Chemistry of Tropan-3-yl Ethers. Part I. Synthesis of Tropan-3-yl Ethers

By G. Kraiss,† P. Scheiber,† and K. Nádor,*† Institute for Experimental Medicine, Hungarian Academy of Sciences, Budapest

Tropan-3α-yl methanesulphonate reacts with sodium alcoxides or phenoxides to form tropan-3β-yl ethers with inversion at C-3. The reaction of 3α-chlorotropane with sodium phenoxides or benzyl oxide leads to tropan-3α-yl ethers. The configuration at C-3 of the alkyl and benzyl tropan-3-yl ethers has been established by chemical methods.

APART from the diphenylmethyl ether and its derivatives,[1] it has so far proved impossible to prepare ethers of tropine and pseudotropine by any of the usual methods. The compound described as a methyl ether of tropine [2] has since been shown to be a quaternary salt.[3]

We have now found that when tropan-3α-yl methanesulphonate reacts with alkoxides or phenoxides, tropan-3β-yl ethers are formed; further, tropan-3α-yl phenyl ether can be prepared by treating 3α-chlorotropane with phenoxides.

There are several reasons why it has proved difficult to make ethers of tropine or pseudotropine. First, the reaction of either tropine or pseudotropine with alkyl and aralkyl halides gives rise primarily to quaternary salts. Secondly, tropines do not react with aryl halides, such as bromobenzene, or even with more reactive compounds such as diphenyliodonium bromide. Thirdly, the 3-halogenotropanes are very unreactive. Willstätter[4]

† *Present address:* Department of Chemistry, The Veterinary University, Budapest.

[1] U.S.P. 2,595,405/1952; U.S.P. 2,782,200/1956.
[2] G.P. 106,492/1900.
[3] K. Nádor, unpublished data.
[4] R. Willstätter, *Annalen*, 1903, **326**, 32.

TABLE 1

Tropan-3α-yl sulphonates (I; R^1 = Me, n = 1)

R^2	R^3	R^4	Deriv.	Yield (%)	M.p. (°C)	(From)	Found (%) C	H	N	S	Cl	Formula	Required (%) C	H	N	S	Cl
Me	H	Me	HCl	32·8 *	149	($CHCl_3$)	44·4	7·4	5·45	11·8	13·05	$C_{10}H_{20}ClNO_3S$	44·5	7·5	5·2	11·9	13·1
H	OMe	Me	Picrate	91·0 *	168—169	(EtOH)	40·2	4·4	11·6	6·7		$C_{16}H_{22}N_4O_{11}S$	40·2	4·6	11·7	6·7	
H	H	Et	TsOH	36·0	139—140	(EtOH–Et_2O)				15·6		$C_{17}H_{27}NO_6S_2$				15·8	
N-Methylpiperidine 4-methanesulphonate			HCl	74·6	153	(EtOH–Et_2O)	36·9	7·0	6·0	14·3	15·2	$C_7H_{16}ClNO_3S$	36·7	7·0	6·1	14·0	15·4

* Yield of base.

TABLE 2

Tropan-3β-yl ethers (II; R^1 = Me, R^2 = R^3 = H, n = 1)

