

above). However, the barriers in *N*-methylpyrrolidine (**5**) and in the bicyclic compound **6** are significantly higher (8–9 kcal/mol),²² probably because of the ring strain associated with a cyclic sp² hybridized nitrogen atom in the transition state for nitrogen inversion.

An interesting feature of the low-temperature nmr spectra of dibenzylmethylamine (Figure 1) is the large and unequal line broadening of the NCH₃ and NCH₂ signals. Thus at –135° the NCH₃ signal has a line width of 11 Hz whereas the NCH₂ signal has a natural width of ~6 Hz (see above). The solvent signal remained comparatively sharp down to –150°. Anderson, Griffith, and Roberts²³ observed similar effects in the spectra of benzyltrimethylhydrazine and attributed the excess broadening to incomplete quadrupole-induced relaxation of the nitrogen atoms at low temperature. A similar quadrupole effect has recently been suggested as an explanation of the line broadening of the NCH₃ signal in dibenzylmethylamine at low tempera-

tures.¹³ These proposals are surprising since quadrupole-induced relaxation of the ¹⁴N nucleus becomes more facile at low temperatures as a result of the longer correlation time. This results in broadening of the ¹⁴N nmr signals but *narrowing* of adjacent proton signals due to the effective removal of any coupling between the nitrogen and hydrogen nuclei. The theory has been discussed by Pople,²⁴ and has been verified experimentally.²⁵ We therefore prefer to attribute the excess line broadening of the NCH₃ and NCH₂ signals of dibenzylmethylamine at low temperatures to effects resulting from the slowing down of molecular motions such as tumbling and rotation around the C–C and C–N bonds.

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Stereochemistry of Tropane Quaternization

Gabor Fodor,*¹ Roger V. Chastain, Jr.,¹ Daniel Frehel,²
Mehru J. Cooper,² Nagabhushanam Mandava,^{3a} and Ernest L. Gooden^{3a,b}

*Contribution from the Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506,
the Department of Chemistry, Laval University, Quebec, Canada,
and Crops and Entomology Research Divisions, Agricultural Research Service,
U. S. Department of Agriculture, Beltsville, Maryland 20705.
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Abstract: Chemical correlation of major products of *N*-alkoxycarbonylmethylation of tropane, tropine, pseudotropine, and tropinone with that of 3 α ,6 β -tropanediol **7f** of unequivocal geometry has proven the preferred equatorial steric course for all these quaternizations. Pseudotropine-*N*-acetic acid by X-ray investigation also proved to be the N_b isomer, **12d**. Furthermore, conversion of *N*-ethoxycarbonylmethyltropinium bromide (**3b**) into *N*_b-ethylmethylnortropinium bromide having structure **2**, known from X-ray studies, clearly indicated consistence of preferred equatorial course in ethylation, hydroxyethylation, chloroethylation, and alkoxycarbonylmethylation throughout the tropane series. Critical survey of correlation of *N*-Me nmr signals with stereochemistry is presented, also supported by correlation between the main product of deuteriomethylation of tropine and of 3 α ,6 β -tropanediol with that of methoxycarbonylmethylation of the same two amines. Amine oxide formation from scopalamine was shown by X-ray to give preferentially the N_b oxide.

This and a forthcoming paper⁴ by Bottini, *et al.*, present conclusive experimental evidence for preferred equatorial quaternization with different reagents throughout the tropane series.

It has long been known⁵ that quaternization of tropine with ethyl iodoacetate resulted in isolation of one product. The geometry of the N stereoisomer that had formed stereospecifically,^{6a} as we now know

rather stereoselectively, from 3 α ,6 β -tropanediol with the same reagent, proved by its conversion into lactone salt **7f** to be the N_b-carboxymethyl derivative.

Reversal of sequence of quaternization with noramines, which means methylation in the last step, rendered the N_a-carboxymethyl N stereoisomers unable to undergo cyclization,^{6a,b} indicating preferential equatorial course of quaternization. Selectivity of reaction of ethyl iodoacetate was confirmed with tropine,

(1) West Virginia University.

(2) Laval University.

(3) (a) Agricultural Research Service, USDA; (b) deceased Dec 1970.

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and was also found with 6 β ,7 β -epoxy-,^{6b} 3 α ,6 α -oxido-, 7 β -hydroxy-, 3 α ,6 β ,7 β -trihydroxy-,^{6b} 3 β -hydroxy-,^{6c} and 2 β -hydroxymethyltropans.^{6d} Lactone salts were formed in excellent yields with those tropane derivatives having oxygen function(s) in the pyrrolidine moiety, while pseudotropine and ecgoninol *N*-acetic acids^{6c,d} showed low conversion; however, all indicated equatorial preference of ethoxycarbonylmethylation and methylation, respectively.

Furthermore, *N*-ethylnortropan-3 α -ol methobromide by X-ray crystallography⁷ indicated structure **1**; thus, the concept of an equatorial course of quaternization deduced from chemical facts^{6a-d} was further corroborated. Use of nmr spectroscopy later permitted determination of product ratios and assignment of axial configuration to the lower field methyl signal in tropane deuteriohalides⁸ and methiodides.^{8,9} It is generally accepted that equatorial methyl groups in carbocycles^{10,11} and by analogy in heterocycles¹² are more deshielded than axial ones, a conclusion opposite to the earlier hypothesis.

Ethoxycarbonylmethylation of 6 β -hydroxytropine followed by nmr indicates formation of 92% equatorial isomer **7b** (δ_{N-Me} 3.31) and 8% axial ester (δ_{N-Me} 3.45) which supports the second-mentioned view.

The concept of equatorial tropane quaternization, however, has attracted persistent criticism by McKenna and his coworkers^{9a,13a-c} who favored axial quaternization on the following grounds: (1) lactone salt from pseudotropine,^{6c} and also the *N*-ethyl stereoisomer from tropine, analyzed by X-ray,⁷ were minor rather than major products; (2) the product ratio of direct and reverse quaternization with various alkyl groups showed different degrees of selectivity;^{13a-c} (3) dealkylation of tropanium salts with lithium aluminum hydride^{13e} and thiophenoxide^{13e} seemed to reveal a certain degree of stereoselectivity in favor of axial attack in quaternizations; (4) empirical ir criteria in the 840–900-cm⁻¹ region were considered by these authors as diagnostic for axial or equatorial *N*-Me configuration.^{13a,b} Although ir and (5) empirical nmr^{9a} data of products isolated from *N* quaternizations indicated equatorial attack these were arbitrarily disregarded.^{13b-d}

We were challenged to reinvestigate with modern tools part of our previous work, and also to complete the same with a series of derivatives. First, the so-called ir criteria were checked with a number of tropanes. Unfortunately, most tertiary bases and also nortropine and norpseudotropine bearing no methyl group at all, show considerable absorption in this region, while tropinone methiodide has no maximum.¹⁴

Secondly, deuteriomethylation of a series of tropane derivatives, followed by nmr product analysis, was undertaken¹⁴ by assigning the lower field signal to the equatorial *N*-methyl group. However, this led to two distinctly different series, one comprising tropane, 3 α -, and 3 β -tropanols and the other series containing those with oxygen functions in the five-membered ring. We later recognized¹⁵ that a neighboring oxygen function has stronger deshielding effect upon *N*-methyl, as in the case of angular methyls in steroids,¹⁶ than overall deshielding effect upon an equatorial substituent. These two effects may act either parallel or opposite, thus making our previous assignments to methyl-*d*₃ derivatives rather equivocal.¹⁷

Obviously, empirical nmr has led to confusion because (a) it was used by analogy with carbocyclic compounds for *N*-Me signals and (b) we did not reckon with other important shielding effects.^{15,16} These uncertainties prompted us to reexamine this problem by correlating alkoxycarbonylmethyltropanium salts with compounds whose geometry is unequivocally established, for instance, *N*-ethylnortropine methobromide (**1**) or, alternately, with a β -hydroxytropane *N*-acetic acid lactone of unambiguous geometry. Thut and Bottini¹⁸ and two of us independently¹⁹ found that *O*-bromoacetyl pseudotropine undergoes internal²⁰ quaternization to a solid, supposedly a lactone bromide, the iodide of which had previously been obtained^{6c} in low yield on reverse quaternization of norpseudotropine. Hydrolysis of this salt led to a carboxylic acid believed then to be **10d**, also prepared by direct quaternization of pseudotropine. Therefore, our previous configurational assignments^{6c} ought to be reversed.¹⁸ The "lactone" **17** seemed to be a reliable reference compound for correlations. However, osmometric measurements (apparent mol wt 513–520) as contrasted with low-resolution mass spectral data (*m/e* 182, 261, and 263) were compatible with an oligomer arising from indefinite steric course rather than from intramolecular cyclization. Furthermore, high-resolution mass spectrometry indicated a number of fragments much higher than the expected *M*⁺ for **10d**.

