287. *Stereochemistry of Tropane Alkaloids. Part IX.*[*] *Selective Quaternisation of Tropan-3α-ol and Tropan-3β-ol and of their Derivatives.*

By Gábor Fodor, Károly Koczka, and János Lestyán.

" Direct " and " reverse " quaternisation of tropan-3β-ol and nortropan-3β-ol has given *N*-epimeric *N*-ethoxycarbonylmethyl- and *N*-carboxymethyl-tropanium salts to which definite configurations have been allotted. Tropan-3α-ol ethiodide and *N*-ethylnortropan-3α-ol methiodide have been shown to differ, as have the epimeric *N*-ethoxycarbonylmethyl-3α-hydroxytropanium iodides and the derived betaines.

The formation of a particular *N*-epimer, depending upon the order of attachment of groups A and B (*e.g.*, methyl and ethoxycarbonylmethyl) to the nitrogen atom of nor-*ψ*-tropine,[1] nortropine,[2,3] (±)-tropane-3α : 6β-diol,[4] and norecgoninol [5] has already been

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[*] Part VIII, Fodor, Kovács, and Halmos, *J.*, 1956, 873.

[1] Fodor, Meeting Hung. Chem. Soc., Sept. 19th, 1952; Fodor, Koczka, and Lestyán, *Magyar Kém. Folyóirat*, 1953, **59**, 242.

[2] Tóth, Lecture, Meeting Soc. Hung. Chemists, Debrecen, September 26th, 1953; Fodor, Tóth, Lestyán, and Vincze, *Vegyip. Kut. Int. Közl.*, 1953, **4**, 293.

[3] Cf. Findlay, *J. Amer. Chem. Soc.*, 1953, **75**, 3204.

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

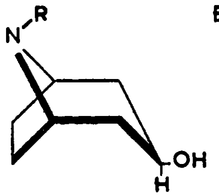
[5] Fodor, XIVth Congress Int. Union Pure Appl. Chem., Zürich, July 21st, 1955; Kovács, Fodor, and Halmos, *J.*, 1956, 873.

discussed.[6] " Direct " and " reverse " quaternisations of nortropane-3β- and -3α-ol * are now reported.

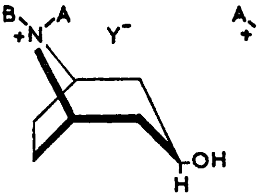
With ethyl iodoacetate tropan-3β-ol (I*a*) gave *N*-ethoxycarbonylmethyl-3β-hydroxytropanium iodide (II*a*). *N*-Ethoxycarbonylmethylnortropan-3β-ol (I*c*) [from nortropane-3β-ol (I*b*) and ethyl *O*-toluene-*p*-sulphonylglycollate] gave, with methyl iodide, the *N*-epimer (III*a*) of (II*a*). The bromides were similarly prepared. The diastereoisomers, formed from the tertiary bases under identical conditions, showed different m. p.s, solubilities, and crystal forms.

The betaine (IV), obtained by hydrolysis of the ester (III*a*), readily lost a molecule of water of crystallisation, but the betaine hydrate (V) formed from the epimeric ester (II*a*) was not dehydrated even after 2 hr. at 110°/30 mm. This highly stereospecific behaviour may be explained by assuming hydrogen bonding between water and carboxylate anion, pointing to the configuration (V) for the betaine hydrate. The stability of the anhydrous form of the epimeric betaine might be due to hydrogen bonding between carboxylate anion and the 3-hydroxyl group as permitted by the configuration (IV). The two betaine picrates showed different solubilities and crystal forms.

With hydrogen bromide and iodide the betaines gave *N*-epimeric carboxymethyl derivatives (II*b*) and (III*b*). The reconversion of the bromide (II*b*) into the *N*-ethoxycarbonylmethyl-3β-hydroxytropanium bromide (II*a*) by diazoethane is evidence for the absence of stereomutation during these changes.



