The Stereochemistry of the Tropane Alkaloids. Part VI. The Configuration of the Nitrogen Atom in Tropane-3α : 6β-diol, Oscine, and the Derived Quaternary Salts.*

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The ester salt from (±)-tropane-3α : 6β-diol and ethyl iodoacetate readily gave a lactone salt, whereas the ester salt from (±)-*N*-ethoxycarbonylmethylnortropane-3α : 6β-diol and methyl iodide was incapable of lactonising. This selectivity of quaternisation, producing *N*-epimers, is contrasted with the behaviour of oscine and noroscine, and is discussed in terms of the Pitzer effect and of the possibility of hydrogen-bonding. Definite configurations are ascribed to the nitrogen atoms in a number of the compounds discussed.

THE steric orientation of the oxygen-containing functional groups at $C_{(2)}$, $C_{(3)}$, and $C_{(6/7)}$ in the tropane alkaloids, relative to the —NMe bridge as a whole, has already been established (Parts I—V of this series). In subsequent investigations tropan-3β-ol (for nomenclature see Part I, *J.*, 1953, 721) was found to give with ethyl iodoacetate a single quaternary salt, *N*-ethoxycarbonylmethyl-3β-hydroxytropanium iodide [Scholtz and Bode (*Arch. Pharm.*, 1904, **242**, 568) earlier obtained only one of the two possible *N*-epimers from the quaternisation of tropine, atropine, brucine, and strychnine]. However, nortropan-3β-ol furnished, *via* *N*-ethoxycarbonylmethylnortropan-3β-ol and quaternisation with methyl iodide, a different, obviously *N*-epimeric form of the tropanium iodide. These stereoisomers had different crystal forms, melting points, solubilities and Debye-Scherrer diagrams (Fodor, Meeting Hungarian Chem. Soc., Szeged, September 18th, 1952; cf. Fodor, Koczka, and Lestyán, *Magyar Kém. Folyóirat*, 1953, **59**, 243). Similarly, tropine and ethyl iodide gave a salt different from that arising from *N*-ethylnortropine and methyl iodide (Tóth, Meeting Hungarian Chem. Soc., Debrecen, September 27th, 1953; Fodor, Lestyán, Tóth, and Vincze, *Vegyipari Kutató Intézetek Közleményei*, 1954, **4**, 293; Fodor, *Experientia*, 1955, **11**, 129), a result at variance with the findings of Findlay (*J. Amer. Chem. Soc.*, 1953, **75**, 3204) who claimed to have obtained the same salt by both methods, although he found *N*-propylnortropine and ethyl iodide to give a salt isomeric with that from *N*-ethylnortropine and propyl iodide. This special problem will be discussed later.

The formation, in fairly good yields and with none of the *N*-epimers, of lactone iodide such as (III), *via* the ester salt (II), from ethyl iodoacetate and (±)-tropane-3α : 6β-diol (I), (±)-oscine (VII*a*), or teloidine has been regarded previously as definite evidence for the β-orientation of the functional groups on the *endo*ethylene bridge of these alkaloids (Part V, *loc. cit.*). It also indicates the relative configuration of the asymmetric nitrogen atom in these quaternary lactone salts, the $-CH_2{\cdot}CO-$ groups being oriented towards the pyrrolidine ring, the methyl group in the opposite direction. Von Braun degradation of the base (I) to the previously unknown (±)-nortropane-3α : 6β-diol (IV), followed by treatment with ethyl iodoacetate, gave (±)-*N*-ethoxycarbonylmethylnortropane-3α : 6β-diol (V*b*) which with methyl iodide gave the salt (VI*b*), the *N*-epimer of (II). Acid hydrolysis of the ester (V*b*) gave only *N*-carboxymethylnortropane-3α : 6β-diol hydrochloride (V*a*) which showed no tendency to lactonise, a fact which points to its being *Na*-carboxymethylnortropane-3α : 6β-diol hydrochloride.† Further, the methiodide (VI*b*), in contrast to its *N*-epimer (II), could not be transesterified to the lactone (III). Hydrolysis of the ester (VI*b*) to the betaine, and treatment of the latter with hydriodic acid, gave no trace of lactone (III), most of the material being converted into the salt of the hydroxy-carboxylic acid (VI*a*).