Pursuant to confirming the configuration about the quaternary nitrogen atom, a crystal-structure analysis has been undertaken of the hydrate²¹ of sodium *N*-carboxymethyl-3 β -hydroxytropanium bromide prepared from this "lactone" or on direct quaternization of pseudo-

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(10) (a) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957); (b) J. I. Musher, *J. Amer. Chem. Soc.*, **83**, 1146 (1961).

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(13) (a) J. McKenna, J. M. McKenna, A. Tulley, and J. White, *J. Chem. Soc.*, 1711 (1965); (b) D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *ibid.*, **B**, 1184 (1967); (c) D. R. Brown, J. McKenna, J. M. McKenna, J. M. Stuart, and B. G. Hutley, *Chem. Commun.*, 380 (1967); (d) R. Brettie, D. R. Brown, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 696 (1969); (e) J. McKenna, B. G. Hutley, and J. J. White, *J. Chem. Soc.*, 1729 (1965).

tropine and hydrolysis. Betaine **12e** gave with sodium bromide the same sodium salt. The hydrate crystallized from acetonitrile in the orthorhombic space group $Pbn2_1$ (established by systematically absent reflections and the structure determination) with the cell constants of $a = 12.96$, $b = 15.78$, and $c = 6.42$ Å. An asymmetric set of three-dimensional data consisting of 1211 reflections out to 50° in 2θ was collected using Mo $K\alpha$ radiation and an Automated Full-Circle Picker diffractometer. Analysis of electron density maps initially phased by the bromide ion located from a Patterson map provided the atomic positional parameters and an overall isotropic temperature factor of all nonhydrogen atoms. These positional parameters and individual isotropic thermal parameters were subsequently refined by full-matrix least squares using a statistical weighting scheme, reducing the residual factor, R , to 0.14. The atomic designations of the *N*-carboxymethyl 3β -hydroxytropinium ion are given²² in Figure 1.

Consider plane 1 to be defined by C(1), C(2), C(4), and C(5), and plane 2 by C(1), C(5), C(6), and C(7). If the carboxymethyl group is equatorially disposed from the nitrogen atom of the pseudotropine skeleton, the C(8)–N bond should be nearly parallel to plane 1 and nearly orthogonal to plane 2. These angles are observed to be 1.1 and 69.8° , respectively. In addition, the C(9)–N bond is observed to be 69.2° out of plane 1 and 1.5° out of plane 2. These results are consistent with the structure of the N_b derivative **12d**, and not **10d**.

Hence, it was an error^{18,19} to base any configurational assignments on the so-called lactone. We have then put emphasis on chemical correlation of tropine *N*-acetic

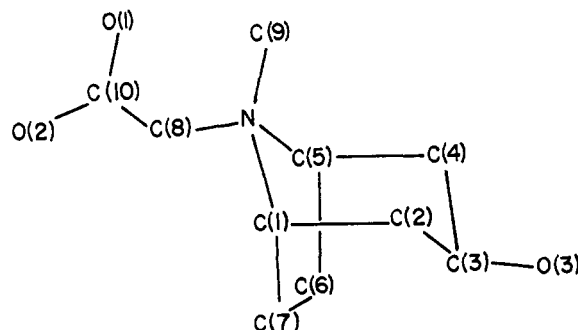
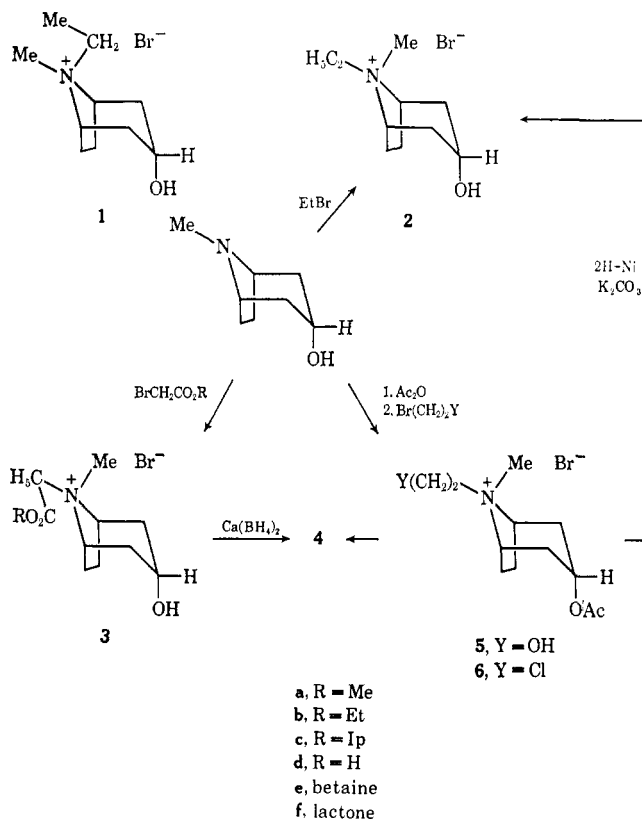


Figure 1. The *N*-carboxymethyl- 3β -hydroxytropinium ion.

ester with methobromide **1**, or its *N* stereoisomer **2**, also with the new firm reference compound **12d**.

The ethyl ester bromide (**3b**) formed in about 90% *N* isomeric purity²³ from 3α -tropanol. This and **3b** bromide were reduced to hydroxyethyl compound **4**, which is also available from acetyltropine and 2-bromoethanol *via* **5**. Conversion of 3-monoacetyl derivative **5** gave 2-chloroethyl derivative **6** also obtained as a major product by β -chloroethylating acetyltropine. Hydrogenolysis of **6** actually led to the major product of direct ethylation of tropine (nmr N -Me 3.00, N -CH₂ 3.34 (q)), which coalesces on irradiation at 124.5 cps upfield. The equatorial *N*-Me isomer **1**, investigated by X-ray crystallography,^{7,24} showed in the nmr δ_{N-Me} 2.98, δ_{N-CH_2} 3.42 ppm (q), collapsing when irradiated at 128.5 cps upfield at 60 Mcps. Hence, quaternization of tropine with ethyl bromide led to N_b -ethyl compound **2** and, by inference, alkylations with ethyl bromoacetate, 2-bromoethanol, and 2-chloroethyl bromide proceeded on a preferentially equatorial course.

As the next step, in this series, in particular tropine derivative **3b**, was correlated with a pseudotropinium salt, *via* *N*-ethoxycarbonylmethyltropinium bromide (**8b**). Catalytic hydrogenation of the product of quaternization of tropinone, δ_{N-Me} 3.59 and 3.36 (4.5:1), resulted indeed in the same salt **3b** as direct ethoxycarbonylmethylation of tropine, δ_{N-Me} 3.27. However, Meerwein reduction afforded the isopropyl ester **10c** of pseudotropine *N*-acetic acid (δ_{N-Me} 3.09, $CHMe_2$ 1.28 (d)), which was also interconverted with the product of *N* methylation of *N*-ethoxycarbonylmethylpseudotropine. This could mean either that 3α -tropanol and its 3β -epimer quaternize by different course, or that *N* inversion had taken place prior to, or after reduction. Since **10b** and **12b** equilibrated very slowly under comparable conditions, probably *via* oxidation to ketones,^{25a} the latter mentioned alternative is ruled out. Also, *N*-stereoisomeric tropinium salts **8a** and **8b** (δ_{N-Me} 3.55), when heated separately in *tert*-butyl alcohol with aluminum *tert*-butoxide, gave rise to a new nmr signal at δ 3.33 and 3.34 corresponding to *N*-stereoisomers **9a** and **9b**, respectively, which we prepared from nortropinone^{25b} by reverse quaternization. The pres-

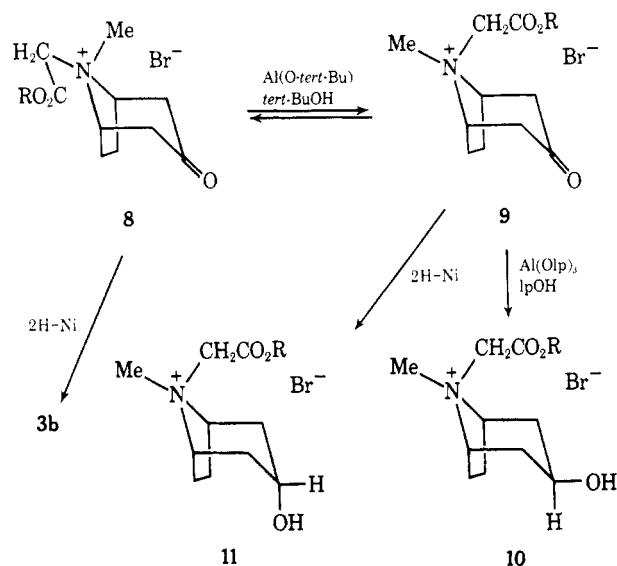


(22) Details of this X-ray work will be published elsewhere by R. V. Chastain, Jr., and P. F. Method.