(I)



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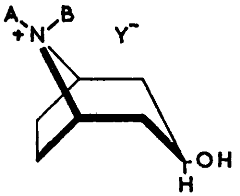

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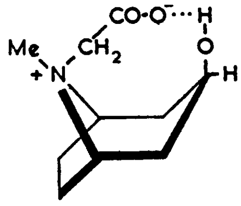
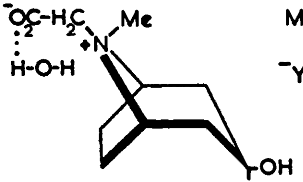


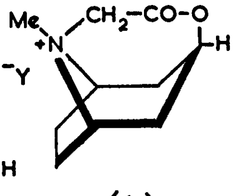
(IV)

R = (*a*) Me
(*b*) H
(*c*) $CH_2 \cdot CO_2Et$

	A	B	Y
(*a*)	Me	$CH_2 \cdot CO_2Et$	I
(*b*)	Me	$CH_2 \cdot CO_2H$	I, Br, Cl } or picrate

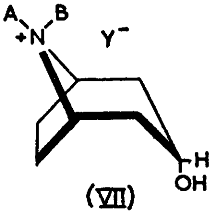


(V)



(VI)

Y = I or Br



(VII)

	A	B	Y
(*a*)	Me	Et	I
(*b*)	Et	Me	I
(*c*)	Me	$CH_2 \cdot CO_2Et$	I
(*d*)	$CH_2 \cdot CO_2Et$	Me	I } or picrate

Unfortunately, although the epimeric carboxylic acids behaved differently towards lactonising reagents, quantitative cyclisation could not be achieved. Even concentrated sulphuric acid at 0° left the acid from tropan-3β-ol intact. Evaporation of the betaine (IV) with hydrobromic and hydriodic acid caused partial cyclisation, and although separation of the lactone (VI) and of the acid (III*b*) proved difficult, infra-red † maxima characteristic

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* For nomenclature see *J.*, 1953, 721 and 1955, 3504.

† We are indebted to Dr. Pliva (Institute for Organic Chemical Research, Czechoslovakian Academy of Science, Prague) for these spectra.

[6] Fodor, *Acta Chim. Acad. Sci. Hung.*, 1955, **5**, 379; *Experientia*, 1955, **11**, 129; Meeting, Chem. Soc. DDR, Leipzig, October 23rd, 1954; *Angew. Chem.*, 1955, **67**, 211.

of lactones (at 1750 and 1623 cm.$^{-1}$) were detected in a selected crop of crystals. With acetic anhydride the acid chloride gave only the acetate of a mixed anhydride. Although pyrolysis of *N*-ethoxycarbonylmethyl-3β-hydroxynortropanium toluene-*p*-sulphonate gave only 3β-hydroxytropanium toluene-*p*-sulphonate (presumably by loss of ethylene followed by decarboxylation [7]), ethoxycarbonylmethyltropanium iodides were observed to resolidify above their m. p.s, forming a mixture from which were isolated tropan-3β-ol methiodide, the lactone (VI), and (probably) *NN*-di(ethoxycarbonylmethyl)-3β-hydroxynortropanium iodide. Thus stereomutation, intermolecular alkyl-cation exchange, and lactonisation of the intermediate *Na*-ethoxycarbonylmethyl compound occur.

