151. *The Stereochemistry of the Tropane Alkaloids. Part II.* The Configurations of the Cocaines.*

By GÁBOR FODOR and (in part) ODÖN KOVÁCS.

The configurations of the epimers, ecgonine (I*a*) and ψ-ecgonine (II*a*), and cocaine and ψ-cocaine, have been established by acyl migration and other stereospecific reactions. The $C_{(3)}$-hydroxyl group proved to be α in ecgonine and β in ψ-ecgonine.†

Ecgonine readily formed anhydroecgonine by *trans*-elimination of water from $C_{(2)}$ and $C_{(3)}$, but ψ-ecgonine did not under a comparable reaction.

Acyl migration in the 2-benzamidotropan-3-ols, prepared from ecgonine and ψ-ecgonine by Curtius reaction, showed that the $C_{(2)}$-carboxyl and the $C_{(3)}$-hydroxyl group are *cis* in ecgonine and *trans* in ψ-ecgonine.

Ecgoninol and ψ-ecgoninol were prepared; only the former forms a cyclic benzylidene acetal.

These facts strongly suggest that cocaine is (−)-3α-benzoyloxy-2α-carbomethoxytropane, whilst ψ-cocaine is the 2α : 3β-epimer.

THE determination of the relative configuration of the nitrogen bridge and the $C_{(3)}$-hydroxyl group in the epimeric tropines (Fodor and Nádor, *Nature*, 1952, **169**, 462; Part I *) appears to be extensible to other amino-alcohols having rigid ring systems, and the elucidation of the configurations of the ecgonines and cocaines therefore seems practical.

With hydrogen chloride in dioxan *N*-acetylnor-ψ-ecgonine (II*c*) ethyl ester gives *O*-acetylnor-ψ-ecgonine ethyl ester hydrochloride, whereas, under identical conditions, the corresponding ecgonine (I*c*) ester does not give an amino-ester salt. Further, when *O*-benzoylnorecgonine (I*b*) is liberated the resulting base does not rearrange into the *N*-acyl derivative but titrates towards 0·1N-acid as a univalent base. It therefore appears that the $C_{(3)}$-hydroxyl group in nor-ψ-ecgonine is β-oriented with respect to the nitrogen bridge, and α- in norecgonine and cocaine.

Ecgonine (I*a*) and ψ-ecgonine (II*a*) are the main reduction products of the same methyl ketotropine-2-carboxylate (Willstätter, Wolfes, and Mäder, *Annalen*, 1923, **434**, 111), but this fact alone does not indicate conclusively that they are $C_{(3)}$-epimers, as racemisation may have occurred at $C_{(2)}$, through enolisation. However, ecgonine epimerises under the conditions required for the $C_{(3)}$-epimerisation of tropine into ψ-tropine (Einhorn and Marquardt, *Ber.*, 1890, **23**, 468), and the anæsthetic properties of ψ-cocaine more closely resemble those of benzoyl-ψ-tropine than those of cocaine (Willstätter, *loc. cit.*).

These facts, together with the acyl-migration experiments now reported, indicate for ecgonine the 3α- and for ψ-ecgonine the 3β-tropanol structure. Eichengrün and Einhorn (*Ber.*, 1890, **23**, 2870) reported that anhydroecgonine dibromide, in the presence of alkali, yields an unstable "α-bromoecgonine-β-lactone," which would suggest that the $C_{(2)}$-carboxyl group is *cis* to the $C_{(3)}$-hydroxyl group. However, there is no evidence of the relative configuration of this lactone to ecgonine.