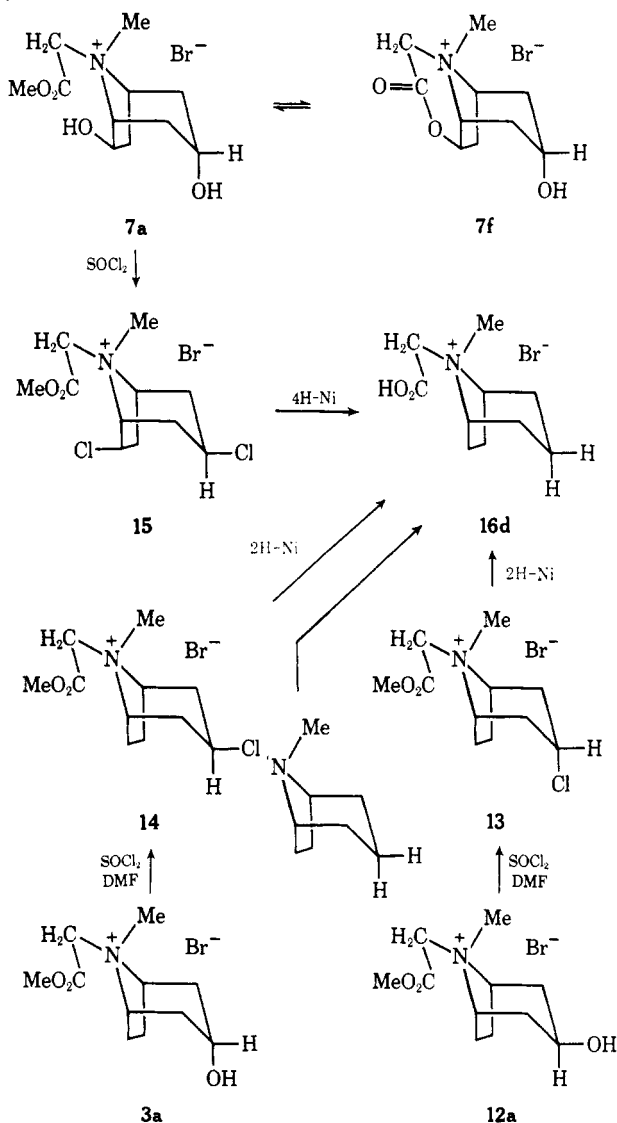
(23) Alkyl bromides and bromoacetates reacted with remarkably higher stereoselectivity than did iodides.

(24) Diffraction study of **2** was difficult because of the sensitivity of crystals toward X-rays. Exposure at liquid air temperature, by C. H. MacGillavry, Stam, and Benci (*Tetrahedron Lett.*, in press), now helped to overcome this difficulty. They proved that the ethyl group is equatorial.

(25) (a) W. von E. Doering and T. E. Aschner, *J. Amer. Chem. Soc.*, **75**, 397 (1953); cf. M. Halmos, Ö. Kovács, and G. Fodor, *J. Org. Chem.*, **22**, 1699 (1957). (b) A novel synthesis of nortropinone is described in the Experimental Section.



ence of this signal indicated that equilibration took place prior to reduction of the ketone. The mechanism of this epimerization, hitherto completely unknown in tropanes,²⁶ seems to be limited to the ketoammonium salts.⁴



(26) J. McKenna, J. M. McKenna, and J. White, *J. Chem. Soc.*, 1733 (1965).

A kinetic nmr study with methyl-*d*₃ and methoxycarbonyl-*d*₂ derivatives of **8a** and **9a** has to be undertaken in order to choose between a spiroazetidinone or a Hofmann product as an intermediate. In view of the preference of this transformation to ketones, we are inclined to the second alternative.

Another valid correlation of tropine and pseudotropine *N*-acetic esters was achieved by deoxygenating **3a** and **12a** via the 3 β - and 3 α -chlorotropanium salts **14** and **13** to the same *N*-carboxymethyltropanium bromide (**16d**) (nmr N-Me 3.34:3.44 (3:1)) and the same betaine **16e** (nmr N-Me 3.24:3.34 (3:1), NCH₂ 3.70, 3.75). Identical data were obtained for the acid betaine **16e** prepared from tropane-3 α ,6 β -diol via **7a** of unequivocal structure^{6a} by carrying out a similar series of reactions (**7a** $\rightarrow$ **15** $\rightarrow$ **16**). Hence, tropane, tropine, pseudotropine, tropinone, and 3 α ,6 β -tropanediol all followed the same preferred equatorial course of alkoxy carbonylmethylation.

In consequence, most of our configurational assignments^{6a-d,7} based on chemical or X-ray evidence are correct; so is the concept of equatorial quaternization, although nmr studies proved that it is valid as a major and not as a unique pattern. Therefore, very little, if any, of the criticism by the Sheffield group¹³ can be accepted.

At this stage, solid knowledge of N configurations in a number of compounds does now allow correlating the position of nmr *N*-methyl signals with configuration. Ethyl methyl nortropanium salts **1** and **2**, and pseudotropine ethobromide also analyzed by X-rays by Bottini, *et al.*,⁴ show the axial methyl signal in a lower field than the equatorial one, in harmony with Closs' early assignments.⁸ The same applied to *N*-stereoisomeric pairs with methyl and alkoxy carbonylmethyl derivatives of 3 α - and 3 β -tropanols, 3-tropanone, and tropane while those of 3 α ,6 β -tropanediol show stronger deshielding^{15,16} of equatorial *N*-methyl signal by neighboring oxygen, leading to an opposite pattern. 2 β -Hydroxymethyl and 2 β -hydroxytropanes show a stronger deshielding of axial *N*-methyl by adjacent oxygen atom. The situation becomes more complex when other shielding effects enter the picture. For example, among tropane *N*-acetic acid **16d** and betaine **16e**, and their N isomers, the equatorial methyl signal is in lower field. Furthermore, 2-hydroxyethyl-3 α -acetoxytropanium salt (**5**) when converted into the 2-chloroethyl salt **6**, shows a reversal of the position of *N*-methyl signals. Since 2-chloroethylation gave the same major product no N inversion has taken place. Removal of chlorine in **6** to give **2** by hydrogenolysis again results in a reversal of chemical shifts, proving that chlorine has an exceptional effect.²⁷

A recent X-ray study²⁸ proved that scopolamine *N*-oxide hydrobromide has an axial *N*-methyl group opposite to previous conclusions¹⁵ based on empirical nmr. This shows that amine oxide formation is also equatorial. In the light of these findings our previous interpretation¹⁴ of the steric course of deuteriomethylations seemed confusing. To check this crucial point the *N*₆-methoxycarbonylmethyl tropanium bromide (**3d**)

(27) It seems likely that chlorine of the axial chloroethyl group in **6** is compelled by the 2,4- β -hydrogens to approach and hence deshield the equatorial methyl, thus contributing to the low-field position of *N*-methyl signals. The equatorial chloroethyl group is not compressed so it has no such effect upon the axial N-Me in the N isomer.

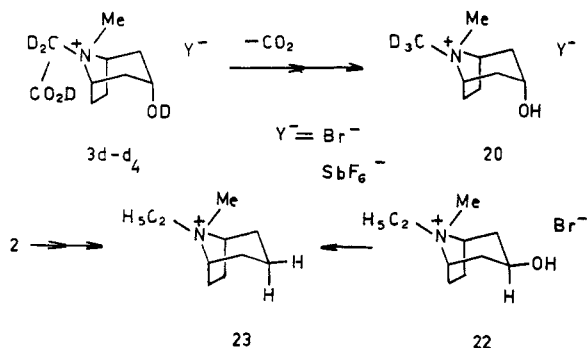
(28) Private communication by Dr. Carol Huber. Details to be published elsewhere.