X-*Ray diffraction patterns.**

N-Ethoxycarbonylmethyl-3α-hydroxytropanium iodide (VII*c* or *d*)		*N*-Ethoxycarbonylmethylnortropine methiodide (VII*b* or *a*)		*Na*-(?)Carboxymethyl-3α-hydroxytropanium betaine		*Nb*-(?)Carboxymethyl-3α-hydroxytropanium betaine		*N*-Ethylnortropine methiodide (VII*a* or *b*)		Tropine ethiodide (VII*b* or *a*)	
d	*r*	*d*	*r*	*d*	*r*	*d*	*r*	*d*	*r*	*d*	*r*
7·06	M	8·00	VW	6·84	VW	7·99	W	5·986	VW	6·058	VW
6·50	M	7·07	S	6·38	S	6·68	M	5·546	M	5·63	VW
5·63	VW	6·61	S	6·11	VW	6·08	M	5·250	S	5·233	VS
5·22	M	5·19	VS	5·68	W	5·57	VS	5·078	VW	3·919	VW
4·90	W	4·64	M	5·40	VW	5·11	S	4·641	M	3·731	S
4·69	W	4·45	M	5·26	VW	4·88	M	3·909	VW	3·334	VW
4·45	W	4·16	S	5·01	S	4·21	S	3·762	VS	3·191	S
4·24	S	3·88	W	4·76	VW	3·93	M	3·620	VW	3·069	M
4·11	S	3·61	S	4·67	W	3·48	M	3·441	VW	2·653	VW
3·92	W	3·51	S	4·59	VW	3·20	W	3·310	S	2·441	M
3·53	W	3·37	S	4·45	VW	2·95	VS	3·210	M	2·384	M
3·44	VS	3·30	S	4·34	NS	2·82	M	3·115	S	2·178	M
3·35	W	3·13	S	4·10	W	2·66	M	3·042	VW	2·057	M
3·15	S	2·95	VW	3·91	VW	2·58	W	2·812	M	1·891	VW
2·80	M	2·83	W	3·81	S	2·49	M	2·609	VW	1·806	M
2·53	M	2·70	W	3·65	VW	2·37	W	2·454	M	1·783	M
2·43	M	2·59	VW	3·38	S	2·31	VW	2·344	VW	1·797	VW
2·35	W	2·52	VW	3·34	VW	2·24	W	2·257	VW	1·623	VW
2·30	W	2·46	VW	3·24	W	2·16	M	2·223	VW		
2·25	W	2·39	M	2·97	M	2·10	M	2·129	M		
2·19	VW	2·28	S	2·89	S	1·988	W	2·018	VW		
2·14	VW	2·13	W	2·73	W	1·933	VW	1·986	VW		
2·07	M	2·07	W	2·66	VW	1·899	VW	1·959	VW		
2·000	M	1·991	M	2·52	W	1·842	M	1·905	W		
1·900	M	1·905	W	2·43	M	1·789	VW	1·805	VW		
1·811	VW	1·871	VW	2·33	VW	1·724	VW	1·787	VW		
1·779	M	1·822	M	2·24	M	1·662	M	1·693	VW		
1·736	W	1·791	VW	2·15	M	1·594	VW	1·642	VW		
1·692	W	1·760	VW	2·13	VW	1·561	VW	1·612	VW		
1·644	VW	1·729	VW	2·03	W	1·487	W	1·569	VW		
1·605	W	1·660	W	1·952	W	1·433	VW	1·499	VW		
1·559	W	1·605	VW	1·812	M	1·398	VW	1·417	VW		
1·502	W	1·589	VW	1·741	W	1·331	VW	1·365	VW		
1·448	VW	1·555	W	1·655	W	1·272	VW	1·320	VW		
1·404	VW	1·507	W	1·563	VW	1·241	VW	1·294	VW		
1·367	VW	1·496	VW			1·225	VW				
1·326	VW	1·455	W			1·202	VW				
1·264	VW	1·423	W			1·122	VW				
1·221	VW	1·382	VW			1·101	VW				
1·154	VW	1·363	VW			1·070	VW				
1·101	VW	1·307	W								
1·058	VW	1·273	VW								
		1·222	VW								
		1·197	W								
		1·147	VW								
		1·123	VW								
		1·110	VW								
		1·101	VW								
		1·092	VW								
		1·069	VW								

* Cu-K_α radiation was employed with a nickel-foil filter.
d = Interplanar spacing (Å).
r = Relative line strength (visually determined).
VS = very strong; VW = very weak; S = strong; W = weak;
M = medium.

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[7] Cf. Jeffreys, *J.*, 1955, 2475.

Lactone formation by the *N*-epimer from "reverse" quaternisation permits the specification of the *N*-substituents as *Na*-methyl and *Na*-ethoxycarbonylmethyl in the compounds (I*a*) and (I*c*), in agreement with the predictions from conformational analysis [8,4,5] of the greater stability of an axial 2-substituent in 1 : 3-diaxially substituted *cyclo*hexanes.

The difficulty of lactone formation from ψ-nortropine, as contrasted with the cases of oscine and tropane-3α : 6β-diol, may be due to the prevalence of the chair-form in tropan-3β-ol derivatives.[9,6] The formation of a lactone-salt,[10] involving the primary hydroxyl group, by the action of methyl iodide upon *N*-ethoxycarbonylmethylnorecgoninol diacetate agrees with this assumption, since in this case lactonisation can occur even with the ring in chair-form.

