar, but small, significant differences were evident in the 1093—1075, 987, 937—938, and 870 cm.$^{-1}$ regions.

Rate of Formation of Rubremetinium Salt from Emetine and Isoemetine (*Stereoisomer, Ab*$_2$).—(+)-Emetine dihydrochloride and synthetic (±)-isoemetine (Ab_2) were dehydrogenated [10] to rubremetinium salts, the rate of reaction being followed kinetically in the following way. The dihydrochloride (0·1000 g.) in water (50 c.c.) at 80—90° was treated with mercuric acetate (0·43 g.) in acetic acid (0·5 c.c.) and water (49·5 c.c.) previously warmed to 60°. The solution was then kept in a boiling-water bath under a reflux condenser. From this solution a portion (5 c.c.) was extracted every 15 min. and diluted to 250 c.c. with distilled water. The ultraviolet absorption was then measured at 434 mμ; the rubremetinium ion has a maximum absorption at this wavelength whereas intermediate dehydrogenated products, such as the dehydro- and tetradehydro-isoquinoline moieties, do not absorb there. After 30 and 180 min. the extinction coefficients (*E*) for emetine were 0·015 and 0·116, and for isoemetine 0·025 and 0·22; all other results fell on straight lines between these values. The straight-line graph shows that (±)-isoemetine is converted into the rubremetinium salt *ca.* twice as fast as is emetine.

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