185. *The Stereochemistry of the Tropane Alkaloids. Part VIII.* The Absolute Configurations of the Nitrogen Atoms in Some Optically Active Tropanols and Derived Quaternary Salts.*

By ÖDÖN KOVÁCS, GÁBOR FODOR, and MIKLÓS HALMOS.

Absolute configurations have been assigned to the nitrogen atoms in quaternary salts prepared from (−)-ecgoninol and ethyl iodoacetate, and from (−)-norecgoninol with ethyl iodoacetate and methyl iodide. In the products from the first route the *N*-acetic acid residue is oriented towards the pyrrolidine ring, in those from the second route towards the piperidine ring. These findings are related to results obtained in other series.

THE recent observation of the formation of lactone salts from the tertiary bases and ethyl iodoacetate, and of *N*-epimeric ester-ammonium salts from the nor-compounds by reaction with ethyl iodoacetate and subsequent quaternisation with methyl iodide, made possible the assignment of definite configurations to the nitrogen atoms in tropane-3α : 6β-diol, oscine, and derived quaternary salts.

In order further to evaluate the relative importance of the two factors (the Pitzer effect arising from strain in the five-membered ring, and the occurrence of hydrogen-bonding between the unshared electron pair of the nitrogen atom and the hydroxyl group attached to the pyrrolidine ring) which were considered [1] to give rise to this selectivity of quaternisation we have now extended the investigation to ecgoninol (2β-hydroxymethyltropan-3β-ol) and norecgoninol, compounds related to cocaine,[2] to which absolute configurations [3] could be assigned. The availability of optically pure ecgoninol makes it possible to distinguish between optically active *N*-epimers in this group more easily and reliably by measurement of $[\alpha]^{20}_{D}$ than by m. p.s and crystal photographs.

With ethyl iodoacetate, diacetylecgoninol (I*b*) gave the ester-salt (II*a*) from which were prepared, in the usual way, the betaine (II*b*) and the slightly dextrorotatory carboxymethyl-compound (II*c*). Similarly, there was obtained from norecgoninol (I*d*) [prepared by von Braun degradation of (I*b*)] *N*-ethoxycarbonylmethyl-3β-hydroxy-2β-hydroxymethyl-nortropanium chloride (III*a*). This was converted into the free acid (III*c*), the betaine (III*b*), and the diacetyl ester (III*d*). With methyl iodide in toluene at 120° the free base from (III*d*) gave the lactone salt (IV), together with an amorphous mixture, presumably of partially acetylated isomeric lactones and ester salts. However, upon hydrolysis this mixture furnished only the carboxymethyl compound (V*a*) and the corresponding betaine (V*b*).

The carboxymethyl derivatives and betaines from these two reaction sequences show striking differences in rotational values. Quaternisation of ecgoninol produced a strong positive shift in rotation, whilst the reverse sequence gave compounds in which the original lævorotation was maintained or increased. Although the lactone salt (IV) is an exception to this rule, its reconversion into the strongly lævorotatory (V*a*) and (V*b*) excludes the possibility that racemisation may have occurred during quaternisation. The optical inactivity of the salt (IV) is perhaps not surprising since such bridged tropanes as the cyclic ureide of *N*-carbamoylnorecgonine and the $C_{(2)}$-epimeric tetrahydro-1 : 3-oxazines from the 2-methylnortropan-3-ols show a dextro-shift by comparison with their unbridged parents.[2b] The correlation of conformational changes with rotational values in this field requires closer examination.

The uncertainty as to whether the formula (IV) correctly represents the lactone, or whether the 3-hydroxyl group is involved in lactonisation, does not affect the conclusion that this lactone is derived from *N*a-carboxymethyl-3β-hydroxy-2β-hydroxymethyltropanium iodide (see Part VI [1] for nomenclature), and that identical configurations at the nitrogen can

---

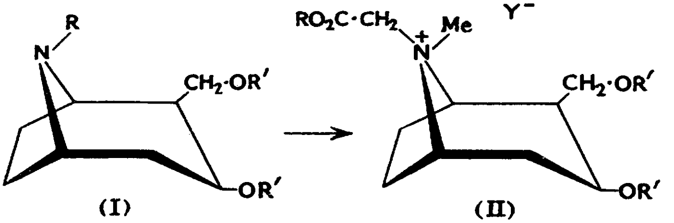
* Part VII, Kovács, Weisz, Zoller, and Fodor, *Helv. Chim. Acta*, 1956, **39**, 99.