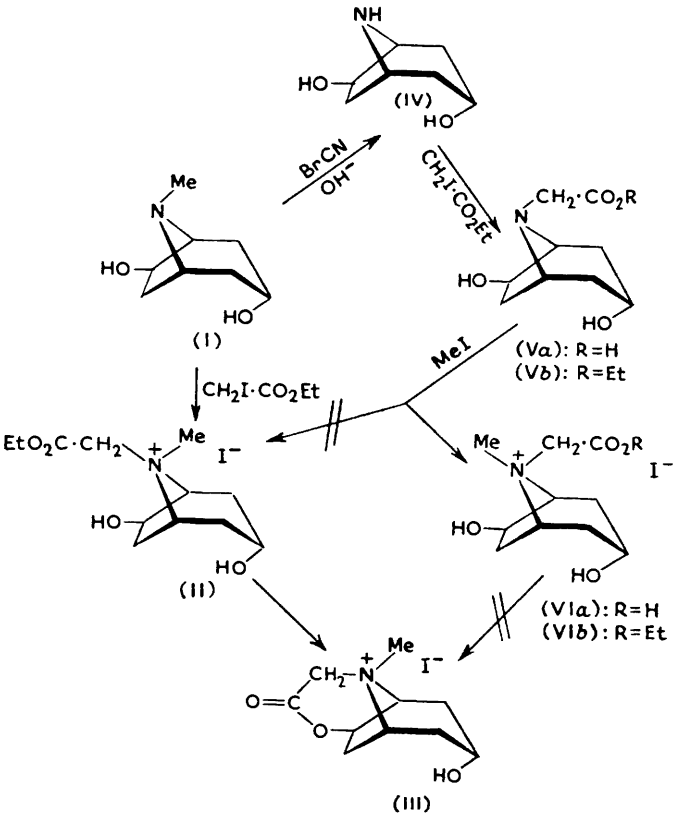
Thus, the methiodide is certainly *Na*-ethoxycarbonylmethyl-3α : 6β-dihydroxytropanium

* Part V, *Helv. Chim. Acta*, 1953, **37**, 907.

† The use of "α" and "β" to indicate the configurations of hydroxyl groups will be familiar from previous papers in this series. The further convention is now proposed, that substituents on the nitrogen atom which are directed towards the piperidine ring [see, for example, (II)] be given the prefix "*a*," and those directed to the pyrrolidine ring the prefix "*b*."

iodide (VI*b*), this being the first reported determination of the configuration of a quaternary ammonium salt. The method used should be capable of extension.

The question arises, whether knowledge of the configurations of the quaternary salts permits deduction of those of the parent tertiary amines, relatively high configurational stability being assumed for the latter. In forming the salts (II) and (VI*b*) the quaternising cation must approach the nitrogen atom from the pyrrolidine side of the molecule, which suggests that in each case the acyclic nitrogen substituent initially present is oriented more frequently towards the piperidine ring. Otherwise, quaternisation of the base (I) or (V*b*) should give both *N*-epimers (II) and (VI*b*). Hitherto, however, only the Troeger base, containing two rigidly bound nitrogen atoms, has been resolved (Prelog and Wieland,