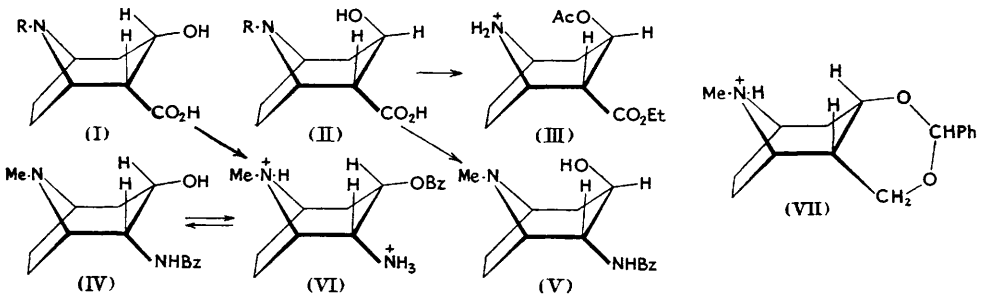
There are no generally applicable methods for the determination of configuration in β-hydroxy-acids, but Toivonen's method (*Acta Chem. Scand.*, 1949, **3**, 991) gave satisfactory results for the isomeric β-hydroxycamphoric acids. However, even under the mildest conditions of condensation with chloral hydrate, ecgonine dehydrates, whereas ψ-ecgonine does not react at all. This agrees with earlier findings (cf. Manske and Holmes, "The Alkaloids," p. 299, Acad. Press, 1950) of the ready dehydration of ecgonine. This indicates that in ecgonine the $C_{(2)}$-carboxyl and the $C_{(3)}$-hydroxyl group are *cis*-placed, a *trans*-arrangement following for the epimer (II). Only an ionic *trans*-elimination (polar–polar in the boat form of the *cyclo*heptane ring) (Alexander, "Principles of Ionic Organic Reactions," p. 118, Chapman and Hall, London, 1950) would favour dehydration.

For supporting evidence the two ecgonine $C_{(3)}$-epimers have been converted into the corresponding 2-benzamidotropan-3-ols. By establishing the relative configuration of the 2-amino-group and the 3-hydroxyl group in these compounds it is possible to infer the

* Part I, preceding paper. † For the stereochemical notation used, see Part I.

configuration of the $C_{(2)}$-carboxyl group in the two ecgonines, since in the Curtius degration the original configuration should be retained (Alexander, *op. cit.*, p. 64; cf. Wheland, "Advanced Organic Chemistry," p. 525, Wiley, New York, 1949). The only reported example of inversion in this reaction relates to the diazide from *trans-cyclo*hexane-1 : 3-dicarboxylic acid (Skita and Rössler, *Ber.*, 1939, **72**, 461).

The 2-benzamidotropanol from 3α-ecgonine, with ethanolic hydrogen chloride at 80°, rapidly underwent N→O acyl migration, and (VI), obtained by degradation of *O*-benzoyl-3α-ecgonine, instantaneously underwent O→N acyl migration, in the presence



(*a*) R = H; (*b*) R = Me; (*c*) R = Ac.

of alkali, yielding 2α-benzamidotropan-3α-ol (IV), which titrated as a univalent base. Curtius degradation of *O*-benzoyl-3β-ecgonine, on the other hand, gave a rather poor yield of the benzamidotropanol (V), in which the benzoyl group showed no appreciable tendency to migrate in the presence of alcoholic hydrogen chloride. The $C_{(2)}$-carboxyl group and the $C_{(3)}$-hydroxyl group are therefore *cis*-oriented in 3α-ecgonine and *trans* in 3β-ecgonine.

The lithium aluminium hydride reduction of cocaine and ψ-ecgonine methyl ester to ecgoninol (recently prepared by Rosenmund and Zymalkovski, *Ber.*, 1952, **85**, 152, from ecgonine ester) and ψ-ecgoninol, respectively, does not affect the configurations in the two systems. While the conductivities of the boric acid complexes show no clear distinction between the two epimeric diols, ecgoninol readily affords a well-defined, though sensitive, benzylidene acetal, whereas ψ-ecgoninol does not. Ecgonine and cocaine are therefore (−)-2α-carboxytropan-3α-ol and (−)-3α-benzoyloxy-2α-carbomethoxytropane, respectively, whilst ψ-ecgonine and ψ-cocaine contain the 2α : 3β-configuration.