	Deriv.	Yield [m] (%)	B.p. (°C/mmHg)	M.p. (°C)	(From)	Found (%) C	H	N	Cl	X	Formula	Required (%) C	H	N	Cl	X
Ph	CH_2Br			257	EtOH	57·7	7·6	4·7		25·6 [h]	$C_{15}H_{22}BrNO$	57·7	7·1	4·5		25·6 [h]
2,4-$Cl_2C_6H_4$	Base	33·2	155/0·25 [b]			58·75	6·0	4·9	24·8		$C_{14}H_{17}Cl_2NO$	58·75	6·0	4·9	24·8	
	HCl			262 [l]	EtOH–Et_2O	52·5	5·8	4·5	11·1 [i]		$C_{14}H_{18}Cl_3NO$	52·1	5·6	4·3	11·0 [i]	
3,4-$Cl_2C_6H_4$	Base	36·7	155/0·3 [c]			58·75	5·8	5·2	24·7		$C_{14}H_{17}Cl_2NO$	58·75	6·0	4·9	24·8	
	HCl			264 [l]	EtOH–Et_2O	51·9	5·4	4·5	10·9 [i]		$C_{14}H_{18}Cl_3NO$	52·1	5·6	4·3	11·0 [i]	
C_6Cl_5	Base	19·0		137—138	Acetone	43·0	3·5	3·7	45·4		$C_{14}H_{14}Cl_5NO$	43·2	3·6	3·6	45·5	
	HCl			264 [l]	Acetone	39·25	3·4	3·0			$C_{14}H_{15}Cl_6NO$	39·5	3·55	3·3		
p-BrC_6H_4	Base	32·0		110	EtOH	56·8	6·3	4·9		27·45 [h]	$C_{14}H_{18}BrNO$	56·8	6·1	4·7		27·0 [h]
	HCl			286 [l]	MeOH	50·6	5·8	4·1	10·25		$C_{14}H_{19}BrClNO$	50·5	5·7	4·2	10·7	
p-IC_6H_4	Base	47·7		169—170	EtOH	49·1	5·3	4·1		36·7 [j]	$C_{14}H_{18}INO$	49·0	5·3	4·1		37·0 [j]
	HCl			296 [l]	MeOH	44·3	5·4	3·4	9·2		$C_{14}H_{19}ClINO$	44·3	5·0	3·7	9·3	
m-$CF_3C_6H_4$	Base	26·4	99—100/0·15 [d]			63·15	6·5	5·1			$C_{15}H_{18}F_3NO$	63·15	6·4	4·9		
	HCl			262 [l]	EtOH–Et_2O	56·1	6·1	4·5			$C_{15}H_{19}ClF_3NO$	56·0	5·95	4·35		
3-Me-4-ClC_6H_3	Base	30·5	145/0·2	83	Pet [a]	67·7	7·8	5·3	13·2		$C_{15}H_{20}ClNO$	67·8	7·6	5·3	13·3	
	HCl			273 [l]	EtOH–Et_2O	59·4	7·4	4·6	11·7 [i]	5·3 [k]	$C_{15}H_{21}Cl_2NO$	59·6	7·0	4·6	11·7 [i]	5·3 [k]
3,5-Me_2-4-ClC_6H_2	Base	34·7	152/0·15	98	EtOH–Pet	68·9	7·8	4·9	12·5		$C_{16}H_{24}ClNO$	68·7	7·9	5·0	12·7	
	HCl			295 [l]	EtOH	60·5	7·2	4·5	11·0 [i]		$C_{16}H_{25}Cl_2NO$	60·8	7·3	4·4	11·2 [i]	
m-MeC_6H_4	Base	33·0	120—122/0·1 [e]			77·6	9·05	6·1			$C_{15}H_{21}NO$	77·9	9·15	6·1		
	HCl			285 [l]	EtOH	67·0	8·0	5·4	13·2		$C_{15}H_{22}ClNO$	67·3	8·3	5·2	13·2	
3,5-$Me_2C_6H_3$	Base	42·8	133—135/0·4	86	Pet	78·25	9·8	5·4			$C_{16}H_{23}NO$	78·3	9·45	5·7		
	HCl			284 [l]	EtOH–Et_2O	68·0	8·7	5·0	12·7		$C_{16}H_{24}ClNO$	68·2	8·6	5·0	12·6	
3,4-$Me_2C_6H_3$	Base	33·2	153/0·4	52	Et_2O	78·1	9·7	5·7			$C_{16}H_{23}NO$	78·3	9·45	5·7		
	HCl			286 [l]	EtOH–Et_2O	68·0	8·7	4·8	12·3		$C_{16}H_{24}ClNO$	68·2	8·6	5·0	12·6	
3,4,5-$Me_3C_6H_2$	Base	32·8	190—195/0·4	76·5	EtOH	78·8	10·05	5·6			$C_{17}H_{25}NO$	78·7	9·7	5·6		
	HCl			301 [l]	EtOH–Et_2O	68·8	8·9	4·9	11·7		$C_{17}H_{26}ClNO$	69·0	8·9	4·7	12·0	
p-$ButC_6H_4$	Base	34·8	166/0·15 [f]			79·1	10·05	5·1			$C_{18}H_{27}NO$	79·1	9·95	5·1		
	HCl			301 [l]	EtOH–Et_2O	70·1	9·4	4·7	11·2		$C_{18}H_{28}ClNO$	69·8	9·1	4·5	11·4	
p-$OctC_6H_4$	Base	24·0	172/0·4 [g]			80·1	11·0	3·9			$C_{22}H_{35}NO$	80·2	10·7	4·25		
	HCl			315 [l]	EtOH–Et_2O	72·2	10·2	3·8	9·6		$C_{22}H_{36}ClNO$	72·2	9·9	3·8	9·7	
Biphenyl-2-yl	Base	21·2		85	Acetone	81·6	7·6	4·7			$C_{20}H_{23}NO$	81·9	7·9	4·8		
	HCl			253 [l]	EtOH–Et_2O			4·2	10·55		$C_{20}H_{24}ClNO$			4·25	10·75	
m-$Me_2NC_6H_4$	Base	49·1	165—166/0·3	84	Pet			10·7			$C_{16}H_{24}N_2O$			10·8		
	2HCl			238 [l]	EtOH–Et_2O	57·7	8·1	8·6	20·9		$C_{16}H_{26}Cl_2N_2O$	57·7	7·9	8·4	21·3	
p-$NO_2C_6H_4$	Base	16·0		106—109	Toluene			10·4			$C_{14}H_{18}N_2O_3$			10·7		
	HCl			293 [l]	EtOH–Et_2O			9·3	11·6		$C_{14}H_{19}ClN_2O_3$			9·4	11·9	