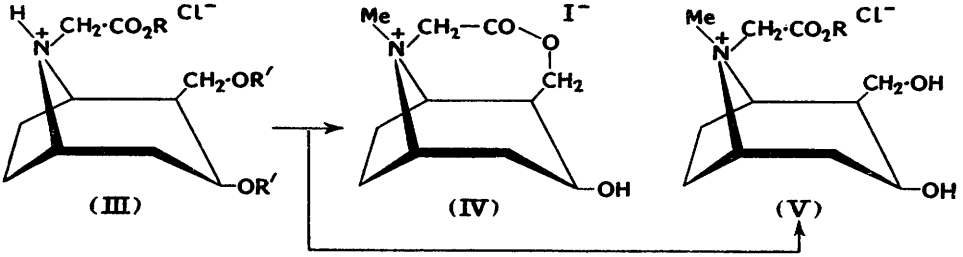
[1] Fodor, Tóth, and Vincze, Part VI, *J.*, 1955, 3504.

[2] (*a*) Fodor and Kovács, *J.*, 1953, 724; (*b*) Fodor, Kovács, and Weisz, *Nature*, 1954, **174**, 131.

[3] Hardegger and Ott, *Helv. Chim. Acta*, 1955, **38**, 312.

be deduced for the salts (III) and (V), the opposite configuration occurring in the quaternary salts (II*a*—*c*). Thus the *N*-methyl groups in (I*a*) and (I*b*) and the ethoxycarbonylmethyl group in the *free base* related to (III) appear to be predominantly oriented towards the piperidine ring. These findings thus indicate the predominating importance of the Pitzer effect, for strong hydrogen bonding between hydroxyl and nitrogen in the tertiary bases would orient *N*-substituents in the latter towards the pyrrolidine ring.





	R	R′	$[\alpha]_D^{20}$	R	R′	Y⁻	$[\alpha]_D^{20}$		R	R′	$[\alpha]_D^{20}$	R	R′	Y⁻	$[\alpha]_D^{20}$
	Formula (I)			Formula (II)					Formula (III)			Formula (V)			
(*a*)	Me	H	−23·3°	Et	Ac	I	−21°	(*a*)	Et	H	−42·6°	H	—	Cl	−38·6°
(*b*)	Me	Ac	−57	*	H	*	+8·5	(*b*)	*‡	H	−64·3	*	—	*	−60·8
(*c*)	CN	Ac	−72·4	H	H	Cl	+4·1	(*c*)	H	H	−45				
(*d*)	H	H	†					(*d*)	Et	Ac	−38·4				

* Absent. † No data. ‡ Also no Cl^-.

Quaternisations of the tropines are now being studied.

EXPERIMENTAL

Unless otherwise stated, rotations were measured in dry MeOH.

3β-*Acetoxy*-2β-*acetoxymethyltropane* (*Diacetylecgoninol*) (I*b*).—The oily residue (59·7 g.) obtained by refluxing ecgoninol hydrochloride[2a] (41·5 g.) with acetic anhydride (120 ml.) for ½ hr. and concentrating the solution under reduced pressure was treated with water (200 ml.) and potassium carbonate and extracted with ether (300 ml. in all). Distillation gave the product (48·1 g.), b. p. 155—157°/4 mm., $[\alpha]_D^{20}$ −57·0 ± 1° (*c* 2·105). The base (2·55 g.) in dry acetone (30 ml.), with dry ethanolic hydrogen chloride (2·38 ml. of 15·3%), gave, on addition of dry ether (10 ml.), the *diacetate hydrochloride* (2·7 g.), m. p. 198° (decomp.), $[\alpha]_D^{20}$ −32·8° ± 1° (*c* 1·917) (Found: C, 53·3; H, 7·7; N, 4·9; Cl^-, 12·2. $C_{13}H_{22}O_4NCl$ requires C, 53·5; H, 7·6; N, 4·8; Cl^-, 12·2%).

3β-*Acetoxy*-2β-*acetoxymethyl*-Nb-*ethoxycarbonylmethyltropanium Iodide* (II*a*).—Ecgoninol diacetate (12·27 g.) and ethyl iodoacetate (32·1 g.) were heated in a sealed tube at 70° for 48 hr. The product was washed with chloroform, dried, and recrystallised from dry ethanol–ether, to give the *iodide* (18·9 g.), m. p. 153°, $[\alpha_D^{20}]$ −2·1° ± 1° (*c* 1·888) (Found: C, 43·6; H, 6·2; N, 3·15; I^-, 27·0. $C_{17}H_{28}O_6NI$ requires C, 43·5; H, 6·0; N, 3·0; I^-, 27·0%).