Some experiments with tropan-3α-ol have also been done. With ethyl iodoacetate it gave an *N*-epimer (VII*c* or *d*) different from that (VII*d* or *c*) obtained by ethoxycarbonylmethylation and methylation of nortropan-3α-ol. In addition to crystal photographs, *X*-ray examination [11] (see below) proved these epimers different. The related betaines were also prepared.

Whilst this work was in progress Findlay [3] claimed that, although *N*-ethylnortropine propiodide differed from *N*-propylnortropine ethiodide, the salts from tropine and ethyl iodide and from *N*-ethylnortropine and methyl iodide were the same. This last finding was not consistent with our observations [1,4,5] on the ethoxycarbonylmethyl derivatives and we therefore examined the methylation of *N*-ethylnortropine and the ethylation of tropine. Professor S. Koch and Dr. Gy. Grasselly of the Institute of Mineralogy, Szeged University, found the resulting tropine ethiodide to form optically isotropic crystals whilst the *N*-ethylnortropine crystal was anisotropic. The picrates were even more strikingly different. Thus, with these tropine bases also the order of quaternisation determines the *N*-configuration. Unfortunately, apart from *X*-ray examination (being undertaken by C. H. McGillavry, Amsterdam), methods are not available for determining the configuration of these compounds with α-hydroxyl groups, and at present particular orientations (VII*a* or *b*, *c* or *d*) can only be assigned by analogy with tropan-3β-ol and ecgoninol derivatives.

Findlay's interpretation of his findings cannot be maintained. Our observations and ideas have recently been corroborated by Zeile and Schulz [12] from infrared examination of a series of *N*-epimeric tropan-3α- and -3β-ols.

EXPERIMENTAL

*Ethyl Toluene-*p*-sulphonylglycollate.*—Ethyl diazoacetate (7·35 g.) in ethyl acetate (50 ml.) was added drop by drop, with shaking, to toluene-*p*-sulphonic acid (11 g.) in the same solvent (50 ml.). After 2 hr. gas evolution had stopped and the solvent was evaporated *in vacuo*. The residue was washed with water (500 ml.) and dissolved in ether. Removal of the latter and crystallisation from alcohol gave the *ester* (5 g.), m. p. 50—52° (Found : C, 51·3; H, 5·3; S, 12·45. $C_{11}H_{14}O_5S$ requires C, 51·15; H, 5·45; S, 12·4%).

N-*Ethoxycarbonylmethylnortropan*-3β-*ol* (I*c*).—Nortropan-3β-ol (1·27 g.), ethyl *O*-toluene-*p*-sulphonylglycollate (7·58 g.), and dry ethanol (20 ml.) were refluxed for 4 hr. Removal of the solvent and trituration with ether gave N-*ethoxycarbonylmethyl*-3β-*hydroxynortropanium toluene-*p*-sulphonate*, m. p. 121—123° (Found : C, 56·3; H, 7·6; N, 3·4. $C_{18}H_{27}O_6NS$ requires C, 56·0; H, 7·0; N, 3·6%), as an oil which slowly crystallised.

Na-*Ethoxycarbonylmethyl*-3β-*hydroxytropanium Iodide* (III*a*).—The above salt (5·15 g.) in dry ethanol (20 ml.) was treated in turn with 1·28N-sodium ethoxide (10·4 ml.) and dry benzene (50 ml.). Sodium toluene-*p*-sulphonate (2·32 g.) was removed and the filtrate and methyl iodide (4·56 g.) were kept in a stoppered flask (100 ml.) at 20° for 20 hr. The crystals [3·085 g.; m. p.

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[8] Barton, *Chem. and Ind.*, 1953, 664.

[9] Jones, *J. Amer. Chem. Soc.*, 1953, **75**, 4839; Archer and Lewis, *Chem. and Ind.*, 1954, 833; Wisser, Manassen, and de Vries, *Acta Cryst.*, 1954, **7**, 288; Nickon, *J. Amer. Chem. Soc.*, 1955, **77**, 4094.