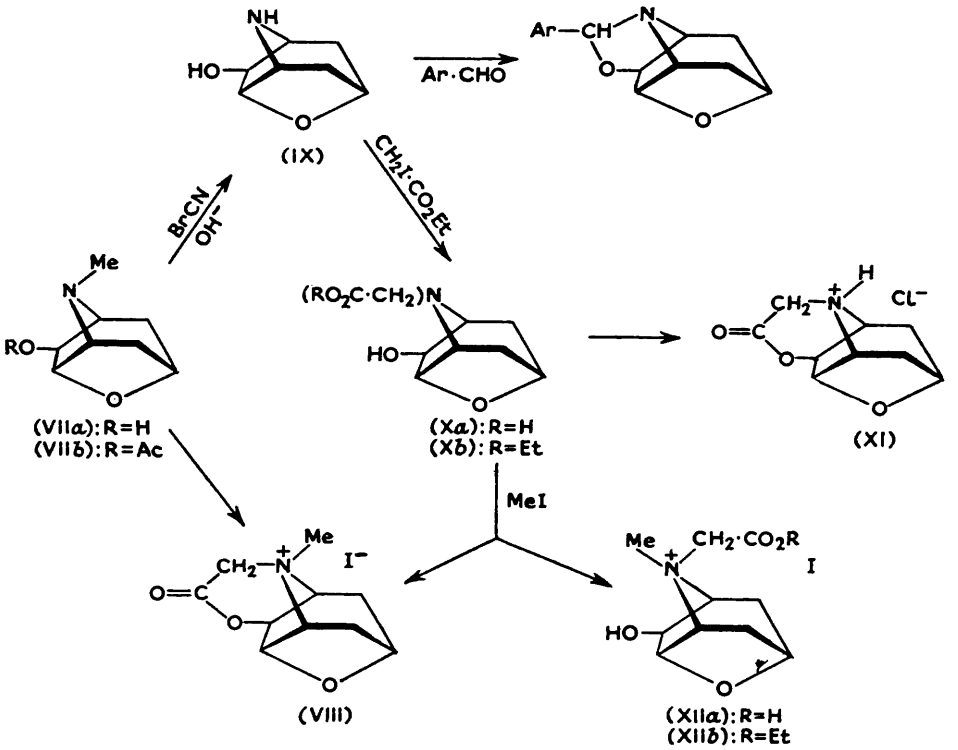


Helv. Chim. Acta, 1944, **27**, 1127; cf. Gilman, "Organic Chemistry," Wiley, 1942, New York, Vol. I, p. 411). Nevertheless, since nitrogen in the tropane system is rigidly bound by two electron pairs, a definite orientation of the third substituent and, according to recent calculations (Lennard-Jones, *Proc. Roy. Soc.*, 1951, *A*, **205**, 357), of the unshared electron pair cannot be excluded.

It remains to explain the more favoured orientation towards the piperidine ring of the acyclic nitrogen substituent in the tertiary bases, especially since this orientation is axial with respect to the six-membered ring. The tropane system might be regarded as a 2 : 6-diaxially substituted piperidine, and since 1 : 3-diaxially substituted *cyclo*hexane rings render a substituent at $C_{(2)}$ more stable when axial than when equatorial (Barton, *Chem. and Ind.*, 1953, **664**), the alkyl group at the nitrogen atom would therefore assume an axial position also. However, the selectivity of quaternisation cannot be referred wholly to the piperidine ring, for *N*-alkylpiperidines such as 4-hydroxy-*N*-methylpiperidine (Mills, Parkin, and Ward, *J.*, 1927, 2625), *N*-methylconiine, conhydrine, and even (—)-2-methyl-6-phenylpiperidine (Scholz, *Ber.*, 1904, **37**, 3627) furnish both possible *N*-epimers on

quaternisation. In tertiary amines of the tropane system the *meta*-annelation must cause deformation of the pyrrolidine ring, and consequent operation of the Pitzer effect (*J. Amer. Chem. Soc.*, 1947, **69**, 2488) will result in a shift of the *N*-methyl group towards the six-membered ring. The configuration of the tertiary nitrogen atom may thus be a factor influencing the ring conformation, for in the chair form the piperidine ring would then avoid repulsion between the *N*-methyl group and the 3-substituent. Further, with tropane-3α : 6β-diol (I) the shift of the *N*-methyl group towards the piperidine ring meets the steric requirement for hydrogen-bonding of the *syn*-hydroxyl group to the unshared electron pair of the nitrogen.

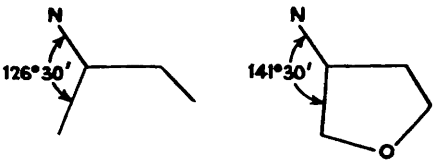
In contrast, the Pitzer effect in the pyrrolidine ring, and the tendency to hydrogen-bonding, are in conflict in other tropane derivatives such as tropan-3β-ol and the ecgonines, where hydrogen-bonding can occur only in the boat form of the piperidine ring.