3β-*Hydroxy*-Nb-*carboxymethyl*-2β-*hydroxymethyltropanium Chloride* (II*c*).—A suspension of alkali-free silver oxide (from 3·4 g. of nitrate) in water (100 c.c.) was shaken with the ester iodide (II*a*) (4·68 g.) for 5 min. and then filtered. The filtrate was treated with concentrated hydrochloric acid (50 ml.), boiled for 4 hr., decolorised (charcoal), and evaporated. Recrystallisation of the residue from ethanol–ether gave the *acid chloride* (2·32 g., 87%), m. p. 210°

(decomp.), $[\alpha]_D^{20}$ +4·1° ± 1° (*c* 1·933) (Found : C, 50·1; H, 7·4; N, 5·3; Cl⁻, 13·0. $C_{11}H_{20}O_4NCl$ requires C, 49·7; H, 7·6; N, 5·3; Cl, 13·3%).

Nb-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethyltropanium Betaine* (II*b*).—By the method described below for (V*b*) the above chloride (2·65 g.) and silver oxide provided the *betaine* (2·02 g.), m. p. 272° (decomp.), $[\alpha]_D^{20}$ +8·5° ± 1° (*c* 0·939 in 90% MeOH) (Found : C, 57·7; H, 8·4; N, 6·2. $C_{11}H_{19}O_4N$ requires C, 57·6; N, 8·35; N, 6·1%).

3β-*Acetoxy*-2β-*acetoxymethyl*-N-*cyanonortropane* (I*c*).—Diacetylecgoninol (38·3 g.) in benzene (300 ml.) was added drop by drop during 4 hr. to a vigorously stirred solution (previously dried over calcium chloride) of freshly distilled cyanogen bromide (35 g.) in benzene (350 ml.). The mixture was refluxed for 5 hr. and evaporated to dryness. The yellow crystals (25·65 g.) were washed with ether (2 × 30 ml.) and then extracted with this solvent for 18 hr. Concentration of the combined extract and a further washing gave the *cyano-compound* (24·5 g.), m. p. 109°, $[\alpha]_D^{20}$ −72·4° ± 1° (*c* 2·015) (Found : C, 59·0; H, 6·6; N, 10·4. $C_{13}H_{18}O_4N_2$ requires C, 58·6; H, 6·8; N, 10·5%). From the ethereal mother-liquors diacetylecgoninol (8 g.) was recovered.

3β-*Hydroxy*-2β-*hydroxymethylnortropane* (*Norecgoninol*) (I*d*).—The cyano-compound (36 g.), sodium hydroxide (36 g.), and water (350 ml.) were refluxed for 8 hr. The residue obtained by acidifying (Congo-red) the solution with hydrochloric acid and evaporating it to dryness was extracted with dry ethanol (8 × 100 ml.), and the extract was concentrated to 60 ml. and treated with the calculated quantity of sodium methoxide. Evaporation, extraction with chloroform (200 ml.), and distillation gave the nor-base, b. p. 146—150°/5 mm. The base (0·314 g.) and picric acid (0·460 g.) in ethanol (7 ml.) gave the *picrate* (0·45 g. after recrystallisation from ethanol), m. p. 180° (Found : C, 43·5; H, 4·6; N, 14·7. $C_{14}H_{18}O_9N_4$ requires C, 43·5; H, 4·7; N, 14·5%).

N-*Ethoxycarbonylmethyl*-3β-*hydroxy*-2β-*hydroxymethylnortropanium Chloride* (III*a*).—Crude norecgoninol (19·1 g.), ethyl iodoacetate (12·83 g.), and dry ethanol (90 ml.) were kept at room temperature for 36 hr. The solution in chloroform (150 ml.) of the brownish syrupy residue obtained by evaporating the mixture *in vacuo* was washed with water. The water was extracted with chloroform (50 ml.), and the combined chloroform solutions were dried ($MgSO_4$), acidified with dry alcoholic hydrogen chloride, and evaporated. Crystallised from alcohol–ether the residue gave the *chloride* (12 g.), m. p. 195—196° (decomp.), $[\alpha]_D^{20}$ −42·6° ± 1° (*c* 2·015) (Found : C, 51·8; H, 7·8; N, 5·3; Cl⁻, 12·8. $C_{12}H_{22}O_4NCl$ requires C, 51·7; H, 7·6; N, 5·0; Cl⁻, 12·7%).