(now being correlated with compounds **12d** and **2**, of known structure, also with lactone **7f**) was converted into *N_b*-deuteriomethyltropanium salt (**20**), via deuteration of **3a** in the *N*-methylene group, followed by hydrolysis in D₂O and catalytic decarboxylation. The nmr spectrum of this *N_b*-methyl-*d*₃ salt was superimposable on that of the main product of tropine with methyl-*d*₃ bromide (nmr N-Me 3.065:3.04 (90:10)), i.e., in favor of axial N-Me signal, thus proving equatorial course also in deuteriomethylation. Comparison with the spectrum of nondeuterated *N*-methyltropanium hexafluoroantimonate showed $\delta_{\text{N-Me}}$ 3.04:3.02, slightly shifted, that again may have caused confusion when taking nmr data of *N,N*-dimethyl derivatives as references.

An analogous sequence of reaction was carried out with *N*-methoxycarbonylmethyl-3 α ,6 β -dihydroxytropanium bromide (**7a** $\rightarrow$ **7d-d₅**) leading to *N_b*-methyl-*d*₃ derivative **21**, also obtained as the major product in the quaternization of 3 α ,6 β -dihydroxytropane with methyl-*d*₃ bromide, and ion exchange.

Both products have $\delta_{\text{N-Me}}$ 3.01 ppm, coinciding with the high-field N-Me signal of *N,N*-dimethyldihydroxytropanium bromide. So, in this case, the equatorial methyl group is more deshielded as contrasted with quaternary 3 α -tropanols. In conclusion, equatorial deuteriomethylation prevails throughout this series, consistent with other N alkylations.

Recent X-ray crystallographic investigation of pseudotropine ethobromide by Bottini, *et al.*,⁴ proved structure **22** for the same compound. Also, on mild oxidation it gave a ketone obtained from **2** under similar conditions. This correlation was now lent additional support by deoxygenating **2** and **22** via the 3 α - and 3 β -chloro compounds to tropane ethobromide (**23**). Similar correlation by oxidation had



been achieved with epimeric 3-hydroxy *N*-ethoxycarbonylmethyltropanium salts,⁴ thus providing complementary evidence to ours. In view of all these results we feel that a long-lasting dispute has now been brought to an end.

Application of the Curtin-Hammett principle for the transition state in tropane quaternization offers the most likely explanation of our findings. We now know that the angles at C-2 and C-4 in piperidine moiety, e.g., in pseudotropine, correspond to 141°, whereas the angles at C-1 and C-5 in the pyrrolidine ring measure 137° (Figure 2), thereby forming a flattened six-membered ring and angularly deformed five-membered ring in the tropane molecule. Diaxial interaction by 2,4 β -hydrogens is greater, due to this flattened^{7,29,30} six-membered ring for the axial attack

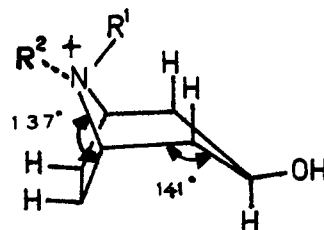


Figure 2. Probable transition state in the quaternization of pseudotropine.

at the nitrogen, than compression by 6,7-hydrogens on the equatorial side. Angular deformation^{7,30} of the five-membered ring helps to diminish this compression; therefore, the transition state described in Figure 2 will have the lowest energy. Moreover, a bulkier group at C-2 results in a decrease of reaction rates, consistent with observed facts.³¹ Furthermore, the group already covalently bound to nitrogen can accommodate more easily to 2,4-diaxial compression than can the incoming group. This also explains the decrease in rates of N methylation of amines having a bulkier group on nitrogen. Piperidines can overcome such effects more easily than tropanes, due to possible swinging over into another conformation.

Experimental Section

All melting points were taken in open capillary tubes, using Electrothermal melting point apparatus, and are uncorrected. The ir spectra were run on a Beckman-IR 4 spectrophotometer as films on NaCl cells or as KBr pellets. The 60-Mcps nmr spectra were recorded on a Varian A-60 spectrometer equipped with a Varian Model V-6058A spin decoupler. The 100-Mcps spectra were obtained on a Varian HA-100 nmr spectrometer operated in the frequency-sweep mode with a normal probe temperature of 30 $\pm$ 1°. Tetramethylsilane (TMS) was used as an internal standard when the samples were run in deuterated organic solvents and when the spectra were recorded in D₂O, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (Tiers' salt) was provided as an internal reference. These served as the field-frequency lock signal on the HA-100 nmr spectrometer. Chemical shifts are expressed either on the δ scale in parts per million or cycles per second and the accuracy of $\pm$ 1 cps was obtained throughout. The following letters were used throughout for the signal splittings due to proton-proton coupling and also for signals separation: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra were recorded on a Varian M-66 spectrometer and a Model AEI MS 902 high-resolution mass spectrometer. Elemental analyses were performed by E. Beetz and Dr. E. Pascher, Germany, Galbraith Laboratories, and R. Dulude, Laval University. Molecular weight determinations were carried out on a Mechrolab Model 301A vapor pressure osmometer. Most spectral and analytical data are reported only in Tables I and II.

Bromoacetyl pseudotropine. (a) Following the method for 4-*tert*-butylpiperidine^{20b} derivatives, to a solution containing *tert*-butyllithium in 116 ml of pentane, 2.95 g (0.0218 mol) of pseudotropine was added in small portions. The mixture was diluted with 50 ml of pentane. Then a solution of 4.04 g (0.02 mol)

(29) Dipole moment and nmr data by R. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton, and F. J. Swinbourne, *J. Chem. Soc. C*, 74 (1966).

(30) X-Ray analysis of pseudotropine, combined with nmr data, by H. Schenk, C. H. MacGillavry, S. Skolnik, and J. Laan, *Acta Crystallogr.*, 23, 423 (1967).

(31) I. Weisz, P. Agocs, M. Halmos, and K. Kovacs, *Acta Chim. (Budapest)*, 56, 195 (1967). NOTE ADDED IN PROOF. A recent paper by I. Weisz, *et al.*, claims [*ibid.*, 64, 257 (1970)] that tropanium salts with bulky groups at both N_a and C-2 are incapable of existence. We now proved the opposite: *internal N*-carboxymethylation of 2 β -hydroxymethyl-3 β -tropanol and of 2 β -tropanol gave the N_a-lactones while *direct* methoxycarbonylmethylation of the same amines is preferentially equatorial at 80° in CH₃CN. Details are to be published elsewhere.

Table I

No.	Tropanium bromide	Mp, °C	Formula	Calcd, %				Anal.		Found, %			
				C	Hr	Br	N	S	C	H	Br	N	S
3a	N _b -Methoxycarbonyl-methyl-3α-hydroxy-	192	C ₁₁ H ₂₀ BrNO ₃	44.91	7.01		4.76		45.95	7.00		4.79	
4	N _b -2-Hydroxyethyl-3α-hydroxy-	302	C ₁₀ H ₂₀ BrNO ₂	45.18	7.66	30.02			45.15	7.66	30.13		
5	N _b -2-Hydroxyethyl-3α-acetoxy-	308	C ₁₀ H ₂₀ INO ₂	38.55	6.58	40.52			38.12	6.21	40.86		
5	N _b -2-Hydroxyethyl-3α-acetoxy-	260	C ₁₂ H ₂₂ BrNO ₃	46.76	7.20		4.55		46.79	7.28		4.55	
6	N _b -2-Chloroethyl-3α-acetoxy-	197	C ₁₂ H ₂₁ BrClNO ₂	44.27	6.48		4.29		43.96	6.50			
7	N _b -Methoxycarbonyl-methyl-3α,6β-dihydroxy-	170–175 Second mp, 264	C ₁₁ H ₂₀ BrNO ₄	42.59	6.44		4.52		44.33	6.66 ^a		4.52 ^a	
									42.04	6.47		4.41	
9a	N _a -Methoxycarbonyl-methyl-3-oxo-	172	C ₁₁ H ₁₈ BrNO ₃	45.20	6.22				42.26	6.25		4.49	
									45.82	6.37			
10c	N _a -Isopropoxy-carbonylmethyl-3β-hydroxy-	190	C ₁₃ H ₂₄ BrNO ₃				4.34					4.17	
12a	N _b -Methoxycarbonyl-methyl-3β-hydroxy-	227	C ₁₁ H ₂₀ BrNO ₃	44.91	7.01		4.76		45.77	7.05		4.68	
13	N _b -Methoxycarbonyl-methyl-3α-chloro-	192	C ₁₁ H ₁₉ BrClNO ₂	42.25	6.14	51.44	4.48		42.44	6.11	50.90	4.53	
14	N _b -Methoxycarbonyl-methyl-3β-chloro-	183	C ₁₁ H ₁₉ BrClNO ₂	42.25	6.14	51.44	4.48		43.25	6.18		4.60	
15d	N _b -Carboxymethyl-3,6-dichloro ^b	232	C ₁₀ H ₁₆ Cl ₂ NO ₂	41.59	5.54		4.85		41.42	5.49		4.82	
16d	N _b -Carboxymethyl-	261	C ₁₀ H ₁₈ BrNO ₂	45.46	6.86	30.25	5.30		45.55 ^c	6.84		5.28	
									45.42 ^d	6.71	30.43	5.18	
									45.34 ^e	6.87		5.23	
17	(Polymeric) lactone of N _b -carboxymethyl-pseudotropinium bromide	240	C ₁₀ H ₁₆ BrNO ₂	45.81	8.15	30.48			40.97	6.05	28.65		
18	N-Carbamylnor-tropinone hydrogen sulfate	156–157	C ₈ H ₁₄ N ₂ O ₆ S	36.60	5.19			11.85	36.11	5.38		12.01	
19	N-Ethoxycarbonyl-methyl-3-oxonor-tropane	Oil	C ₁₁ H ₁₇ NO ₃	62.54	8.06		6.63		63.06	8.11		7.53	
20	N _b -Methyl- <i>d</i> ₃ -3α-hydroxyhexafluoroantimonate	351 dec	C ₉ H ₁₅ D ₃ NOSbF ₆	27.15	4.55		3.52		27.28	4.54		3.44	
21	N _b -Methyl- <i>d</i> ₃ -3α,6β-dihydroxyhexafluoroantimonate	265	C ₉ H ₁₅ D ₃ NO ₂ SbF ₆	26.28	4.38 (H + D)		3.40		26.39	4.42		3.38	
23	N _b -Ethyl-	345 dec	C ₁₀ H ₂₀ BrN	51.28	8.54	34.18	5.94		51.23	8.63	34.00	6.12	