[10] Kovács, Fodor, and Halmos, Part VIII, *J.*, 1956, 873.

[11] For these measurements we are grateful to Dr. A. Almásy, Research Institute for Heavy Chemical Industry, Veszprém, and to Dr. Gy. Bácskay, Head of the same Department.

[12] *Chem. Ber.*, 1955, **88**, 1078.

209° (decomp.)] (Found : C, 40·2; H, 6·5; N, 4·0; I^-, 35·3. $C_{12}H_{22}O_3NI$ requires C, 40·6; H, 6·2; N, 4·0; I^-, 35·7%) were collected and washed with benzene (12 ml.) and ethanol (3 ml.). Evaporation of the mother-liquor gave a wet crystalline powder (1·41 g.) which was collected with the help of dry acetone, giving a second crop (0·695 g.) of *iodide*, m. p. 200°, identical with the first.

N*b-Ethoxycarbonylmethyl*-3β-*hydroxytropanium Bromide* (II*a*).—(*a*) Tropan-3β-ol (2·82 g.), ethyl bromoacetate (3·34 g.), and benzene (20 ml.) were kept at 25° for 24 hr. The product (5·75 g.) gave prisms of the *bromide* (3·08 g.), m. p. 214° (Found : Br^-, 25·1. $C_{12}H_{22}O_3NBr$ requires Br^-, 26%), on crystallisation from ethanol.

(*b*) The salt (II*b*) (0·5 g. ; see below) in alcohol (70 ml.) was treated with ethereal diazoethane (0·024 g./ml.), and when nitrogen evolution ceased more diazoethane solution (10 ml.) was added. After ½ hr. the solvent was removed and the product, m. p. 206—208° (alone and mixed with the above specimen), was collected with acetone.

N*b-Ethoxycarbonylmethyl*-3β-*hydroxytropanium Iodide* (II*a*).—Tropan-3β-ol (2·15 g.), dry ethanol (30 ml.), benzene (50 ml.), and ethyl iodoacetate (3·9 g.) were kept for 17 hr. ; a first crop of crystals [4·23 g.; m. p. 204° (decomp.) (Found: C, 40·5; H, 6·4; N, 4·2; I^-, 35·8. $C_{12}H_{22}O_3NI$ requires C, 40·5; H, 6·2; N, 4·0; I^-, 35·7%)] was collected. Evaporation of the mother-liquor and trituration with acetone gave a second crop (0·81 g.), m. p. 199—201°.

10 Ml. of dry ethanol dissolved 1·4 g. of the salt (III*a*) and 0·31 g. of the epimer (II*a*).

Betaines from the Ester Salts.—An aqueous solution of the salt (II*b*) or (III*a*) (2·2 g.) was shaken with silver oxide (2·2 g.) for ½ hr. Filtration, evaporation, and recrystallisation, from ethanol (10 ml.), of the product from (II*a*) gave the *betaine* (V) (0·3 g.), m. p. 270° (Found : C, 55·25; H, 8·9; N, 6·7. $C_{10}H_{17}O_3N,H_2O$ requires C, 55·2; H, 8·75; N, 6·4%) after drying at 110°/30 mm. for 2 hr. A second crop (0·7 g.) separated later. Evaporation of a solution of the betaine (V) (5·6 g.) in constant-boiling hydriodic acid, and crystallisation of the residue from ethanol, gave the *iodide* (II*b*) (6·7 g.), m. p. 214° (Found : C, 36·2; H, 6·0; N, 4·5; I^-, 37·4. $C_{10}H_{18}O_3NI$ requires C, 36·7; H, 5·5; N, 4·3; I^-, 38·8%). The betaine (V) (0·22 g.) with picric acid (0·23 g.) in ethanol (10 ml.) gave, after 24 hr. at 0°, yellow needles of the *picrate*, m. p. 188° (Found : C, 45·2; H, 5·2. $C_{16}H_{20}O_{10}N_4$ requires C, 44·9; H, 4·7%). In the way described below the betaine (V) gave the *chloride* (II*b*), m. p. 252° (Found : Cl^-, 15·1. $C_{10}H_{18}O_3NCl$ requires Cl^-, 15·05%).