[a] Pet = light petroleum (b.p. 40—60°). [b] n_D^{20} 1·5630. [c] n_D^{20} 1·5670. [d] n_D^{20} 1·4980. [e] n_D^{20} 1·5342. [f] n_D^{20} 1·5312. [g] n_D^{20} 1·5280. [h] Bromine. [i] Only for chloride ion. [j] Iodine. [k] Oxygen. [l] Decomposition. [m] Solvent was dimethylformamide in all experiments.

TABLE 3

Tropan-3β-yl ethers (II; R^1 = Me, R^5 = Ph, n = 1)

R^2	R^3	Deriv.	Yield [g] (%)	B.p. (°C/mmHg)	Mp. (°C)	(From)	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S
Me	H	Base	19·4	168/10 [b]											
		Reinecke salt			159—160	(H_2O–Acetone)	41·1	5·0	17·7	23·4	$C_{19}H_{28}CrN_7OS_4$	41·4	5·1	17·8	23·3
H	OMe	Base	20·8	141—142/0·6 [c]			72·65	8·4	5·7		$C_{15}H_{21}NO_2$	72·8	8·6	5·7	
		Fumaric acid			190—191	(EtOH–Et_2O)	62·6	7·0	3·6		$C_{19}H_{25}NO_6$	62·8	6·9	3·85	
H [a]	H	CH_3Br			248	(EtOH)	54·7	6·55	4·45	9·8 [e]	$C_{15}H_{22}BrNS$	54·9	6·75	4·3	9·8 [f]
N-Methyl-4-phenoxy piperidine		Base	20·6	80/0·2 [d]			75·3	8·6			$C_{12}H_{17}NO$	75·35	9·0		

[a] Sulphide. [b] n_D^{20} 1·5362. [c] n_D^{20} 1·5390. [d] n_D^{20} 1·5270. [e] Bromine, 24·4. [f] Bromine, 24·3. [g] Solvent was dimethylformamide in all experiments.

for example, treated 3-bromotropane with sodium ethoxide and observed only partial elimination with the formation of trop-2-ene, even after prolonged heating. No ether was formed.

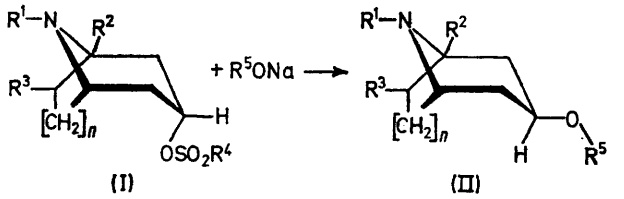
Since an attempt by Braun *et al.*[5] to synthesize the methyl ether of tropine by methylation in an aqueous medium with a 6 molar excess of dimethyl sulphate gave only a quaternary salt, these workers concluded that *O*-methylation of tropine was impossible. We have found however, that a reaction at a higher temperature and for a longer time gives a reasonable yield of the

[5] J. Braun, B. Anton, and K. Weissbach, *Ber.*, 1930, **63**, 2847.

methiodide of tropan-3α-yl methyl ether; this when treated with 2-aminoethanol gave tropan-3α-yl methyl ether.