To estimate the contribution of the deformation in the five-membered ring to the relative configurational stability of nitrogen, oscine (VII*a*) and noroscine (IX) were chosen as models for further " direct " and " reverse " quaternisation experiments. (±)-Oscine acetate (VII*b*) furnished with ethyl iodoacetate the lactone iodide (VIII) in far better yield than does oscine (VII*a*) itself. This may be due to the absence from the acetate (VII*b*) of a hydrogen bond which might hinder quaternisation. (±)-Noroscine (IX), on the other hand, gave with ethyl iodoacetate, (±)-*N*-ethoxycarbonylmethylnoroscine (X*b*), hydrolysis of which was accompanied by spontaneous lactonisation to the hydrochloride (XI). This contrasts with the inability of *N*-carboxymethylnortropane-3α : 6β-diol (V*a*) to lactonise. Further, with methyl iodide the ester (X*b*) gave both the *N*-ethoxycarbonylmethyl derivative (XII*b*) and the lactone of the *N*-epimeric tropanium iodide (VIII). With hydriodic acid the betaine obtained by hydrolysis of the ester salt (XII*b*) afforded the acid (XII*a*) which showed no tendency to cyclise to (VIII). The acid and ester are therefore *Na*-carboxymethyloscinium iodide (XII*a*) and *Na*-ethoxycarbonylmethyloscinium iodide (XII*b*) respectively.

These findings seem to indicate a marked decrease in the configurational stability of the nitrogen atom when $C_{(3)}$ and $C_{(6)}$ in the tropane system are joined by an ether bridge. The bridge draws these carbon atoms towards each other, decreasing simultaneously the deformation of the pyrrolidine ring. Thus, coplanarity is more nearly approached than in the 3 : 6-unbridged skeleton, and the influence of the Pitzer effect in determining the preferred orientation of the acyclic substituent on the nitrogen may be strikingly diminished.

By using values for interatomic distances and unstrained valency angles given in Landolt–Börnstein's tables, scale models of 3α : 6β-dihydroxytropane and oscine have been constructed. In making the projections the interatomic distances were kept unaltered and deformations of the individual valency angles were distributed over the entire molecule. On this basis the angle " α " (see diagram) would be 15° larger in oscine (VII*a*) than in tropane-3α : 6β-diol (I), in accordance with our assumption.



Granatan-3β-ol did not show any appreciable selectivity in quaternisation reactions. Here both rings are flexible (*i.e.*, able to assume chair forms) and no interference of the Pitzer type can be reasonably expected, though this inference needs the support of experimental evidence for the chair form of both rings.

In extension of this work, and in order to establish the limitation of the selectivity, the " direct " and " reverse " quaternisation of tropines with a pseudoasymmetric nitrogen atom, and subsequently of some single pyrrolidines such as γ-hydroxyproline, will be discussed. The curarine-like activity of *N*-epimeric tropanium salts of known *N*-configuration is being investigated by Dr. Gyermek.

Experimental

(*A*) *Derivatives of* (±)-*tropane*-3α : 6β-*diol.*

Direct Quaternisation of (±)-*Tropane*-3α : 6β-*diol* (I).—Ethyl iodoacetate (7·5 ml.) in benzene (50 ml.) was added to (±)-tropane-3α : 6β-diol (5 g.) in dry ethanol (30 ml.), and the mixture refluxed for 14 hr. Filtration and washing with alcohol gave (±)-*Nb*-carboxymethyl-3α : 6β-dihydroxytropanium iodide lactone (III) (4·6 g.), m. p. 263° (decomp.) (Fodor, Tóth, and Vincze, *loc. cit.*), or 259° after crystallisation from alcohol. From alcohol the amorphous residue obtained by evaporating the mother-liquor provided crystals (2·2 g.) which on repeated crystallisation from this solvent gave (±)-Nb-*ethoxycarbonylmethyl*-3α : 6β-*dihydroxytropanium iodide* (II), m. p. 151° (Found : C, 38·5; H, 6·1; I^-, 34·2. $C_{12}H_{22}O_4NI$ requires C, 38·8; H, 6·0; I, 34·2%), which resolidified after melting and remelted at the m. p. of the lactone (III). By refluxing the ester iodide (II) (0·43 g.) in dry alcohol (10 ml.) for 4 hr., evaporating the solution, and recrystallising the residue from dry alcohol, the lactone (III) (0·29 g.), m. p. 258° (decomp.) (Found : C, 37·1; H, 4·8; I, 39·0. Calc. for $C_{10}H_{16}O_3NI$: C, 36·9; H, 5·0; I, 39·0%), was obtained.