Since the synthetic "third racemate" of ecgonine (Willstätter, Wolfes, and Mäder, *Annalen*, 1923, **434**, 111) does not epimerise, but dehydrates instead to anhydroecgonine, it appears that the $C_{(3)}$-hydroxyl group and the $C_{(2)}$-hydrogen atom are *trans*-oriented. The $C_{(3)}$-hydroxyl group must therefore be β with respect to the nitrogen bridge. A fourth racemate, based on 2β-carboxytropan-3α-ol, is predictable; these two racemates will be investigated.

Experimental

M. p.s are corrected.

N-Acetylnor-3β-ecgonine (IIc) *Ethyl Ester.*—(+)-Nor-3β-ecgonine (II; R = H) ethyl ester (Einhorn and Friedländer, *Ber.*, 1893, **26**, 1482) (2·14 g.) was acetylated with acetic anhydride (2 ml.). The N-*acetyl* derivative (2 g.) formed drab crystals (from ethyl acetate), m. p. **112°** (Found : C, 59·6; H, 7·7; N, 6·0. $C_{12}H_{19}O_4N$ requires C, 59·6; H, 7·85; N, 6·0%).

N→O *acyl migration.* The *N*-acetyl derivative (0·**213** g.) in anhydrous dioxan (2 ml.) was heated with 7·5N-hydrogen chloride in dioxan (2 ml.) on the steam-bath for 4 hours.

O-*Acetylnor-3β-ecgonine ethyl ester hydrochloride* (III) (0·10 g.) had m. p. 228—229°, $[\alpha]_D^{20}$ +27·3° (*c*, 2 in water) (Found : C, **52·1**; H, 6·95; N, 5·4; Cl^-, 12·3. $C_{12}H_{19}O_4N$,HCl requires C, 51·9; H, 7·25; N, 5·05; Cl^-, **12·8**%). This salt is quite stable in water, the solution having pH ~7. This stability, together with the high m. p., suggests an amino-ester rather than an acylamide salt.

O→N *acyl migration.* The *O*-acetyl hydrochloride (0·584 g.) in anhydrous ethanol (2 ml.) was treated with N-ethanolic sodium ethoxide (2·1 ml.); the product was proved to be the *N*-acetyl compound by m. p. and mixed m. p.

N-Acetylnor-3α-ecgonine (I; R = Ac) *Ethyl Ester.*—Norecgonine (I; R = H) ethyl ester

(Einhorn, *Ber.*, 1888. **21**, 3029) (1·6 g.) was acetylated (steam-bath) with acetic anhydride (3 ml.) for ½ hour. The N-*acetyl* derivative formed needles (0·485 g.) (from ethyl acetate), m. p. 150°, $[\alpha]_D^{20}$ −19·4° (*c*, 2 in ethanol) (Found: C, 59·5; H, 7·6; N, 6·2. $C_{12}H_{19}O_4N$ requires C, 59·6; H, 7·85; N, 5·8%).

N→O *acyl migration.* Under the conditions used above for the N→O migration in the nor-3β-ecgonine derivative, the 3β-epimer did not yield an amino-ester salt.

O→N *acyl migration.* When the free amino-ester was liberated from *O*-benzoylnor-3α-ecgonine hydrochloride (obtained by oxidative degration of *O*-benzoylecgonine with potassium permanganate), the *N*-benzoyl derivative could not be detected. The product was monobasic towards 0·1N-hydrochloric acid.