The *betaine* (IV), m. p. >300° (Found : C, 60·4; H, 8·7; N, 7·0. $C_{10}H_{17}O_3N$ requires C, 60·3; H, 8·5; N, 7·0%) (after drying as above), from the salt (III*a*) crystallised from ethanol–ether. This betaine (0·20 g.) with picric acid (0·3 g.) and ethanol (10 ml.) gave crystals (0·15 g.) after 1 day at 0°, and ether precipitated a second crop (0·1804 g.). The pure *picrate*, m. p. 168° (Found : C, 45·3; H, 5·0; N, 12·9, 13·3. $C_{16}H_{20}O_{10}N_4$ requires C, 44·9; H, 4·7; N, 13·1%), crystallised from ethanol. The betaine (IV) (0·140 g.) in dry ethanol (20 ml.) gave with 5N-hydrogen chloride in ethanol (1·2 ml.) crystals of N*a-carboxymethyl*-3β-*hydroxytropanium chloride* (III*b*), m. p. 220° (decomp.) (Found : Cl^-, 14·9%).

Hydrazide of N*b-Carboxymethyl*-3β-*hydroxytropanium Iodide.*—The iodide (II*a*) (1·775 g.), hydrazine hydrate (2 ml.), and ethanol (65 ml.) were refluxed for 2 hr. Set aside overnight, the solution deposited needles (1·10 g.) which from ethanol gave the *hydrazide*, m. p. 209—211° (Found : C, 35·5; H, 6·1; N, 12·1; I^-, 36·65. $C_{10}H_{20}O_2N_3I$ requires C, 35·15; H, 5·95; N, 12·3; I^-, 37·1%).

In the same way the epimer (III*a*) (0·43 g.), hydrazine hydrate (0·5 ml.), and ethanol (15 ml.) gave the N-*epimeric hydrazide* as plates, m. p. 191° (Found : C, 35·1; H, 6·1; N, 12·2; I^-, 35·95, 36·2%). The mixed m. p. was 180—182°.

Lactone of N*a-Carboxymethyl*-3β-*hydroxytropanium Iodide.*—(*a*) The solution of the acid methiodide (III*b*) (1·05 g.) in fuming hydriodic acid (10 ml.) was evaporated to dryness under reduced pressure. The residue was crystallised repeatedly from ethanol–ether, the iodide-ion content of each fraction being checked. Unchanged starting material occurred in the first three crops, while the *lactone iodide* (VI), m. p. 281° (decomp.) (Found : C, 39·1; H, 5·9: I^-, 41·85. OEt, 0. $C_{10}H_{16}O_2NCl$ requires C, 38·8; H, 5·2; I^-, 41·1%), was obtained from crops (4) and (5). The infrared spectrum showed bands at 1750 and 1625 cm.$^{-1}$.

(*b*) *Nb*-Ethoxycarbonylmethyl-3β-hydroxytropanium iodide (II*a*) (12·6 g.) in a glass tube was placed directly into an oil-bath at 230°. Melting was complete in 7 min. and the melt resolidified (the loss in weight was 1·89 g.). It was extracted with water (130 ml.), leaving some solid undissolved (0·39 g.). The solution was shaken for 2 hr. with charcoal, filtered, and then concentrated *in vacuo*, giving a total of 9·07 g. of crystals. The portion (4·80 g.) of these left undissolved by boiling acetone (74 ml.) consisted mainly of tropan-3β-ol methiodide, obtained pure (Found : I^-, 44·75. Calc. for $C_9H_{18}ONI$: I^-, 44·8%) by crystallisation from methanol. The acetone extract gave, on cooling, the lactone (0·5 g.), m. p. 281° (decomp.) (Found : I^-, 41·8, 41·9%). [Recrystallisation from dimethylformamide and methanol–ether gave a specimen, m. p. 276° (decomp.) (Found : C, 38·5; H, 6·2; N, 4·7, 4·8; I^-, 41·3, 41·3%).] Two further crops appeared to consist mainly of the *di-*(N*-ethoxycarbonylmethyl*) *compound* (Found : I^-, 29·0. $C_{15}H_{26}O_5NI$ requires I^-, 29·7%). The salt (III*a*) gave essentially the same products on heating.

