A Quantitative Study of the Quaternisation of Tropanes

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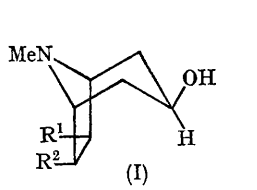
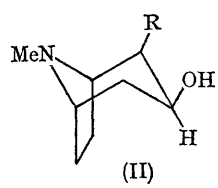
IN a series of papers[1] on selective[2] quaternisations, the reaction of hydroxy- and epoxy-tropanes with ethyl iodoacetate, leading to lactone salts,[3,4] served to establish the configuration of the neighbouring hydroxyl-bearing carbon and, inversely, that of the tropanium nitrogen. This has been extended later to codeines, morphines, *Lycopodium* alkaloids, tetrahydroisoquinolines,[3] and also to pyrrolizidines,[4a] 4-t-butylpiperidines,[4b] and 3-azabicyclo[3,2,1^{1,5}]octanes,[4c] and their ring homologues.

Our previous results were based necessarily on classical methods of separation and on the chemical or *X*-ray analysis of a few isolated products. However, the n.m.r. approach[5] to the steric course of quaternisations led to conflicting results.[6a–f,7] For instance, McKenna and his co-workers[6a,g] claim a preferentially axial course of quaternisation for piperidines while we observed in many cases an equatorial attack. Our recent n.m.r. work on scopolamine and tropine *N*-oxides showed[8] that in amine-oxide formation the approach of oxygen is axial.

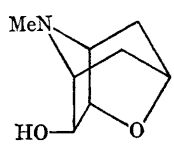
In view of all these results, product analysis of quaternisations of tropanes using n.m.r. seemed indispensable. First, methylation with [$^2H_3$]-methyl iodide was investigated with tropane and its derivatives bearing hydroxyl (and/or epoxide) function(s) at C-3, C-2′, C-6 and/or C-7 (I—III). This approach seemed justified on the basis that deuteriomethyl is slightly smaller than methyl.[4b] Methiodides and deuteriochlorides of piperidines present two distinct *N*–Me signals as singlets, the equatorial one being more deshielded. With conformationally flexible azabicyclo-octanes, or if the character of an adjacent group is changed (C–OH → C=O), reversal of the relative positions of the methyl signals has been observed.[4c] However, the premise of a lower-field equatorial *N*–Me signal and hence the high-field axial *N*–Me signal proved consistent for conformationally rigid systems, *e.g.* 4-t-butylpiperidines.[4b] Tropanes, from recent n.m.r. and dipole moment studies,[10] belong to this second category.



(I)



(II)



(III)

In order to avoid any uncertainty arising from solvent effects in quaternisation, deuteriomethylations were carried out in [$^2H_6$]dimethyl sulphoxide in which the reaction is fast and the quaternary salts are soluble. The *NN*-dimethyl salts were used as reference.[1,4b] Any trace of unchanged

tertiary amine should have been detected by the *N*–Me signal around 125 c./sec. Appearance of a singlet in a few cases was not accepted as evidence of 100% stereospecificity unless confirmed by the spectra of the same products in [$^2H_3$]acetonitrile or D_2O. "Reverse" quaternisation, *i.e.* *N*-methylation of *N*-[$^2H_3$]methylnortropine, indicated no difference in the ratio of products, so the possibility of a secondary isotopic effect was ruled out.

The long-range shielding effect associated with the magnetic anisotropy of C–C bonds and hydroxyl groups is more strongly reflected by the equatorial than by the axial methyl, and hence the equatorial methyl should be more deshielded.[9] Inspection of the chemical shifts reveals nearly constant values for the high-field methyl signal while the low-field one is very sensitive to any hydroxyl introduced in the tropane skeleton. This again seems to support the view that the lower-field *N*-methyl signal is equatorial.

(i) Tropane and its 3α- and 3β-hydroxyl-derivatives (I, II; $R^1=R^2=H$) undergo *axial* methylation preferentially in agreement with simple piperidines[4b] and with McKenna's predictions.[6e,f]

(ii) The presence at C-2 of an axial substituent bulkier than hydrogen results in a considerable decrease in the rate of axial quaternisation.

(iii) The presence of a hydroxyl on C-6, or an epoxide group on C-6 and C-7, restores the pattern indicating preferential equatorial quaternisation. This might be explained by nucleophilic assistance of quaternisation in the equatorial position by the neighbouring oxygen function,[4c] as observed in the epoxidation[12a] of cyclo-olefins having an oxygen function, and also in carbon alkylations.[12b] This agrees with qualitative, preparative results achieved formerly[1a] concerning preferential or exclusive lactone salt formation from tropane-3α,6β-diol and also from the 6β,7β-dihydroxylated bases with ethyl iodoacetate.

(iv) Tropanes substituted by a hydroxyl function at C-6, having an *endo*-oxygen bridge between carbons 3 and 7 in case of oscine (III) show a slight decrease in the selectivity of quaternisation (*cf.* ref. 1a).