Previously [6] we have reported that the reaction of tropan-3α-yl methanesulphonate with sodium alkoxides and sodium phenoxide and thiophenoxide led to the formation of tropan-3β-yl ether. We have prepared compounds listed in Tables 2 and 3.

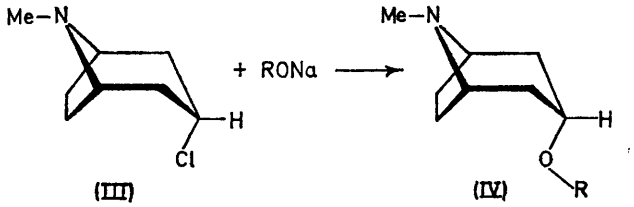
Ether formation was highly stereospecific, the reaction giving 94% of the β- and 6% of the α-isomer (g.l.c.).



(I) (II)

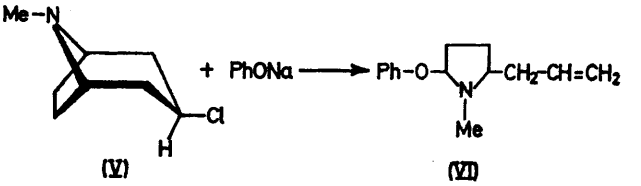
The reaction was accompanied by elimination to give trop-2-ene (30—60%).

When tropan-3α-yl methanesulphonate was treated with sodium cyclohexyl oxide in cyclohexanol or with sodium benzyloxide in a benzyl alcohol only elimination occurred. The cyclohexyl compound was therefore prepared by hydrogenation of the phenyl ether. The configuration of tropan-3β-yl alkyl ethers at C-3 was proved by splitting the ether bond with hydroiodic acid,[6] while that of the aryl ethers was established by physiochemical methods and spectroscopic examination (see following paper). When 3α-chlorotropane was treated with sodium methoxide in methanol under vigorous conditions, as described by Willstätter [4] for 3-bromotropane, only elimination occurred. However, if 3α-chlorotropane was treated with sodium phenoxide, tropan-3α-yl phenyl ether was formed. In addition, we have prepared a number of tropan-3α-yl ethers with substituents in the aromatic ring, tropan-3α-yl phenyl sulphide from sodium thiophenoxide, and tropan-3α-yl benzyl ether from sodium benzyl oxide in benzyl alcohol (Table 4).



(III) (IV)

The reaction of 3α-chlorotropane with sodium phen-



(V) (VI)

oxide was less stereospecific than was ether synthesis with methanesulphonate. G.l.c. indicated 80% of the α- and 20% of the β-isomers. The formation of these ethers was accompanied by little, if any, elimination. In preparing tropan-3α-yl benzyl ether elimination products amounted to 40%. When 3α-chlorotropane was treated with sodium cyclohexyl oxide in cyclohexanol only elimination occurred.

The configuration of tropan-3α-yl benzyl ether at C-3 was proved by splitting the ether bond with hydroiodic acid in the same way as for tropan-3β-yl alkyl ethers. This gave material which had the same melting point and i.r. spectrum as tropine hydroiodide.

When 3β-chlorotropane was treated with sodium phenoxide, fragmentation occurred with the formation of 2-allyl-1-methyl-5-phenoxypyrrolidine which was identified by microanalysis and spectroscopy.

This finding is similar to that of Archer *et al.*[7] who also observed fragmentation when 3β-chlorotropane was treated with potassium cyanide; 2-allyl-5-cyano-1-methylpyrrolidine was identified as a product of the reaction.