N-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethylnortropanium Chloride* (III*c*).—The ester (2·78 g.), water (20 ml.), and concentrated hydrochloric acid (10 ml.) were refluxed 3 hr. and evaporated to dryness. Recrystallisation of the residue from methanol–ether gave the *chloride* (2·22 g.), m. p. 181° (decomp.), $[\alpha]_D^{20}$ −45° ± 1° (*c* 1·997) (Found : C, 47·9; H, 7·4; N, 5·5; Cl⁻, 13·8. $C_{10}H_{18}O_4NCl$ requires C, 47·7; H, 7·2; N, 5·6; Cl⁻, 14·1%).

This specimen, water (20 ml.), and fresh silver oxide (3·4 g.) were shaken for 5 min. Filtration (charcoal) and evaporation *in vacuo* gave the *betaine* (III*b*) (1·95 g.), m. p. 247° (decomp.), $[\alpha]_D^{20}$ −64·3° ± 1° (*c* 0·932) (Found : C, 55·6; H, 7·8; N, 6·5. $C_{10}H_{17}O_4N$ requires C, 55·8; H, 7·8; N, 6·5%), after crystallisation from ethanol–ether.

3β-*Acetoxy*-2β-*acetoxymethyl*-N-*ethoxycarbonylmethylnortropanium Chloride* (III*d*).—The ester-salt (III*a*) (2·78 g.) and acetic anhydride (25 ml.) were heated for 4 hr. on the steam-bath and kept overnight at room temperature. The residue obtained by concentration *in vacuo* was crystallised from dry acetone and dry ether, giving the *diacetyl derivative* (2·69 g.), m. p. 164°, $[\alpha]_D^{20}$ −38·4° ± 1° (*c* 1·971) (Found : C, 52·8; H, 7·3; N, 3·8; Cl⁻, 9·7. $C_{16}H_{26}O_6NCl$ requires C, 52·8; H, 7·2; N, 3·85; Cl⁻, 9·7%).

Na-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethyltropanium Iodide Lactone* (IV).—Ethanolic sodium ethoxide (2·12 ml. of 5·42%) was added to the diacetyl derivative (1·819 g.) in dry acetone (40 ml.). The precipitate was removed at the centrifuge, and the base, freed from acetone, was heated for 10 hr. at 120—125° with toluene (5 ml.) and methyl iodide (4 ml.). The red crystals were collected (the filtrate was retained; see below), washed with acetone, and recrystallised from dry ethanol–ether, giving the *lactone* (0·422 g.), m. p. 200° (decomp.), $[\alpha]_D^{20}$ ±0° (*c* 1·926) (Found : C, 38·7; H, 5·7; N, 3·7; I⁻, 37·4. $C_{11}H_{18}O_3NI$ requires C, 38·95; H, 5·35; N, 3·9; I⁻, 37·4%).

Na-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethyltropanium Chloride* (V*a*).—(*a*) The lactone (0·727 g.), 50% aqueous methanol (30 ml.), freshly precipitated silver chloride (0·43 g.), and water (10 ml.) were shaken for 6 hr. Silver iodide was removed and the solution and concentrated hydrochloric acid (20 ml.) were refluxed for 2 hr., filtered (charcoal), and evaporated *in vacuo*. From dry methanol–ether the residue gave the *chloride* (0·320 g.), m. p. 205°

(decomp.), $[\alpha]_D^{20}$ −38·6° ± 1° (*c* 0·983) (Found: C, 50·0; H, 7·6; N, 5·6; Cl^-, 13·3. $C_{11}H_{20}O_4NCl$ requires C, 49·7; H, 7·6; N, 5·3; Cl^-, 13·35%).

(*b*) The red syrupy residue, from evaporation of the acetone–toluene mother-liquor from (IV), was treated in water (20 ml.) with alkali-free silver oxide (from 1·7 g. of silver nitrate). The residue obtained by filtration, refluxing for 3 hr. with concentrated hydrochloric acid, and evaporation formed from methanol–ether crystals of the chloride (0·795 g.), m. p. 204° alone and mixed with a specimen from (*a*), $[\alpha]_D^{20}$ −38·0° ± 1° (*c* 1·92).

This chloride (0·265 g.), water (5 ml.), and silver oxide (from 0·34 g. of silver nitrate) were shaken for 5 min. Filtration, evaporation to dryness, and recrystallisation from dry methanol–ether gave the *betaine* (V*b*) (0·198 g.), m. p. 238° (decomp.), $[\alpha]_D^{20}$ −60·8° ± 1° (*c* 2·20 in 90% methanol) (Found: C, 58·1; H, 8·2; N, 6·2%).

The investigations were sponsored by the Hungarian Academy of Sciences. We thank our colleagues Dr. Eva Fodor-Varga, Miss C. Láng, and Miss R. Minárovits for microanalyses.

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

[*Received, July 26th*, 1955.]