Tropane-3α : 6β-*diol Diacetate.*—(±)-Tropane-3α : 6β-diol (I) (19 g.) and acetic anhydride (160 ml.) were refluxed for 3 hr. The solution, in water (20 ml.), of the oil left after removal of acetic anhydride was adjusted to pH 8 with sodium carbonate (0·5 g.), and extracted with chloroform (4 × 100 ml.). Careful evaporation of the dried extract (K_2CO_3) gave tropane-3α : 6β-diol diacetate (25·9 g.) as a viscous oil, $n_D^{22\cdot3}$ 1·4744. This (0·24 g.), in dry ethanol (1 ml.), gave, with a saturated ethanolic solution (9 ml.) of picric acid, yellow crystals of (±)-*tropane*-3α : 6β-*diol diacetate picrate* (0·44 g.), m. p. (unchanged after recrystallisation from ethanol) 174—175° (Found : C, 45·7, 45·8, 45·8; H, 4·5, 4·9, 4·8; N, 11·9. $C_{18}H_{26}O_{11}N_4$ requires C, 45·55; H, 5·5; N, 11·8%).

(±)-N-*Cyanonortropane*-3α : 6β-*diol Diacetate.*—(±)-Tropane-3α : 6β-diol diacetate (25·6 g.) in dry benzene (100 ml.) was stirred at 65—70° and treated dropwise during 1 hr. with *carefully dried* cyanogen bromide (20 g.) in benzene (100 ml.). After a further 3 hours' stirring at the

same temperature the white crystalline salt (4·7 g.), m. p. 258° (decomp.), was collected, washed with a little benzene, and recrystallised from dry ethanol (35 ml.) to give (±)-N-*methyl*-3α : 6β-*diacetoxytropanium bromide* (3·55 g.), m. p. 275° (Found : C, 46·8; H, 7·4; N, 4·4; Br^-, 23·4. $C_{13}H_{22}O_4NBr$ requires C, 46·4; H, 6·6; N, 4·2; Br, 23·7%).

The oil obtained by evaporating the reaction mixture under reduced pressure readily crystallised and was collected (22·3 g.; m. p. 111°) with the help of ether. Crystallisation from ethyl acetate–benzene gave the N-*cyano-compound*, m. p. 112—113° (Found : C, 56·8; H, 6·4; N, 11·0. $C_{12}H_{16}O_4N_2$ requires C, 57·1; H, 6·4; N, 11·1%).

(±)-*Nortropane*-3α : 6β-*diol*.—The *N*-cyano-compound (21 g.) and aqueous sodium hydroxide (10%; 210 ml.) were stirred for 12 hr. on the steam-bath. The dried ($MgSO_4$) butanol (3 × 50 ml.) extract of the cooled mixture gave on evaporation a coloured crystalline product (6·7 g.; m. p. 180°). This gave (±)-*nortropane*-3α : 6β-*diol*, m. p. 203—204° (Found : C, 58·6; H, 9·1; N, 9·5. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%), on crystallisation from dry ethanol.

(±)-Na-*Ethoxycarbonylmethylnortropane*-3α : 6β-*diol* (Vb).—Ethyl iodoacetate (0·54 ml.) in benzene (2 ml.) was added at room temperature to (±)-nortropane-3α : 6β-diol (1·3 g.) in anhydrous alcohol (6 ml.), benzene (7 ml.), and nitrobenzene (7 ml.). Some crystals soon appeared and after 2 days the greater part of the solvent was removed at reduced pressure, below 50°. With alcohol the partly crystalline residue furnished (±)-nortropane-3α : 6β-diol hydriodide (1·09 g., 89%), m. p. 220°. The oil obtained by evaporating the mother-liquor below 50° was treated, under cooling, with anhydrous 4N-ethanolic hydrogen chloride (5 ml.). Addition of dry ether (40 ml.) precipitated an oil which formed a white powder (1·37 g., 86%) when rubbed. Recrystallisation from dry ethanol gave Na-*ethoxycarbonylmethylnortropane*-3α : 6β-*diol hydrochloride*, m. p. 175—176° (decomp.) (Found : C, 49·4; H, 7·4; N, 5·3; Cl, 13·4. $C_{11}H_{20}O_4NCl$ requires C, 49·7; H, 7·4; N, 5·3; Cl, 13·3%).