Pyrolysis of N*-Ethoxycarbonylmethyl-*3β*-hydroxynortropanium Toluene-*p*-sulphonate.*—The salt of (I*c*) (0·7 g.; m. p. 123°) was placed in an oil-bath, preheated to 185°, for 15 min. Trituration with acetone (3 ml.), filtration, and washing with acetone (6 ml.) gave a product (m. p. 168—173°) which on recrystallisation from acetone gave white crystals, m. p. 172—173° (Found : C, 57·25; H, 7·3; N, 4·8; S, 10·2. $C_{15}H_{23}O_4NS$ requires C, 57·5; H, 7·4; N, 4·5; S, 10·2%) alone and mixed with authentic 3-β-*hydroxytropanium toluene-*p*-sulphonate.*

Acid Chlorides.—(*a*) Betaine (IV) (0·2 g.) and thionyl chloride (1 ml.) were kept for 12 hr. at 20° and the mixture was then evaporated under reduced pressure. Kept in a desiccator, the oily residue crystallised, and when collected with acetone provided the hygroscopic *acid chloride*, m. p. 220° (decomp.) (Found : C, 46·8; H, 6·8; N, 5·65; Cl, 26·2. $C_{10}H_{17}O_2NCl_2$ requires C, 47·2; H, 6·7; N, 5·5; Cl, 27·9%), which did not react with pyridine during 10 min. on the steam-bath.

(*b*) The betaine (V) gave a sensitive acid chloride which did not react with pyridine.

Mixed Anhydride of Acetic Acid and Na *Carboxymethyl-*3β *acetoxytropanium Picrate.*—Betaine (IV) (0·1 g.) and acetic anhydride (1 ml.) were heated 2 hr. on the steam-bath. Evaporation of the solution *in vacuo* and treatment of the oil [in acetone (5 ml.)] with picric acid (0·2 g.) in ether (2 ml.) gave the *picrate*, m. p. 165—167° (Found: C, 47·05; H, 5·2; N, 10·7. $C_{20}H_{24}O_{12}N_4$ requires C, 46·9; H, 4·7; N, 10·9%).

N*-Ethoxycarbonylmethyl-*3α*-hydroxytropanium Iodide* (VII*c or d*).—Tropine (2·19 g.) [obtained (11·3 g.; m. p. 59—61°) by hydrogenating tropinone (13·5 g.) in ethanol (120 ml.) over Raney nickel[13] at 60—70°/85—100 atm. for 8 hr.], dry ethanol (20 ml.), benzene (20 ml.), and ethyl iodoacetate (3·5 g.) were kept at 20° for 9 hr. Recrystallisation of the product from ethanol gave the *salt* (0·48 g.), m. p. 210° (Found : I^-, 35·7. $C_{12}H_{22}O_3NI$ requires I^-, 35·7%). A second crop (1·2 g.) was obtained from the mother-liquor.

N*-Ethoxycarbonylmethyl-*3α*-hydroxynortropanium Toluene-*p*-sulphonate.*—Nortropine (3·2 g). (obtained best by von Braun degradation of tropine[14]), ethyl *O*-toluene-*p*-sulphonylglycollate (6·48 g.), and ethanol (50 ml.) were refluxed for 8 hr. Evaporation gave an oil which crystallised (8·1 g.) when triturated with dry ether. The *toluene-*p*-sulphonate*, m. p. 152° (Found : C, 56·2; H, 6·8; N, 3·8; S, 8·0. $C_{18}H_{27}O_6NS$ requires C, 56·1; H, 7·1; N, 3·6; S, 8·3%), crystallised from acetone. When carried out in acetone the reaction gave a 52% yield.

N*-Ethoxycarbonylmethyl-*3α*-hydroxytropanium Iodide* (VII*d or c*).—To the toluene-*p*-sulphonate (5·95 g.) in dry ethanol (20 ml.) 1·24N-sodium ethoxide (12·5 ml.) was added. Sodium toluene-*p*-sulphonate was removed and the filtrate was treated with benzene (10 ml.) and methyl iodide (6·8 g.). After 9 hr. at 25° the *iodide* (0·86 g.), m. p. 215° (Found : I^-, 35·8%), was collected. Cooling gave a second crop (3·95 g.), m. p. 214°. Photomicrographs and *X*-ray examination (see Table) proved it different from the *N*-epimer described above.