^a Prepared by 2-chloroethylation from 3α-acetoxytropane. ^b Analyzed as chloride. ^c Sample from pseudotropine. ^d From 3α,6β-tropanediol. ^e From tropine.

of bromoacetyl bromide in 50 ml of pentane was added dropwise and with stirring over a 20-min period to the suspension of lithium 3β-tropanoxide. The solution was diluted with pentane to 400 ml and 2 g of solid sodium bicarbonate was added. The reaction mixture was stirred for an additional 10 min, filtered, and the residue was washed with ether. The combined solutions were dried over anhydrous magnesium sulfate and the solvent evaporated at 25° *in vacuo* to give 2.44 g (44.5%) of crude and hygroscopic bromoacetyl pseudotropine; after softening at 80°, it melts at 242° dec, indicating quaternization of the bromoacetylated base: *ir* 1745 cm⁻¹ (C=O); *nmr* δ 2.55 (s, 3, N-Me) (s, 2, BrCH₂CO).

Hydrobromide. Crude ester base in ethanol with 2 *N* ethanolic hydrogen bromide gave the salt: mp 182–183°; *ir* 1740 (C=O), 1278, 1118, 1090, 1035, and 1008 cm⁻¹; *nmr*, D₂O, TSPSA as internal reference, δ 4.07 (s, 2, CH₂Br) and 2.8 (d, 3, N-Me) (separated by 1.8 cps).

(b) Pseudotropine hydrobromide (4.44 g, 0.002 mol) was gently added to 12 g of bromoacetyl bromide to give a clear solution within 15 min. The solution was then stirred at 25° for 4 hr and the excess bromoacetyl bromide was removed *in vacuo* to give a thick oil which was triturated with acetone. The resultant brownish solid was recrystallized from a mixture of ethanol, benzene, and ether to give 6.2 g (74%) of bromoacetyl pseudotropine hydrobromide,¹⁸ mp 182–184°. This product was found to be identical

by comparison with the sample made by the *tert*-butyllithium method.

This reaction proceeds easily at room temperature while refluxing results in the formation of resinous material.

Polymeric "Lactone" from Bromoacetyl pseudotropine. The crude bromoacetyl pseudotropine (1.2 g, 0.0045 mol), obtained by route a, was refluxed in anhydrous ether (200 ml) for 24 hr. A few crystals deposited. Evaporation of the solvent gave a solid^{18,19} which was recrystallized from acetonitrile as a powder (0.64 g, 53%), mp 244° dec (see also entry 17, Table II). Alternately, to the hydrobromide (2.7 g, 0.0788 mol) obtained by b, 20% aqueous potassium bicarbonate (25 ml) was added and extracted with ether and dried (magnesium sulfate). Evaporation gave an oil (1.62 g) which solidified on standing. This was refluxed in acetonitrile (75 ml) for 24 hr and thereafter evaporated. The crude lactone (1.45 g) was purified by recrystallization from absolute ethanol, mp 244°; yield, 1.08 g (52%). Analyses¹⁸ did not give consistent values for the lactone (entry 17, Table I). It was hydrolyzed¹⁸ to the same acid as the products of direct quaternization, 12a and b. Osmometric determination (*c* 0.0109 and 0.0227, respectively) of its apparent molecular weight gave the values 513.1 and 520.5. Mass spectrum on Varian M-66 indicated *m/e* 182, 261, and 263 as expected for the lactone cation and two bromine-containing species. However, a high-resolution mass spectrometer produced many

Table II. Tropanium Bromides^a Ir and Nmr Spectral^b Data

No.	Compound	Ir (KBr), cm ⁻¹	N ⁺ -CH ₃	N ⁺ -CH ₂	OCH ₃	Other H signals
1	N _a -Ethyl-3 α -hydroxy-	3350, 2850	2.975 2.98 ^c	3.42 (q) Decoupled 3.51 (s) ^c		
2	N _b -Ethyl-3 α -hydroxy-	3350, 2850	3.00 3.01 ^c	3.34 (q) Decoupled 3.41 (s) ^c		
3a	N _b -Methoxycarbonylmethyl-3 α -hydroxy-	3400, 2950 2900, 1750	3.28:3.17 (86:14)	4.28	3.83	
3b	N _b -Ethoxycarbonylmethyl-3 α -hydroxy-	3380, 2800 1750 1225	3.27:3.17 (90:10)	4.22		OCH ₂ , 4.29 (q)
4	N _b -2-Hydroxyethyl-3 α -hydroxy iodide	3350	3.12:3.07 (97:3)	3.47		
	Bromide	3360	3.13	3.47		
5	N _b -2-Hydroxyethyl-3 α -acetoxy-	3225, 1745	3.18:3.10 (85:15)			OCH ₂ , 3.69
6	N _b -2-Chloroethyl-3 α -acetoxy-	1255 1740, 1255	3.24 ^c 3.14:3.20 (20:80)	3.63 3.95:4.25		Ac-CH ₃ , 2.13 Cl-CH ₂ , 3.72 (t)
			3.18 ^c 3.13:3.21 (9:91) ^d	3.70 ^c 3.95-4.25 ^d		3.70 ^c 3.73 (t) ^d
7a	N _b -Methoxycarbonylmethyl-3 α ,6 β -dihydroxy-		3.31:3.45 (92:8) ^c	4.63 ^c	3.84 ^c	
8a	N _b -Methoxycarbonylmethyl-3-oxo-		3.59 (major) 3.36 (minor) 3.55 ^c	4.44 (major) 4.78 (minor) 4.39 ^c	3.86 3.83 ^c	
8b	N _b -Ethoxycarbonylmethyl-3-oxo-	3450, 2970 1750	3.54 ^c	4.37 ^c		
9a	N _a -Methoxycarbonylmethyl-3-oxo-		3.36 (major) 3.59 (minor) 3.33 ^c	4.78 (major) 4.44 (minor) 4.75 ^c	3.83	
9b	N _a -Ethoxycarbonylmethyl-3-oxo-		3.34 ^c	4.77 ^c		OCH ₂ , 4.45
10c	N _a -Isopropoxycarbonylmethyl-3 β -hydroxy-	3400, 2800 1730	3.09 ^c	4.74 ^c		OCH(CH ₃) ₂ , 4.33
10b	N _a -Ethoxycarbonylmethyl-3 β -hydroxy Iodide	3200, 2805 1740, 1215	3.09 ^c	4.72 ^c		OCH ₂ , 4.28 ^c
11b	N _a -Ethoxycarbonylmethyl-3 α -hydroxy-	3300, 1750	3.16 ^c	4.36 ^c		OCH ₂ , 4.28 ^c
12a	N _b -Methoxycarbonylmethyl-3 β -hydroxy-	3300, 2940 1755	3.38 3.39 ^c	4.24 4.21 ^c	3.81 3.78 ^c	
12b	N _b -Ethoxycarbonylmethyl-3 β -hydroxy-	3150, 1744 1225	3.40 ^c	4.21 ^c		OCH ₂ , 4.32 ^c
13	N _b -Methoxycarbonylmethyl-3 α -chloro-	2960, 1750	3.29 ^c	4.31 ^c	3.84 ^c	
14	N _b -Methoxycarbonylmethyl-3 β -chloro-	2950, 1760	3.43:3.35 (96:4)	4.26	3.82	
		1740	3.44 ^c	4.27 ^c	3.83 ^c	
15a	N _b -Methoxycarbonylmethyl-3,6-dichloro	1760 (1720) 775	3.35 ^c	4.75 ^c	3.83 ^c	
15d	N _b -Carboxymethyl-3,6-dichloro-	3450, 2976 1740, 1640 820	3.48 ^c	4.84 ^c		H-6, 5.40 ^c H-1, 5, 4.50 ^c
16d	N _b -Carboxymethyl-	3450, 1760 1740	3.34 (major) 3.44 (minor) 3.35 ^c	4.135 (major) 4.19 (minor) 4.14 ^c		H-1,5 4.20-4.28 (minor) 4.38
16e	N _b -Carboxymethyl betaine		3.24 (major) 3.34 (minor) 3.47 ^c	3.70 (major) 3.75 (minor) 4.33 ^c		H-1,5, 4.07-4.25
17	(Polymer) lactone of N-carboxymethyl pseudotropine bromide	1750				
19	N-Ethoxycarbonylmethyl-3-oxonortropine	3450, 1730 1715		2.3		H-1,5, 3.3.66 OCH ₂ , 4.30
20	N _b -Methyl-d ₃ -3 α -hydroxy-(hexafluoroantimonate)	3600, 2990 1475, 1460 1440, 1140, 1055 660, 240	3.065:3.04 (90:10) 3.00 ^c			H-1,5, 3.82(m) H-3 (eq), 4.03 (t)
21	N _b -Methyl-d ₃ -3 α ,6 β -dihydroxy-hexafluoroantimonate	3600, 1460 1080, 1050, 955, 660, 290	3.01 ^c			H-1,5, 3.96 (q) 3.60 (q)
23	N _b -Ethyl-	2960, 1470 1440, 1000, 760	3.08 ^c	3.20 (q) ^c		H-1,5, 3.88 (m)