From a similar experiment we isolated the free base. Nortropane-3α : 6β-diol in dry alcohol (10·5 ml.), dry benzene (7·5 ml.), and nitrobenzene (7·5 ml.) was treated with freshly distilled ethyl iodoacetate (0·9 ml.) in nitrobenzene (2 ml.). After 1 day at room temperature nortropane-3α : 6β-diol hydriodide (90%) separated, and from the mother-liquor, the product (1·2 g.; m. p. 104—106°). Recrystallisation from alcohol gave (±)-Na-*ethoxycarbonylmethylnortropane*-3α : 6β-*diol*, m. p. 106—107° (Found : C, 57·7; H, 8·7; N, 6·0. $C_{11}H_{19}O_4N$ requires C, 57·6; H, 8·4; N, 6·1%).

(±)-Na-*Carboxymethylnortropane*-3α : 6β-*diol Hydrochloride*.—The solution formed by heating the above ester hydrochloride (0·4 g.) and hydrochloric acid (5 ml.) for 5 hr. on the steam-bath was evaporated to dryness. Water (2 × 5 ml.) was added to the residue and removed under reduced pressure. Crystallisation of the foamy product from alcohol–ether (1 : 4, 5 ml.) gave the *carboxylic acid hydrochloride* (0·22 g., 62%), m. p. 190° (decomp.) (Found : C, 45·3; H, 6·9; N, 5·8; Cl, 15·0. $C_9H_{16}O_4NCl$ requires C, 45·5; H, 6·8; N, 5·9; Cl, 14·9%).

Na-*Ethoxycarbonylmethyl*-3α : 6β-*dihydroxytropanium Iodide* (VIb).—(i) (±)-Nortropane-3α : 6β-diol (1·43 g.) was treated with ethyl iodoacetate as above. Alcohol and benzene were removed below 40°, and nortropane-3α : 6β-diol hydriodide (1·0 g., 73%) was collected from the residue. The remaining nitrobenzene solution was treated with methyl iodide (8 g.) and set aside in darkness. Crystallisation soon began and after 2 days the product (1·15 g.; m. p. 193°) was collected. Recrystallisation from ethanol gave (±)-Na-*ethoxycarbonylmethyl*-3α : 6β-*dihydroxytropanium iodide*, m. p. 194° (Found : C, 39·1; H, 6·6; N, 4·0; I^-, 34·2. $C_{12}H_{22}O_4NI$ requires C, 38·8; H, 6·0; N, 3·8; I′, 34·2%).

(ii) Sodium ethoxide solution (4·86%; 0·71 ml.) was added to (±)-*Na*-ethoxycarbonylmethylnortropane-3α : 6β-diol hydrochloride (0·4 g.) in dry ethanol (3 ml.). After centrifuging, the separated sodium chloride (0·105 g.; theor. 0·086 g.) was washed with benzene (3·5 ml.), and the combined alcoholic and benzene solutions were treated with methyl iodide. In 10 hr. crystals had separated, and after 3 days filtration isolated a product (0·37 g.), m. p. 194° (decomp.), identical with that above. Evaporation of the mother-liquor and treatment with acetone gave a further crop (0·08 g.), m. p. 150—160°.

(±)-Na-*Carboxymethyltropane*-3α : 6β-*diol Betaine*.—(±)-*Na*-Ethoxycarbonylmethyl-3α : 6β-dihydroxytropanium iodide (0·35 g.), water (8 ml.), and silver oxide (0·18 g.) were shaken together for 4 hr. After filtration the solution was evaporated *in vacuo*. The solution of the residue in alcohol (20 ml.) was filtered and repeatedly evaporated. The *betaine* (0·18 g., 90%), m. p. 270° (decomp.) (Found : C, 55·8; H, 8·3; N, 6·3. $C_{10}H_{17}O_4N$ requires C, 55·8; H, 8·0; N, 6·5%), crystallised from dry ethanol.

(±)-Na-*Carboxymethyl*-3α : 6β-*dihydroxytropanium Iodide*.—The betaine (0·4 g.) solution in

concentrated hydriodic acid was evaporated to dryness. Crystallisation of the residue from dry ethanol (3 ml.) gave the *iodide* (0·44 g.), m. p. 202° (decomp.) (Found : C, 35·2; H, 6·1; N, 4·1; I^-, 36·9. $C_{10}H_{18}O_4NI$ requires C, 35·0; H, 5·3; N, 4·1; I, 37·0%).