TABLE 4

Tropan-3α-yl ethers

R	Deriv.	Yield (%)	M.p. (°C)	(From)	Found (%) C	H	N	Cl	Formula	Required (%) C	H	N	Cl
p-BrC_6H_4	Base	35·5	90—91	(n-Hexane)	57·0	6·3	4·75	*a*, *c*	$C_{14}H_{18}BrNO$	56·8	6·1	4·7	*b*, *d*
	HCl		256 *g*	(EtOH–Et_2O)	50·3	5·8	4·0	10·2 *e*	$C_{14}H_{19}BrClNO$	50·5	5·8	4·2	10·7 *f*
m-$CF_3C_6H_4$	Base	29·2	76	(n-Hexane)	63·1	6·5	5·1		$C_{15}H_{18}F_3NO$	63·15	6·4	4·9	
	HCl		236 *g*	(EtOH–Et_2O)	55·9	6·0	4·35	11·2	$C_{15}H_{19}ClF_3NO$	56·0	5·95	4·35	11·0

[a] Bromine 27·0. [b] Bromine 27·0. [c] Oxygen 5·7. [d] Oxygen 5·4. [e] Oxygen 5·1. [f] Oxygen 4·8. [g] Decomposition.

EXPERIMENTAL

All m.p.s were corrected. For gas chromatography an Aerograph HY–FI 600 apparatus was used.

Tropan-3α-yl Methanesulphonate (I; $R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = Me$, $n = 1$).—This compound was prepared by the method of Archer *et al.*[8] (55·8%), m.p. 164—166° (tosyl salt) (lit.,[8] m.p. 160—162°).

N-Isopropyl-3α-methylsulphonylnortropanylium Toluene-p-sulphonate (I; $R^1 = Pr^i$, $R^2 = R^3 = H$, $R^4 = Me$, $n = 1$). —Methanesulphonyl chloride (49 ml) in dry chloroform (100 ml) was added dropwise to a stirred solution of *N*-isopropylnortropine (84·6 g) in dry chloroform (150 ml) at 5—10°. After 70 h at 0° and dilution with water (100 ml)

[6] G. Kraiss, P. Scheiber, and K. Nádor, *J. Org. Chem.*, 1968, **33**, 2601.

[7] S. Archer, T. R. Lewis, and B. Zenitz, *J. Amer. Chem. Soc.*, 1958, **80**, 958.

[8] S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Amer. Chem. Soc.*, 1958, **80**, 4677.

the reaction mixture was made alkaline with potassium carbonate (70 g) and stirred for 30 min; the chloroform layer was separated. The aqueous layer was extracted with more chloroform, and the chloroform extracts were dried, mixed with toluenesulphonic acid monohydrate (95 g) in methanol (100 ml), and diluted with ether while still warm, whereupon crystals began to appear. The mixture was set aside in a refrigerator and then filtered; the product was washed with acetone and recrystallized (chloroform–methanol–ether) to give the *product* m.p. 183·5—184° (78 g, 37·3%) (Found: C, 51·55; H, 6·8; N, 3·3; S, 15·3. $C_{18}H_{29}NO_6S_2$ requires C, 51·5; H, 7·0; N, 3·3; S, 15·3%).

N-Isopropylnortropan-3α-yl Methanesulphonate.—A chilled solution of *N*-isopropyl-3α-methylsulphonylnortropanylium toluene-*p*-sulphonate (94 g) in water (300 ml) was made alkaline with potassium carbonate (100 g) and then extracted with chloroform. The organic solution was dried (Na_2SO_4) and the solvent evaporated off *in vacuo*. Light yellow crystals were obtained (54 g, 97·6%). Recrystallized twice from light petroleum (b.p. 40—60°), m.p. 100—101° (Found: C, 53·3; H, 8·8; N, 5·7; S, 12·75. $C_{11}H_{21}NO_3S$ requires C, 53·4; H, 8·6; N, 5·6; S, 13·0%).

Granatan-3α-yl Methanesulphonate Hydrochloride.—(I; R^1 = Me, R^2 = R^3 = H, R^4 = Me, n = 2).—To an ice-cooled solution of granatan-3α-ol (58 g) in dry chloroform (100 ml) a solution of methanesulphonyl chloride (35 ml) in dry chloroform (100 ml) was added dropwise during 1 h with the temperature kept below 5°. The mixture was then stirred for 1 h at room temperature, and the material which separated out was filtered off and dried (74·3 g). It was crystallized from ethanol–ether (58·6 g) and had m.p. 138° (Found: C, 44·9; H, 7·7; N, 5·4; Cl, 13·1. $C_{10}H_{20}ClNO_3S$ requires C, 44·5; H, 7·5; N, 5·2; Cl, 13·1%).