Derivatives of 3α-*Ecgonine.*—2α-*Benzamidotropan*-3α-*ol* (IV). (−)-Benzoyl-3α-ecgonine (as I; R = Me) (6·94 g.), prepared by hydrolysis of cocaine (Liebermann and Giesel, *Ber.*, 1888, **21**, 3196), was dissolved in thionyl chloride (7 ml.) with cooling. The acid chloride hydrochloride, obtained on removal of the excess of thionyl chloride, was added to sodium azide (1·7 g.) in water (5 ml.) with ice-cooling and vigorous stirring. The mixture was then added to boiling 0·1N-hydrochloric acid (80 ml.) which, after evolution of nitrogen had ceased, was cooled to 15° and treated with 5N-sodium hydroxide (10 ml.). The precipitate was taken up in chloroform, furnishing a brown solid (3·515 g.) which was converted into the hydrochloride by ethanolic hydrogen chloride. 2α-*Benzamidotropan*-3α-*ol hydrochloride* formed colourless crystals (1·702 g.), m. p. 228° (from anhydrous ethanol), $[\alpha]_D^{20}$ −40·5° (*c*, 2 in water) (Found: C, 60·55; H, 6·9; N, 9·3; Cl^-, 11·5. $C_{15}H_{20}O_2N_2$,HCl requires C, 60·4; H, 7·1; N, 9·45; Cl^-, 12·0%). The free *base* formed colourless needles, m. p. 163°, $[\alpha]_D^{20}$ −6° (*c*, 2 in water) from ethanol–hexane [Found: C, 69·5; H, 6·9; N, 10·6%; equiv. (potentiometrically), 265. $C_{15}H_{20}O_2N_2$ requires C, 68·9; H, 7·6; N, 10·7%; equiv., 261].

2α-*Amino*-3α-*benzoyloxytropane dihydrochloride* (VI). 2α-Benzamidotropan-3α-ol hydrochloride (0·25 g.) in anhydrous methanol (2 ml.) was refluxed on the steam-bath for 15 minutes with 3·5N-ethanolic hydrogen chloride (3·3 ml.). The O-*benzoyl dihydrochloride* (0·25 g.), which crystallised from the boiling solution, had m. p. 214—215°, $[\alpha]_D^{20}$ −21·9° (*c*, 2 in water) (Found: C, 54·3, 53·9; H, 7·1, 6·9; N, 8·5, 8·3; Cl^-, 20·9, 20·0. $C_{15}H_{20}O_2N_2$,2HCl requires C, 54·0; H, 6·7; N, 8·4; Cl^-, 21·3%).

The reverse migration occurred instantaneously when the dihydrochloride in water was treated with N-sodium hydroxide. The benzamido-compound, m. p. 163°, was obtained in nearly quantitative yield.

2α-*Aminotropan*-3α-*ol dihydrochloride.* The mother liquors from the preparation of 2α-benzamidotropan-3α-ol hydrochloride (cf. above) were evaporated and the residue hydrolysed with 10% hydrochloric acid (20 ml.) for 2 hours. After extraction with ether, the aqueous solution was evaporated; crystallisation of the residue from methanol–ethyl acetate gave the *dihydrochloride* as prisms (0·63 g.) (Found: C, 41·2; H, 7·5; N, 11·6; Cl^-, 29·5. $C_9H_{16}ON_2$,2HCl requires C, 41·7; H, 7·8; N, 12·2; Cl^-, 30·8%).

Derivatives of 3β-*Ecgonine.*—(−)-O-*Benzoyl*-3β-*ecgonine.* 3β-Ecgonine was treated with benzoyl chloride (0·5 mol.), and the derivative isolated through the well-crystallised *nitrate*, m. p. 187° (Found: C, 55·3; H, 6·0; N, 8·2. $C_{16}H_{20}O_7N_2$ requires C, 54·3; H, 5·7; N, 7·95%), mentioned by Einhorn and Marquardt (*Ber.*, 1890, **23**, 979). The benzoate was obtained by adding sodium ethoxide to an alcoholic solution of the nitrate.