The question may arise whether [$^2H_6$]dimethyl sulphoxide might be regarded merely as a solvent or as a [$^2H_3$]methyl transferring agent[13a–c] *via*

Product analysis of the quaternisation of tropanes by n.m.r. (60Mc./sec.) in [$^2H_6$]DMSO

Formula	Tropane		*N*-Me equatorial	*N*-Me axial	Steric course % (by integration)
	unsubstituted				
		methiodide	197 c./sec.	189 c./sec.	
		[$^2H_3$]methiodide	198	190	82% axial
(I)	3α-hydroxy				
		methiodide	188·5	185·2	
		[$^2H_3$]methiodide	189	185	85% axial
	[$^2H_3$]methylnor-	methiodide	187	182·5	83% axial
(II)	3β-hydroxy-				
		methiodide	194	184	
		methiodide	194	184	84% axial
(II)	2β-hydroxymethyl-3β-hydroxy–				
$R=CD_2OH$		methiodide	196	186	
		[$^2H_3$]methiodide	198	188	62% axial
(I)	3β,6β-dihydroxy-				
$R^1=OH, R^2=H$		methiodide	199	188	
		[$^2H_3$]methiodide	202	189	87% equatorial
(I)					
$R^1,R^2= \rangle O$	3α-hydroxy-6β,7β-epoxy-				
		methiodide	202 (200†)	186 (184†)	
		[$^2H_3$]methiodide	202 (203†)	186 (184†)	90% equatorial (93% equatorial†)
(III)	3α,6α-oxido-7β-hydroxy-				
		methiodide	203 (198‡)	200 (182‡)	
		[$^2H_3$]methiodide	202·5 (198‡)	199 (182‡)	74% equatorial
(I)	3α-hydroxy-*N*-ethyl-				
		ethiodide	198	182	92% equatorial
		methiodide	198	179	50% equatorial
(II)	3β-hydroxy-				
		ethiodide		188	100% equatorial
(I)	3α,6β-dihydroxy				
		ethiodide	195	182	83% equatorial

† in D_2O. ‡ in CD_3CN.

s-[$^2H_9$]trimethyl oxosulphonium iodide. However, reaction of methyl iodide in [$^2H_6$]dimethyl sulphoxide leading to methylation (and no deuteriomethylation) of [$^2H_3$]methylnortropine seems to disprove this second alternative.

The products of ethylation of tropine and pseudotropine were re-investigated by n.m.r. while the *N*-ethylation of tropane-3α,6β-diol was studied for the first time. Tropine ethiodide gave optically isotropic crystals.[1f] The configuration of its *N*-Me group was indirectly proved by *X*-ray studies.[1e] The methyl signal coincides with the high-field methyl in tropane methiodide (Table). A quartet centred at 205 c./sec. (for the *N*-CH_2) coalesces on irradiation of the *C*-methyl triplet at 117 c./sec. upfield, leaving the area below the *N*-Me signal intact. *N*-Ethylation in dimethyl sulphoxide gave an identical pattern which indicates a highly stereo selective equatorial course. The same applies to *N*-ethylation of pseudotropine and of 3α,6β-tropandiol also. "Reverse" quaternisation, *i.e.* *N*-methylation of *N*-ethylnortropine, allowed, by fractional crystallisation, the isolation of anisotropic crystals[1f] of the *N*-epimeric iodide which was converted to the bromide. The latter has shown by *X*-ray diffraction an equatorial methyl group.[1e] Product analysis by n.m.r. of this "reverse" reaction in four different solvents [benzene : ethanol (1 : 4), [$^2H_6$]DMSO, CD_3CN and D_2O] suggested the formation of the equatorial and axial *N*-Me derivatives in a 1 : 1 ratio.

The complete reversal of the steric course of methylation and ethylation of tropine is unexpected and needs clarification. The difference in bulkiness of the alkylating agent alone cannot account for this fact. Methyl iodide is, however, much more reactive than ethyl iodide. Therefore it seemed reasonable to compare quaternisation of tropine with ethyl iodide and with methyl chloride of similar reactivity. No considerable change in the product ratio could be found. The same observation was made in the parallel methylations of *N*-[$^2H_3$]methyl nortropine in dimethyl sulphoxide with methyl iodide and methyl chloride. At present we lack any further explanation for this rather unforeseen result.

All our statements are based on n.m.r. We tried to adopt the i.r. criteria of McKenna,[6a,g] concerning the assignment of the increase of intensity of the bands in the 880—905 $cm.^{-1}$ region in the case of an equatorial and an increase around 840—880 $cm.^{-1}$ in the case of an axial *N*-Me group. Unfortunately most tertiary bases and also nortropine and norpseudotropine bearing no methyl at all, show considerable absorption in these regions, while tropinone methiodide has no maximum. So any empirical assignment of configuration to the *N*-Me based on these bands seems rather dangerous, at least in the tropanes.

We thank the National Research Council of Canada for support of this work.

(*Received, January 23rd*, 1968; *Com.* 089.)

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