Because it is highly unstable, the free methanesulphonate ester of granatan-3α-ol was liberated from its HCl salts by the addition of aqueous potassium carbonate. Extraction with methylene chloride and then evaporation of the solvent under nitrogen at 25° gave an oil which was used at once.

3α-Chlorotropane (III).—This compound was prepared by the method of Archer *et al.*,[8] (76%), n_D^{20} = 1·5040; b.p. 56—57° at 0·2 mmHg (lit.,[8] b.p. 55—56° at 0·2 mmHg). The remaining sulphonates are listed in Table 1.

N-Isopropylnortropan-3β-yl Phenyl Ether (II; R^5 = Ph, R^1 = Pr^i, R^2 = R^3 = H, n = 1).—A solution of *N*-isopropylnortropan-3α-yl methanesulphonate (49·5 g) and sodium phenoxide (30 g) in dimethylformamide (250 ml) was heated at 60° for 2 h. The methanesulphonate was filtered off (22 g, 93%). The solution was acidified to pH 3 with 10N-hydrochloric acid and the solvent evaporated *in vacuo*. The residue was dissolved in water and extracted with ether to remove non-basic products. The aqueous layer was then treated with solid potassium carbonate and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and filtered. The solvent and a large portion of the resulting trop-2-ene were evaporated off *in vacuo*, and the residue was distilled, b.p. 145—146° at 0·7 mmHg n_D^{20} = 1·5333 (21·2 g, 43·3%). (Found: C, 78·0; H, 9·9; N, 5·8. $C_{16}H_{23}NO$ requires C, 78·3; H, 9·5; N, 5·7%). The *N*-isopropylnortropan-3β-yl phenyl ether hydrochloride was crystallized from methanol–ether, and had m.p. 220—221° (Found: C, 68·0; H, 8·6; Cl, 12·35; N, 5·2. $C_{16}H_{24}ClNO$ requires C, 68·2; H, 8·6; Cl, 12·6; N, 5·0%).

p-*Chlorophenyl Tropan-3β-yl Ether* (II; R^5 = *p*-ClC_6H_4, R^1 = Me, R^2 = R^3 = H, n = 1).—A solution of tropan-3α-yl methanesulphonate (219 g) and sodium *p*-chlorophenoxide (180·6 g) in dimethylformamide (800 ml) was heated at 80° for 4 h. The methanesulphonate was filtered off (117 g, 95%). The procedure was similar to that described above; the *product* had b.p. 117—118° at 0·08 mmHg (101·0 g, 40·2%). It solidified immediately after distillation, and was crystallized from hexane; it had m.p. 60° (Found: C, 66·8; H, 7·25; Cl, 14·15; N, 5·6. $C_{14}H_{18}ClNO$ requires C, 66·8; H, 7·2; Cl, 14·1; N, 5·6%). The hydrochloride recrystallized from ethanol–ether had m.p. 284° (Found: Cl, 12·2; N, 4·9. $C_{14}H_{19}Cl_2NO$ requires Cl, 12·3; N, 4·9%).

Granatan-3β-yl Phenyl Ether (II; R^5 = Ph, R^1 = Me, R^2 = R^3 = H, n = 2).—A solution of the base [from the hydrochloride (58·6 g)] and sodium phenoxide (33·2 g) in ethanol (200 ml) was refluxed for 2 h. The methanesulphonate was filtered off (23·4 g, 90%). The ethanolic solution was acidified to pH 3 with 10N-hydrochloric acid, and evaporated under reduced pressure. The residue was dissolved in water and the non-basic products were extracted with ether. The base, liberated from the aqueous layer by the addition of sodium hydroxide (40%), was extracted with ether; the extract was dried (Na_2SO_4) and the solvent was removed. The *residue* had b.p. 130° at 0·4 mmHg, n_D^{20} = 1·5502 (14·1 g, 27·7%) (Found: C, 78·1; H, 9·45; N, 6·3; O, 7·2. $C_{15}H_{21}NO$ requires C, 77·9; H, 9·15; N, 6·1; O, 6·9%). The hydrochloride of 3β-granatanyl phenyl ether, recrystallized from ethanol–ether had m.p. 200° (Found: C, 67·4; H, 8·5; Cl, 13·0; N, 4·95; O, 6·1. $C_{15}H_{22}ClNO$ requires C, 67·3; H, 8·3; Cl, 13·2; N, 5·2; O, 6·0%).