^a Bromides, unless stated otherwise. ^b Solvent is D₂O at 100-Mcps TSPSA internal lock, δ scale. ^c 60-Mcps nmr. ^d Prepared from 3 α -acetoxytropine with 1-chloro-2-bromoethane. ^e In DMSO-d₆, TMS, as internal reference.

fragments, although in lower abundance, above these values. Evaporation of an aqueous solution of betaine 12e with sodium

bromide gave the sodiocarboxymethyltropinium bromide, a crystal of which was subject to X-ray study.

Correlation of *N*-Ethoxycarbonyltropinium Salts with Tropine Ethobromide. *N_b*-Ethoxycarbonylmethyl-3 α -hydroxytropinium Iodide (**3b-Iodide**). To a solution of 4.38 g (0.031 mol) of tropine in 40 ml of anhydrous ethanol and 40 ml of benzene (**7g**) (0.0328 mol), ethyl iodoacetate was added and the mixture was kept at 25° for 8 hr. The crystals were separated by filtration and washed with 40 ml of benzene to give 7.5 g (69%) of the ester salt, mp 218° (reported^{6c} mp 210°). A second crop, 2.7 g (25%), of crystals, mp 217°, was obtained from the mother liquors after standing at 25° for another 15 hr: total yield 10.2 g (94%); ir 3410 (—OH), 1750 cm⁻¹ (C=O); 60-Mcps nmr, in D₂O, indicated two N-Me signals, 3.28 and 3.16 ppm (9:1). The bromide, mp 204°, was prepared as given for **12b**.

N_b-Hydroxyethyl-3 α -hydroxytropinium Iodide (**4-Iodide**). To a well-stirred solution of 2 g (0.105 mol) of sodium borohydride in 120 ml of anhydrous ethanol there was added 4.2 g (0.0284 mol) of calcium chloride dihydrate in 100 ml of ethanol at -20° to give a white slurry. To this 7.5 g (0.0212 mol) of ester salt **3b** was added in small portions over a period of 30 min and diluted with 200 ml of ethanol. The mixture was gradually warmed up to 2.5° and kept at that temperature for 20 hr with stirring. The solid (NaCl) was separated and the clear filtrate was concentrated to 50-ml volume. A mixture of water-ethanol (2:1) (50 ml) was added at 0° and, after removing most of the ethanol, the mixture was acidified with aqueous hydriodic acid. The solvent was evaporated to dryness and then 200 ml of hot ethanol was added to the brown residue. After filtration, the ethanol solution was then treated with ether to give 6.2 g (94%) of hydroxyethyltropinium salt. This was then recrystallized from ethanol: 6.0 g (90%) of white crystals; mp 308°; ir (KBr) 3360 cm⁻¹. For more details of the nmr spectra, see Table II. Reduction of **4b**-bromide proceeded accordingly.

N_b-2-Hydroxyethyl-3 α -acetoxytropinium Bromide (**5**). 3 α -Acetoxytropine (0.77 g, 0.0036 mol) was dissolved in acetonitrile (5 ml) and 1.3 g (0.01 mol) of 2-bromoethanol was added. After standing at 25° for 16 hr, the solvent and the excess bromoethanol were removed *in vacuo* and the residual solid was triturated with anhydrous ether affording 1.26 g of white crystal powder (92%), mp 260° dec. Recrystallization from acetonitrile-ether (1:1) gave the pure product. For ir and nmr data, see Table II.

Deacetylation. Hydroxyethyl derivative **5** (1 g, 0.0032 mol) was dissolved in 5 ml of 45% aqueous hydrobromic acid and then heated on a steam bath for 48 hr. The mixture was thereafter evaporated on a Rotavapor, and the last traces of water were removed by adding benzene and evaporating again. The residue crystallized upon addition of 5 ml of acetone. A white solid (0.7 g, 82%) was obtained, mp 301–302° dec. Nmr and ir spectra indicated identity with the sample **4** obtained by Ca(BH₄)₂ reduction of the ester **3b**.

N_b-2-Chloroethyl-3 α -acetoxytropinium Bromide (**6**). To a solution of 0.625 g (0.0023 mol) of 2-hydroxyethyl derivative **5** in 8 ml of benzene, 5 ml of thionyl chloride was added and refluxed for 90 min with stirring. After cooling to 30°, excess thionyl chloride and benzene were removed *in vacuo* and the residue was treated with 5 ml of acetone to give 0.645 g (87%) of a white solid, mp 196–197°. For analysis (Table I), it was recrystallized from ethanol. Ir and nmr data are recorded in Table II. Treatment of acetyltropine with 2-chloroethyl bromide in MeCN gave the same product.

N_b-Ethyl-3 α -hydroxytropinium Bromide, Tropine Ethobromide^{6c,7} (**2**). (a) By Hydrogenolysis of Chloroethyl Derivative **6**. A solution of 0.64 g (0.00195 mol) of chloroethyl 3 α -acetoxytropinium bromide (**6**) in 10 ml of water was added to a suspension of 3 g of Raney-Ni in 20 ml of water, containing 0.3 g (0.00217 mol) of potassium carbonate, and was hydrogenated under atmospheric pressure. After 30 min, 45 ml of hydrogen was taken up. The filtered solution was acidified with 20 ml (40%) of hydrobromic acid and refluxed for 2 hr to achieve complete deacetylation. The solution was then adjusted to pH 7 with KHCO₃ and evaporated on a Rotavapor to dryness, and the crystalline mixture was extracted several times with hot acetonitrile. Concentration of acetonitrile afforded 0.45 g (92%) of colorless needles of tropine ethobromide: mp 292°; nmr data were completely identical with those of the product of direct ethylation of tropine with ethyl bromide.²⁴ The most significant nmr signals are in D₂O, 3.00 (s, 3, N-Me) and 3.41 (q, 2, N-CH₂), which coalesces on irradiation 124 cps upfield at 60 Mcps.

(b) To a solution of 0.5 g (0.0035 mol) of 3 α -tropanol (tropine) in 1.5 ml of DMSO, 2 g (0.018 mol) of ethyl bromide was added at 20°. Crystallization of the quaternary salt starts immediately,

and is complete in 1 hr. The crystals were filtered after 9 hr and washed with ether to give 0.83 g (93%) of tropine ethobromide²⁴ (**2**), mp 295°.