(*B*) *Derivatives of* (±)-*oscine.*

(±)-*Oscine Acetate.*—(±)-Oscine (3·1 g.), benzene (20 ml.), and acetyl chloride (30 ml.) were kept for 3 hr. at 75°. (±)-*Oscine acetate hydrochloride* (3·3 g., 80·5%), m. p. 199—201° (Found : C, 51·6; H, 6·8; N, 6·2; Cl^-, 15·4. $C_{10}H_{16}O_3NCl$ requires C, 51·4; H, 6·9; N, 6·0; Cl, 15·3%), was collected and washed with acetone. The dried (Na_2CO_3) chloroform (9 × 10 ml.) extract of a basified (to pH 8 with sodium carbonate) solution of this salt (2·7 g.) in water (10 ml.) gave an oily base (2·2 g., 96%) on evaporation.

(±)-Nb-*Carboxymethyloscinium Iodide Lactone* (VIII).—When (±)-oscine acetate (2·5 g.), benzene (2 ml.), and ethyl iodoacetate (3 ml.) were kept for 1 day a viscous oil separated. Triturated with acetone, this gave a solid which from alcohol afforded crystals (2·35 g., 81%), m. p. 246° (decomp.), of the lactone previously described (Fodor, Tóth, and Vincze, *Helv. Chim. Acta*, 1954, **37**, 907).

(±)-N-*Cyanonoroscine Acetate.*—(±)-Oscine acetate (15·8 g.) in dry benzene (60 ml.) was added during 1·5 hr. to cyanogen bromide (17 g.), stirred in dry benzene (80 ml.) at 60—70°. The mixture was kept for 3 hr. more at this temperature and a solid [0·58 g.; m. p. 261° (decomp.), resembling a quaternary salt] removed. Evaporated *in vacuo*, the filtrate provided yellow crystals (14·3 g.; m. p. 83—85°) which by crystallisation from dry alcohol gave the product (10·7 g.), m. p. 90—91°. Further crystallisation gave pure (±)-N-*cyanonoroscine acetate*, m. p. 91° (Found : C, 58·0; H, 6·2; N, 13·4. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·4%).

(±)-*Noroscine.*—The suspension of the cyano-compound (9·7 g.) in aqueous sodium hydroxide (10%; 100 ml.) was kept at 100° for 12 hr. The chloroform extract of the residue obtained by evaporating the solution below 50° *in vacuo* was evaporated. Addition of light petroleum gave a product (5·34 g.), m. p. 190—195°, which on crystallisation from chloroform–light petroleum provided (±)-noroscine (4·82 g.), m. p. 204—205°, identical with a sample obtained by permanganate oxidation of oscine (Hess, Merck, and Uibrig, *Ber.*, 1915, **48**, 1889, 1906).

" *Reverse Quaternisation* " *of* (±)-*Noroscine.*—(±)-Noroscine (2·82 g.) in dry ethanol (5 ml.) and dry benzene (10 ml.) was treated with nitrobenzene (10 ml.) and ethyl iodoacetate (2·14 g.). Crystals soon separated, and after 12 hr. (±)-noroscine hydriodide (2·42 g.), m. p. 298° (decomp.) (Found : I, 46·9. $C_7H_{12}O_2NI$ requires I, 47·2%), was collected. Methyl iodide (10 ml.) was added to the filtrate and after 2 days needles of (±)-*Nb*-carboxymethyloscinium iodide lactone (0·42 g.), m. p. 246° (decomp.) (Fodor *et al.*, *loc. cit.*) were obtained. Evaporation of the filtrate under reduced pressure gave an amorphous residue, which from alcohol (3 ml.) gave after 1 day in the refrigerator a product [0·34 g.; m. p. 175° (decomp.)]. Recrystallisation from the same solvent (6 ml.) gave (±)-Na-*ethoxycarbonylmethyloscinium iodide* (0·23 g.), m. p. 181° (decomp.) (Found : C, 39·2; H, 5·6; N, 3·6; I, 34·1. $C_{12}H_{20}O_4NI$ requires C, 39·0; H, 5·5; N, 3·8; I, 34·4%).