The other tropan-3β-yl ethers listed in Table 2 and 3 were prepared similarly.

Cyclohexyl Tropan-3β-yl Ether (II; R^5 = cyclohexyl, R^1 = Me, R^2 = R^3 = H, n = 1).—A solution of tropan-3β-yl phenyl ether (11·4 g) in ethanol was hydrogenated at 100° and 40 atm in the presence of 5% rhodium on alumina (2 g). The catalyst was filtered off and the solvent was removed; cyclohexyl ether was distilled *in vacuo*, b.p. 111—114° at 0·4 mmHg, n_D^{20} = 1·5015 (7·3 g, 62·5%) (Found: C, 75·1; H, 10·9; N, 6·6. $C_{14}H_{25}NO$ requires C, 75·3; H, 11·3; N, 6·3%). The hydrochloride had m.p. 194—195° (from ethanol–ether) (Found: C, 64·2; H, 10·1; Cl, 13·9; N, 5·0. $C_{14}H_{26}ClNO$ requires C, 64·7; H, 10·1; Cl, 13·65; N, 5·4%).

p-Aminophenyl Tropan-3β-yl Ether Dihydrochloride (II; R^5 = *p*-$NH_2C_6H_4$, R^1 = Me, R^2 = R^3 = H, n = 1).—Tropan-3β-yl *p*-nitrophenyl ether was hydrogenated (Adams platinum oxide in methanol) at atmospheric pressure. The catalyst was filtered off and the mixture was treated with HCl in ether; it was then diluted with ether until crystallization occurred. The mixture was cooled, and the *ether dihydrochloride* was filtered off (72·5%), m.p. 306° (decomp.) (Found: C, 54·9; H, 7·2; Cl, 23·4. $C_{14}H_{22}Cl_2N_2O$ requires C, 55·1; H, 7·3; Cl, 23·2%).

p-*Chlorophenyl Tropan-3α-yl Ether* (IV; R^5 = *p*-ClC_6H_4). A solution of 3α-chlorotropane (47·8 g) and sodium *p*-chlorophenoxide in ethanol (140 ml) was boiled for 10 h and then acidified to pH 3 with 10N-hydrochloric acid. The solvent was evaporated off under reduced pressure. The residue was dissolved in water and extracted with ether to remove excess of phenol. The base, liberated from the aqueous layer by the addition of 40% sodium hydroxide with cooling, was extracted with ether. The extract was dried and the ether was evaporated; the *base* distilled *in vacuo*, b.p. 138—142° at 0·5 mmHg. After distillation the product crystallized from n-hexane; it had m.p. 89—90° (49·2 g,

52·0%) (Found: C, 66·9; H, 7·3; N, 5·5. $C_{14}H_{18}ClNO$ requires C, 66·8; H, 7·2; N, 5·5%). The hydrochloride recrystallized from a mixture of ethanol and ether and had m.p. 215—216° (Found: C, 58·5; H, 6·8; Cl, 12·1; N, 4·9. $C_{14}H_{19}Cl_2NO$ requires C, 58·35; H, 6·65; Cl, 12·3; N, 4·9%).

p-*Iodophenyl Tropan-3α-yl Ether* (IV; $R^5 = p\text{-}IC_6H_4$).—A solution of 3α-chlorotropane (15·9 g) and sodium *p*-iodophenoxide (44 g) in ethanol (140 ml) was boiled for 18 h, acidified with 10N-hydrochloric acid, and evaporated. The residue was dissolved in water (100 ml) and the non-basic material was extracted with ether. To the aqueous solution 40% sodium hydroxide was added slowly, with cooling. The base separated as a solid which was filtered off, washed with water, dried, and recrystallised from ethanol; it had m.p. 107° (21 g, 61·2%) (Found: C, 49·1; H, 5·4; I, 36·9; N, 4·2. $C_{14}H_{18}ION$ requires C, 49·0; H, 5·3; I, 37·0; N, 4·1%).