N-Ethyltropine Methobromide^{6c,7} (**1**). This salt was described earlier as the major product in the methylation of *N*-ethyl-nortropine with methyl iodide in an alcohol-benzene mixture, followed by conversion over Amberlite IR-4B ion exchange resin to the bromide. Purer product was now obtained by adding 1.5 g (0.0158 mol) of methyl bromide to a solution of 0.3 g (0.0019 mol) of *N*-ethyl-nortropine in 1 ml of DMSO and keeping at 10° in a sealed flask for 8 hr; yield, 0.52 g (94%).^{32a} Recrystallization from acetonitrile gave a product, mp 316°, the powder diagram of which was identical with the specimen previously⁷ submitted to X-ray analysis. Most significant nmr signals were: 2.975 ppm (s) for N-Me; 3.41 (q) for N-CH₂. The latter coalesces when irradiated at 128.5 cps upfield at 60 Mcps. It is therefore not identical with **2**, the product of the correlation with *N*-ethoxycarbonylmethyl 3 α -hydroxytropinium salt (**3b**).

Correlation of *N*-Methoxycarbonylmethyl Derivatives of Tropine, Pseudotropine, Tropinone, and 3 α ,6 β -Tropanediol. *N_b*-Ethoxycarbonylmethyl-3 β -hydroxytropinium Bromide (**12b**). To a solution of 0.1 g (0.007 mol) of pseudotropine in 2 ml of acetonitrile, 0.142 g (0.0085 mol) of ethyl bromoacetate was added at 20° under cooling. The crystals that had precipitated soon were filtered off after 30 min and washed with ether: yield, 0.199 g (94%) of **3b**; mp 207–208°. Ir and nmr data are given in Table II. The iodide had earlier been known; this bromide was recently described.¹⁵ Hydrolysis in the presence of silver oxide followed by acidification with 10% hydrobromic acid and evaporation gave *N*-carboxylic acid, bromide as hydrate **12d**. This was identical with the product of similar hydrolysis of the so-called lactone¹⁷ from *O*-bromoacetyl pseudotropine.

N_a-Ethoxycarbonylmethyl-3 β -hydroxytropinium Iodide (**10b**). The technique of an earlier preparation could be improved in the first step by using dimethylformamide as a solvent. This way equimolar amounts of ethyl bromoacetate (1.67 g, 0.01 mol) and norpseudotropine (1.27 g, 0.01 mol) could be used in 30 ml of DMF at 20°. Evaporation after 45 min gave 2.5 g of *N*-ethoxycarbonylmethyl-norpseudotropine hydrobromide, characterized by spectral data: ir 3400 (OH), 2800 (N⁺H), and 1750 cm⁻¹ (C=O ester); nmr δ chloroform-*d*, 1.2 (t, 3, C-Me), 4.15 (q, 2, OCH₂), 4.35 (s, 2, N-CH₂). The tertiary base was obtained by dissolving 2.5 g (0.0085 mol) of the hydrobromide in 50 ml of saturated K₂CO₃ and extracting immediately five times with a total of 25 ml of chloroform; evaporation afforded 1.62 g (90%) of a semicrystalline base: ir 3400 (OH), 1750 (C=O), 1200 cm⁻¹ (C-O stretch); nmr δ chloroform-*d*, 1.2 (t, 3, C-Me), 4.15 (q, 2, OCH₂).

Quaternization of 1.62 g (0.076 mol) of base with 1.3 g (0.011 mol) of methyl iodide in 10 ml of acetonitrile led to the precipitation of 2.43 g (90%) of *N_a*-ethoxycarbonylmethyl-3 β -hydroxytropinium iodide (**10b**), mp 196°. The corresponding bromide is described by Bottini, *et al.*,^{4,32b}

N_b-Ethoxycarbonylmethyl-3 α -hydroxytropinium Bromide (**3b**). To a solution of 0.1 g of tropine (0.077 mol) in 2 ml of acetonitrile, 0.142 g (0.0085 mol) of ethyl bromoacetate was added and kept for 30 min at 20° and then filtered and washed with ether: yield, 0.1911 g (83%); mp 204°. The 100-Mcps nmr spectrum indicated a 90:10 ratio of the isomers, based on integration of δ_{N-Me} 3.26 and 3.16 ppm.

N_b-Ethoxycarbonylmethyl-3-oxotropinium Bromide (**8b**). Quaternization of 12 g (0.0862 mol) of tropanone with 18 g (0.108 mol) of ethyl bromoacetate in 30 ml of acetonitrile at 20° for 1 hr, gave 24 g (91.5%) of the salt: mp 178°; ir 1750 and 1730 (CO ester and ketone); nmr, 60 Mcps, DMSO-*d*₆, 3.54 (s, 3, N-Me), 4.34 (s, 2, N⁺-CH₂). Bottini, *et al.*, report^{4,32b} δ 3.57 (s) for N-Me and 4.38 (s) for N⁺-CH₂, in D₂O.

N-Methoxycarbonylmethyl-3-oxotropinium Bromide (**8a**). This was obtained by the same technique, using methyl bromoacetate as an alkylating agent, mp 178°.

N_a-Ethoxycarbonylmethyl-3-oxotropinium Bromide (**9b**). This compound was prepared from tropinone *via* nortropinone and *N*-ethoxycarbonylmethyl-3-oxonortropine in the following manner.

Nortropinone. This compound had been made by Willstätter^{33a}

(32) (a) Comparable yields have been obtained in acetonitrile as a solvent. (b) A. T. Bottini, *et al.*, private communication.

(33) (a) R. Willstätter, *Ber.*, **29**, 1575 (1896); (b) H. C. Beyerman, P. H. Enthoven, and P. E. Verkade, *Recl. Trav. Chim. Pays-Bas*, **82**, 1199 (1963).

by oxidizing tropinone with potassium permanganate, and recently by Beyerman, *et al.*,^{33b} by the Robinson condensation of succinic aldehyde with ammonia and acetone dicarboxylic acid; however, the yields were far from satisfactory. Therefore, we have hydrolyzed *N*-cyanonortropinone, obtained according to Nickon and Fieser³⁴ in two steps.³⁵

***N*-Carbamylnortropinone Hydrogen Sulfate (18).** To a solution of 7.4 g (0.049 mol) of *N*-cyanonortropinone in 80 ml of glacial acetic acid, 7 ml of 90% sulfuric acid was added under cooling with ice to +5°. The salt of the urea started to crystallize after 3 min, then 125 ml of anhydrous ether was added, and the white precipitate was filtered off to afford 12.8 g (99%) of the hydrogen sulfate: mp 156–157°; ir 3380 and 3200 (NH₂), 2500 (N⁺H), 1735 (C=O), 1690 (CON), 1535 cm⁻¹ (NH deformation). The base 18 was obtained by dissolving 1.8 g of the salt in 50 ml of 20% K₂CO₃ solution and extracting four times with a total of 30 ml of chloroform. Evaporation of the combined extracts afforded, upon trituration with ether, 1.05 g (92%) of crystals of the urea: mp 189–190°; ir 3400, 3200 (NH₂), 1715 (CO), 1660, and 1610 cm⁻¹ (CONH₂).

Conversion of the urea into nortropinone was carried out (a) by adding to a solution of 2.66 g (0.01 mol) of hydrogen sulfate 18 in 42 ml of water dropwise the solution of 0.69 g (0.01 mol) of sodium nitrite at 25° under vigorous stirring. Stirring was continued until no more CO₂ had evolved (baryta). The acidic solution (pH 2) was evaporated again. Extraction with hot ethanol followed by evaporation gave nortropinone hydrogen sulfate as white crystals (1.3 g, 85%); mp 178°. The ir showed a large band for sulfate at 1100–1260, carbonyl at 1735, NH₂⁺ and NH₂ at 2500, 2300, and 3150 cm⁻¹.

(b) **Hydrolysis of the Urea.** A solution of 2 g (0.075 mol) of urea hydrogen sulfate 18 in 25 ml of 2 *N* HCl was refluxed for 6 hr, until CO₂ ceased to evolve. The reaction mixture was then adjusted with 10% KOH to pH 4 and evaporated *in vacuo* to 80-ml volume. Subsequently 50% KOH was added to adjust to pH 11 and extracted five times with a total of 50 ml of chloroform. After drying (MgSO₄) and evaporation, 0.764 g (81%) of crude nortropinone was obtained. Distillation under 0.1-mm pressure from a bath of 150° gave nortropinone as white hygroscopic crystals, mp 60°. Willstätter^{33a} reported mp 69–70°; Beyerman^{33b} characterized the compound merely as a derivative: ir 3350 (enol OH), 3300 (NH), 1720 (CO), 1340 (C–H stretch); nmr, chloroform-*d*, δ 3.92 (m, 2, H-1,5), 2.47 (m, 4, H-2,4), 2.17 (s, 1, NH).