(±)-Na-*Carboxymethyloscine Betaine.*—The above ester iodide (0·37 g.), water (8 ml.) and silver oxide (0·18 g.) were shaken for 6 hr. Filtration, evaporation to dryness, and crystallisation of the resulting mixture of crystals and foam from dry ethanol gave the *betaine*, m. p. 295° (decomp.) (Found : C, 56·3; H, 7·3; N, 6·8. $C_{10}H_{15}O_4N$ requires C, 56·3; H, 7·1; N, 6·6%).

(±)-Na-*Carboxymethyloscinium Iodide.*—The residue obtained by evaporating the betaine (0·11 g.) and freshly distilled hydriodic acid (4 ml.) *in vacuo* on the steam-bath was dissolved in anhydrous ethanol (3 × 5 ml.) and again evaporated. Crystallisation of the product from dry ethanol (2 ml.) gave (±)-Na-*carboxymethyloscinium iodide* (0·09 g.), m. p. 179° (decomp.) (Found : C, 35·2; H, 5·2; N, 4·2; I, 36·6. $C_{10}H_{16}O_4NI$ requires C, 35·2; H, 4·7; N, 4·1; I, 37·1%).

(±)-N-*Ethoxycarbonylmethylnoroscine Hydrochloride.*—(±)-Noroscine (3·94 g.) was treated with ethyl iodoacetate (3 g.) in nitrobenzene, alcohol and benzene. Noroscine hydriodide was removed in nearly theoretical yield and the filtrate was treated with a 20% solution (6 ml.) of hydrogen chloride in dioxan, and with ether (100 ml.). Trituration of the precipitate gave a crystalline powder [3·7 g.; m. p. 198° (decomp.)] which on crystallisation from dry alcohol afforded (±)-N-*ethoxycarbonylmethylnoroscine hydrochloride* (2·51 g.), m. p. 205° (decomp.) (Found : C, 50·3; H, 6·3; N, 5·3; Cl^-, 13·6. $C_{11}H_{18}O_4NCl$ requires C, 50·1; H, 6·8; N, 5·3; Cl, 13·4%).

(±)-Nb-*Carboxymethylnoroscine Lactone Hydrochloride.*—The above hydrochloride (1·16 g.) was thrice evaporated to dryness *in vacuo* with concentrated hydrochloric acid (10 ml.). Trituration of the glass-like residue with acetone and recrystallisation of the filtered product

[0·95 g.; m. p. 275° (decomp.)] from dry ethanol gave the *lactone*, m. p. 276° (decomp.) (Found : C, 49·5; H, 5·7; N, 6·4; Cl^-, 16·3. $C_9H_{12}O_3NCl$ requires C, 49·7; H, 5·6; N, 6·6; Cl, 16·3%).

Quaternisation of N-*Ethoxycarbonylmethylnoroscine.*—(±)-*N*-Ethoxycarbonylmethylnoroscine hydrochloride (1·3 g.), when treated with ethanolic sodium ethoxide (2·17%; 5·25 ml.) in dry ethanol (10 ml.) and with methyl iodide (5 ml.), gave (±)-*Na*-ethoxycarbonylmethyloscinium iodide (0·10 g.) and (±)-*Nb*-carboxymethyloscinium iodide lactone (0·80 g.).

Oxazines from (±)-*Noroscine.*—Solvent was distilled from a solution of (±)-noroscine (0·7 g.), *p*-nitrobenzaldehyde (0·75 g.), and chlorobenzene (50 ml.). This process was repeated three times (no more water was then formed), and the mixture was evaporated to dryness. Recrystallisation of the residue (1·35 g.; m. p. 178—179°) from dry benzene gave the oxazine (1·1 g.), m. p. 183° (Heusner *et al.*, *Chem. Ber.*, 1954, **87**, 1063, give m. p. 183°).

Similarly, (±)-noroscine (0·7 g.) and piperonaldehyde (0·75 g.) gave a product which on crystallisation from benzene gave the *oxazine* (0·55 g.), m. p. 145—146° (Found : C, 65·9; H, 5·5; N, 5·2. $C_{15}H_{15}O_4N$ requires C, 65·9; H, 5·5; N, 5·1%).

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