N*-Epimeric Betaines.*—(*a*) The ester iodide (VII*c* or *d*) (4·2 g.), water (40 ml.) and silver oxide (5·4 g.) were shaken for 1 hr. Filtration, evaporation *in vacuo*, and crystallisation of the residue from ethanol–ether gave the *betaine dihydrate* (transformation temp. 90°), m. p. 284° (Found : C, 51·05; H, 9·2; N, 5·9. $C_{10}H_{17}O_3N,2H_2O$ requires C, 51·05; H, 9·0; N, 5·95%). Drying over phosphoric anhydride (111°/10 mm., 2 hr.) gave the *monohydrate* (Found : C, 55·4; H, 9·8. $C_{10}H_{17}O_3N,H_2O$ requires C, 55·3; H, 9·7%), and with boiling xylene (10 mm., 2 hr.) the *anhydrous betaine* (Found : C, 60·7; H, 9·05. $C_{10}H_{17}O_3N$ requires C, 60·3; H, 8·6%). The dehydration was reversible.

(*b*) The ester iodide (VII*d* or *c*) (3 g.) gave in the same way the betaine (1·47 g.), m. p. 278°. Drying with boiling toluene (111°/10 mm., 1 hr.) gave the *monohydrate* (Found : C, 55·3; H, 8·8; N, 6·4%), and with xylene (140°/10 mm., 5 hr.) the *anhydrous betaine* (Found : C, 60·4; H, 8·8%). Treatment with water and recrystallisation gave the monohydrate again. *X*-Ray examination proved the anhydrous betaines different.

N*-Ethylnortropan-*3α*-ol.*—Nortropine (3 95 g.) and ethyl toluene-*p*-sulphonate (6·43 g.) were

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[13] Cf. Keagle and Hartung, *J. Amer. Chem. Soc.*, 1946, **68**, 1608.

[14] Nickon and Fieser, *ibid.*, 1952, **74**, 5566.

refluxed in dry acetone (40 ml.) for 4 hr. Trituration of the residue with ether gave the salt (6 65 g., m. p. 121—134°). Recrystallisation from acetone gave the *toluene-*p*-sulphonate* (3·95 g.), m. p. 149—150° (Found : C, 58·95; H, 7·8; N, 4·4. $C_{16}H_{25}O_4NS$ requires C, 58·7; H, 7·7; N, 4·3%).

N-*Ethylnortropan-3α-ol Methiodide* (VII*a or b*).—The above salt (3·27 g.) in dry ethanol (10 ml.) and benzene (30 ml.) was treated with 1·87N-sodium ethoxide (5·35 ml.). Sodium toluene-*p*-sulphonate was removed and the filtrate was kept with methyl iodide (7·1 g.) for 20 hr. at room temperature. The crystals (1·7129 g.) and a second crop (0·7331 g.) had m. p. >300° (Found : C, 40·3; H, 7·1; N, 4·5; I^-, 42·85. Calc. for $C_{10}H_{20}ONI$: C, 40·4; H, 6·8; N, 4·7; I^-, 42·7%). Findlay[3] gave m. p. 316°. The *picrate*, m. p. 252—253° (Found : C, 48·2; H, 5·5 N, 13·9. $C_{16}H_{22}O_8N_4$ requires C, 48·2; H, 5·6; N, 14·1%), formed needles from ethanol.

Tropan-3α-ol Ethiodide (VII*b or a*).—Simultaneously with, and under the same conditions as, the above experiment, tropan-3α-ol (1·41 g.) and ethyl iodide (7·8 g.) were allowed to react in ethanol (10 ml.) and benzene (30 ml.). Cubic crystals (0·92 g.) and a second crop (0·3 g.), m. p. >300° (Found : C, 40·3; H, 6·9; N, 4·7; I^-, 42·6%), were obtained. Findlay[3] gave m. p. 316°. The *picrate*, m. p. 233—234° (Found : C, 48·4; H, 5·4; N, 14·1%), gave a marked (30°) mixed m. p. depression with the *N*-epimer described above.

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