2α-*Benzamidotropan*-3β-*ol* (V). The benzoate (2·5 g.) was refluxed with excess of thionyl chloride (16 ml.), and the acid chloride *hydrochloride* (2·54 g.) precipitated with *n*-hexane (Found: C, 55·0; H, 5·5; N, 4·15; Cl^-, 20·7. $C_{16}H_{18}O_3NCl$,HCl requires C, 55·7; H, 5·5; N, 4·1; Cl , 20·6%). The acid chloride (0·933 g.) in chloroform (10 ml.) was added to sodium azide (0·39 g.) in water (1 ml.) with stirring. After 10 minutes, 3·12N-hydrochloric acid (1 ml.) was added, the chloroform then removed on the steam-bath, and more (1 ml.) of the acid added. The solution was boiled for 2 minutes and 4·8N-sodium hydroxide (2 ml.) added with stirring. The precipitated gum was extracted with ethyl acetate, the extract dried (Na_2SO_4) and evaporated, and the amorphous residue (0·474 g.) crystallised from benzene–*n*-hexane. 2α-*Benzamidotropan*-3β-*ol* (0·147 g.) formed needles, m. p. 203°, $[\alpha]_D^{20}$ +82° (*c*, 2 in water) (Found: C, 68·2; H, 7·8; N, 10·5. $C_{15}H_{20}O_2N_2$ requires C, 68·9; H, 7·6; N, 10·7%).

O-*Acetyl*-3β-*ecgonine hydrochloride.* 3β-Ecgonine hydrochloride (5 g.) was acetylated with acetyl chloride (50 ml.) in acetic anhydride (100 ml.) on the steam-bath for 3 hours. The *acetate*, precipitated by carbon tetrachloride (300 ml.), formed needles (3·5 g.), m. p. 238—240° (Found: N, 5·3; Cl^-, 13·6; Ac, 17·0. $C_{11}H_{17}O_4N$,HCl requires N, 5·3; Cl^-, 13·5; Ac, 15·9%). Treatment with hot thionyl chloride gave the acid chloride *hydrochloride*, m. p. 205—

207° (decomp.) (Found : Cl, 24·9. $C_{11}H_{16}O_3NCl$,HCl requires Cl, 25·1%), which was subjected to Curtius degradation in a manner similar to that used for the *O*-benzoyl compound. The product was benzoylated with benzoyl chloride and N-sodium hydroxide, but the precipitated gum could not be crystallised.

Attempted N→O *acyl migration.* Under the conditions used for attempted migration of the 2α : 3α-epimer, 2α-benzamidotropan-3β-ol gave a monohydrochloride (Found : N, 8·4; Cl^-, 11·5. Calc. for $C_{15}H_{20}O_2N_2$,HCl : N, 9·4; Cl^-, 11·95%), which with an excess of ethanolic picric acid gave a monopicrate, m. p. 220° (decomp.) (Found : N, 14·1. Calc. for $C_{15}H_{20}O_2N_2,C_6H_3O_7N$: N, 14·3%).

(−)-3α-*Ecgoninol.*—A solution of cocaine (30·3 g.) in dry ether (300 ml.) was added with ice-cooling and mechanical stirring, during 50 minutes, to an ethereal solution (0·5M ; 600 ml.) of lithium aluminium hydride ; stirring was continued for a further 30 minutes. Water (25 ml.) was then added dropwise and agitation continued for 50 minutes. The precipitated aluminium hydroxide was extracted with ethanol (total, 450 ml.), the pH of the combined extracts adjusted with ethanolic hydrochloric acid to pH 3, and the solvent then evaporated *in vacuo*. 3α-Ecgoninol hydrochloride (16·8 g.) had m. p. 270—272° after several crystallisations from ethanol [Rosenmund (*loc. cit.*) recorded m. p. 276° for the product of hydrogenation of (−)-ecgonine], $[\alpha]_D^{20}$ −37·3° (*c*, 3 in water) (Found : C, 51·8; H, 8·5; N, 6·7; Cl^-, 16·9. Calc. for $C_9H_{17}O_2N$,HCl : C, 52·0; H, 8·7; N, 6·75; Cl^-, 17·1%). Shaking an aqueous solution of the hydrochloride with silver oxide for 2 hours liberated the free base as an oil.