Benzyl Tropan-3α-yl Ether (IV; R^5 = benzyl).—To sodium (10·12 g) dissolved in benzyl alcohol (200 ml) at 100° 3-α-chlorotropane (63·3 g) was added with vigorous stirring during 20 h at 100—120°. The reaction mixture was cooled, acidified with HCl–ether, and the benzyl alcohol evaporated under 2—3 mmHg. The residue was dissolved in water (150 ml) and shaken with ether to remove non-basic products. The aqueous portion was saturated with potassium carbonate and extracted with ether. The extract was dried and the solvent was evaporated; the residue was distilled *in vacuo*, b.p. 118—120° at 0·04 mmHg, n_D^{20} = 1·5355 (36 g, 39%) (Found: C, 77·9; H, 9·35; N, 6·1. $C_{15}H_{21}NO$ requires C, 77·9; H, 9·15; N, 6·1%). The hydrochloride had m.p. 231—233° (from acetone) (Found: C, 67·3; H, 8·4; Cl, 13·1; N, 5·4. $C_{15}H_{22}ClNO$ requires C, 67·25; H, 8·3; Cl, 13·2; N, 5·2%).

The other tropan-3α-yl ethers listed in Table 4 were prepared similarly.

Methyl Tropan-3α-yl Ether Methiodide.—Dimethyl sulphate (151·2 g) was added dropwise with vigorous stirring to a solution of tropine (28·2 g) and sodium hydroxide (112 g) in water (250 ml) at 40—50°. The solution was heated to 80—90° and stirred for 3 h. Sodium iodide (37·5 g) was then added. The solution was cooled and the precipitate was filtered off, washed with cold water, and dried to leave pale yellow *crystals* (27 g, 45·3%), m.p. 260° (Found: I, 42·4. $C_{10}H_{21}INO$ requires I, 42·55%); $\nu_{max.}$ 1098 cm^{-1} (C–O–C).

Methyl Tropan-3α-yl Ether (IV; R = Me).—A mixture of tropan-3α-yl methyl ether methiodide (23 g) and 2-aminoethanol (25 g) was refluxed for 6 h. Two layers separated out. 20% Sodium hydroxide (50 ml) was added and the mixture extracted with light petroleum. The combined extracts were dried (K_2CO_3) and distilled, b.p. 82° at 15 mmHg to give a colourless *oil*, n_D^{20} = 1·4771 (10·6 g, 88·5%) (Found: N, 9·0. $C_9H_{17}NO$ requires N, 8·7%). The hydrochloride (from ethanol–ether) had m.p. 198·5°, and was hygroscopic (Found: C, 56·1; H, 10·1; Cl, 18·7; N, 7·0. $C_9H_{18}ClNO$ requires C, 56·4; H, 9·5; Cl, 18·5; N, 7·3%).

To investigate the structure of the alkyl and benzyl ethers a portion (1 g) was refluxed for 30 min. with 48% hydroiodic acid (5 ml), and allowed to cool. The hydroiodic salt was then induced to crystallize by the addition of acetone and ether. The hydroiodide salt so produced had m.p. and mixed m.p. (with pseudotropine hydroiodide) 277—280°. The i.r. spectra of the two substances were identical. The compounds obtained after degradation of tropan-3α-yl methyl and benzyl ethers, as well as tropine hydroiodide all had m.p. 228—230°; mixed m.p. and i.r. spectra of these compounds were also identical.

2-*Allyl*-1-*methyl*-5-*phenoxypyrrolidine* (VI).—A solution of 3β-chlorotropane [7] (13·1 g) and sodium phenoxide (19 g) in ethanol (50 ml) was refluxed for 8 h. The mixture was acidified to pH 3 with 10N-hydrochloric acid and evaporated. The residue was dissolved in water and extracted with ether to remove non-basic products. It was then made alkaline with 40% sodium hydroxide, and again extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and distilled, b.p. 121° at 0·06 mmHg, n_D^{25} = 1·5350 (3·8 g, 21·4%) (Found: C, 77·0; H, 9·1; N, 6·2. $C_{14}H_{19}NO$ requires C, 77·4; H, 8·8; N, 6·5%); $\nu_{max.}$ spectrum: 1655 cm^{-1} (C=C), 1270 cm^{-1} (C–O–C), 695 and 760 cm^{-1} (monosubstituted benzene). The spectrum is very similar to that of 2-allyl-5-cyano-1-methylpyrrolidine which Archer *et al.*[7] obtained in the course of the reaction of 3β-chlorotropane with potassium cyanide, and the structure of which they have proved by degradation and partial synthesis.

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