(+)-3β-*Ecgoninol.*—To an ethereal solution (0·5M ; 800 ml.) of lithium aluminium hydride an ethereal suspension (300 ml.) of (+)-3β-ecgonine methyl ester (19·9 g. ; m. p. 116°) was added with stirring during 2 hours, and the stirring was continued a further 2 hours. The complex salt was decomposed with water (30 ml.) added dropwise, the precipitate taken up in ethanol (3 × 200 ml.), the solution evaporated to dryness, and the residue crystallised from acetone. 3β-*Ecgoninol* (10·1 g.) had m. p. 131—133°, $[\alpha]_D^{20}$ +58·3° (*c*, 3 in water) (Found : C, 63·3; H, 9·8; N, 8·3. $C_9H_{17}O_2N$ requires C, 63·3; H, 9·95; N, 8·2%). The *hydrochloride*, prepared from the base and 5N-ethanolic hydrochloric acid, formed needles m. p. 232—233°, $[\alpha]_D^{20}$ +46·3° (*c*, 3 in water) (Found : C, 51·7; H, 8·5; N, 7·0; Cl^-, 16·9%).

OO′-*Benzylidene*-3α-*ecgoninol* (VII) *Benzenesulphonate.*—3α-Ecgoninol (5·13 g.) was dissolved in freshly distilled benzaldehyde (50 ml.), and benzenesulphonic acid (5·70 g.) added. After the transitory violet fluorescence had disappeared the solution was heated at 85°/40 mm. for 5 hours, some of the benzaldehyde distilling off into concentrated sulphuric acid. During the night needles crystallised from the solution and more were obtained by addition of light petroleum. The *benzenesulphonate* formed colourless needles (from ethanol–ether) (6·5 g.), m. p. 192—194°, $[\alpha]_D^{20}$ −9·43° (*c*, 2 in ethanol) (Found : C, 63·1; H, 6·2; N, 3·8; S, 7·7. $C_{22}H_{27}O_5NS$ requires C, 63·3; H, 6·5; N, 3·35; S, 7·7%) This compound was very sensitive to water and alcoholic mineral acids ; excess of alcoholic hydrochloric acid cause immediate cleavage into 3α-ecgoninol hydrochloride.

Similar treatment of 3β-ecgoninol failed to give any benzylidene derivative ; the product gave correct analytical data for 3β-*ecgoninol benzenesulphonate* (Found : C, 54·3; H, 6·95; N, 3·8; S, 9·25. $C_{15}H_{23}O_5NS$ requires C, 54·65; H, 7·0; N, 4·25; S, 9·7%).

Reaction of the Ecgonines with Chloral Hydrate.—(*a*) (2α : 3α)-Ecgonine hydrochloride (2·22 g.) and chloral hydrate (1·66 g., 1 mol.) were intimately mixed and 98% sulphuric acid (4 ml.) added with stirring. After 2 hours at 20° the solution was treated with dry ether (5 × 15 ml.), and the residue washed with dry ethanol–ether (1 : 1 ; 5 × 10 ml.) in the centrifuge tube. The white product (1·25 g.), m. p. 247—249° (decomp.), gave analytical data suggestive of *anhydroecgonine hydrogen sulphate* (Found : C, 40·4; H, 5·7; N, 4·8; S, 12·5. $C_9H_{15}O_6NS$ requires C, 40·7; H, 5·7; N, 5·3; S, 12·1%). Addition of barium chloride to an aqueous solution of the salt gave anhydroecgonine hydrochloride, m. p. 238—240° (Liebermann, *Ber.*, 1907, **40**, 3602, gave m. p. 241°).

(*b*) (2α : 3β)-Ecgonine (2·22 g.) similarly treated gave (2α : 3β)-*ecgonine hydrogen sulphate* (1·15 g.), m. p. 225° (Found : C, 37·9; H, 6·0; N, 4·85; S, 11·45. $C_9H_{17}O_7NS$ requires C, 38·15; H, 6·0; N, 4·95; S, 11·3%).

This work reported in this and the preceding paper was supported by the Hungarian Academy of Science. The author is indebted to Dr. Eva Fodor-Varga for microanalyses and conductometric titrations, to Miss C. Láng for nitrogen and halogen estimations, and to Misses E. Füzessy and A. Borbás for their technical assistance.

INSTITUTE OF ORGANIC CHEMISTRY,
THE UNIVERSITY, SZEGED, HUNGARY.

[*Received, April 30th*, 1952.]