The bispiperonylidene derivative has also been prepared, mp 221°.

***N*-Ethoxycarbonylmethyl-3-oxonortropane (19) hydrobromide** was prepared by the technique described for alkylation of norpseudotropine. Here 0.210 g (0.0017 mol) of nortropinone and 0.15 ml of ethyl bromoacetate in 0.5 ml of DMF gave 0.305 g (70%) of the hydrobromide of 19: mp 145°; ir 2500–2800 (N⁺H), 1730 and 1710 (CO); nmr, chloroform-*d*, δ 4.35 (q, 2, O–CH₂), 4.15 (s, 2, N⁺–CH₂), 3.75 ppm (m, 2, H-1, 5). The base (1.1 g, 90%) was obtained by basification of 1.6 g of salt (0.0055 mol) with 50% K₂CO₃, extraction with chloroform, and evaporation.

All its analytical and spectroscopic data are comprised in Tables I and II. The same technique was used for preparing *N*-methoxycarbonylmethylnortropinone.

Quaternization of *N*-Ethoxycarbonylmethyl-3-oxonortropane to 9b. To a solution of 0.284 g (0.00135 mol) of base in 4 ml of acetonitrile, 1 ml of methyl bromide was added at 10° and the flask kept sealed overnight in a refrigerator. The crystals of *N*-ethoxycarbonylmethyl-3-oxotropanium bromide (9b), 0.35 g (82%), mp 150–151°, were filtered and dried. Analytical and spectroscopic data are shown in Tables I and II.

***N*-Methoxycarbonylmethyl-3-oxotropanium Bromide (9a)** was prepared, mp 172°, by an analogous procedure, from nortropinone via *N*-methoxycarbonylmethylnortropinone and subsequent methylation with methyl bromide; see Tables I and II.

Catalytic Hydrogenation of *N*-Ethoxycarbonylmethyl-3-oxotropanium Bromide (8b). A solution of 3.06 g (0.01 mol) of the quaternary tropinonium salt 8b in 25 ml of water was added to a suspension of 3 g of Raney-Ni in 10 ml of water, saturated with hydrogen. After shaking for 5 hr, 260 ml of hydrogen was taken up (1.1 mol). After filtering from the catalyst, the solvent was removed to give a solid that was recrystallized from ethanol–ether

(1:1): yield, 2.8 g (90%); mp 205–206°. Its ir and nmr data corresponded with those of the product 3b of direct quaternization of 3α-tropanol; N–Me 3.27 (s), N⁺–CH₂ 4.24 (s), in DMSO-*d*₆. Catalytic hydrogenation of 8b in water over Adams Pt catalyst led to the same product in 98% yield.

Catalytic Hydrogenation of *N*-Ethoxycarbonylmethyl-3-oxotropanium Bromide (9b). Using exactly the same technique as mentioned above, 0.5 g (0.0016 mol) of “reverse” quaternized tropinone when hydrogenated in 45 ml of water over 1 g of Raney-Ni afforded 0.45 g (90%) of crystals, mp 196°. Ir and nmr data were identical with those of the major product of “reverse” quaternization of nortropine, *i.e.*, addition of methyl bromide onto *N*-ethoxycarbonylmethylnortropine. These operations were carried out essentially as described for norpseudotropine and nortropinone. Thus, from 0.306 g (0.00237 mol) of nortropine and 0.45 g (0.0029 mol) of ethyl bromoacetate in 10 ml of DMF, 0.623 g (88%) of *N*-ethoxycarbonylmethyl-3α-hydroxynortropane hydrobromide were obtained: ir 3400 (OH), 2800 (N⁺H), 1740 cm⁻¹ (C=O); nmr, chloroform-*d*, δ 4.35 (s, 2, N⁺–CH₂), 4.09 (q, 2, OCH₂). Basification thereof with K₂CO₃ gave 0.507 g (89%) of base which has no absorption at 2800 cm⁻¹. Quaternization of 0.507 g (0.0019 mol) in 10 ml of acetonitrile with 1 ml of acetonitrile with 1 ml of methyl bromide gave the *N*-ethoxycarbonylmethyl-3α-hydroxytropanium bromide (11b), mp 214° (see Table II).

Meerwein–Ponndorff Reduction of the Quaternary Salts of Tropinone (8b and 9b). (a) A solution of 3.06 g (0.01 mol) of *N*-ethoxycarbonylmethyl-3-oxotropanium bromide and 4.84 g (0.02 mol) of aluminum *tert*-butoxide in 100 ml of isopropyl alcohol was refluxed for 60 hr. The mixture was filtered and then evaporated on a Rotavapor to give 1.9 g (62%) of a white solid; recrystallized from ethanol, mp 196°. The ir spectrum indicated an ester (1735, 1235 cm⁻¹). Nmr showed a doublet at δ 1.28 for C-methyl and integrated for six protons. Elemental analysis also proved transesterification to an isopropyl ester, 10c. The position of δ_{N–Me} 3.09 and also the lack of C-3 equatorial proton were consistent with that of a quaternary pseudotropinium salt. The most important signals were much closer to those of a reverse product 10b, δ_{N–Me} 3.11, than to δ_{N–Me} 3.40 of the ester from “direct” quaternization 12b. As a further check, the isopropyl ester (1.9 g) was refluxed for 17 hr with 50 ml of ethanol, presaturated with HBr. After having evaporated the solvent, a mixture of the isopropyl and ethyl ester resulted, based on nmr analysis. Therefore, further refluxing with 200 ml of ethanolic HBr was undertaken and then the excess acid was neutralized with KHCO₃, the solvent was evaporated, and the ester salt was recrystallized from ethanol. This product showed mp 166°, a triplet at δ 1.31 for C–Me, and a singlet at 3.09 for N–Me, identical with the product of “reverse” quaternization of norpseudotropine.

(b) Meerwein reduction of 0.5 g (0.0015 mol) of *N*-ethoxycarbonylmethyl-3-oxonortropane methobromide (9a) in 100 ml of isopropyl alcohol in the presence of 0.73 g of aluminum *tert*-butoxide (0.003 mol) and working up as under (a) gave 0.4 g of isopropyl ester, mp 190–194°, with ir and nmr data δ_{N–Me} 3.09, δ_{C–Me} 1.33 (d, 6), identical with those reported previously.

Isomerizations of Pseudotropine and Tropinone *N*-Acetic Acid Esters under Meerwein Conditions. (a) A solution of 1.5 g (0.0042 mol) of *N*-ethoxycarbonylmethyl-3β-hydroxytropanium bromide (12b) and 3 g (0.012 mol) of aluminum *tert*-butoxide in 60 ml of isopropyl alcohol was refluxed for 112 hr. Samples were withdrawn after 16 and 25 hr and analyzed by nmr by integrating both the areas beneath N–Me signals 3.40 and 3.09. After 16 hr, the ratio 9:1 of “direct” to “reverse” N–Me signal positions was found; after 25 hr, that changed to 8:2 and the transesterification to isopropyl ester completed.

(b) To a warm solution of 0.5 g (0.0014 mol) of *N*-ethoxycarbonylmethyl-3-oxotropanium bromide (8b) (δ_{N–Me} 3.54) in 60 ml of absolute dry *tert*-butyl alcohol, 1 g (0.004 mol) of aluminum *tert*-butoxide was added and the suspension stirred at room temperature for 72 hr. After filtration, the solution was evaporated to dryness. Aluminum *tert*-butoxide was extracted with hot benzene and the solid residue taken up in dry ethanol, filtered, evaporated again, dissolved in DMSO-*d*₆, and the nmr spectrum taken. The ratio of areas under signals δ 3.54 and 3.34 was 60:40. Roughly similar, a 3:1 ratio could be reached when starting with a product of “reverse” quaternization 9b, δ_{N–Me} 3.34. Similar equilibration has been found by Bottini, *et al.*,^{32b} in D₂O, on the action of pyridine.

Configurational Correlation of *N*-Methoxycarbonylmethyl Derivatives of Different Tropenes. In order to follow each step of interconversion by nmr, methyl esters, instead of ethyl esters, have

(34) A. Nickon and L. Fieser, *J. Amer. Chem. Soc.*, **74**, 5566 (1952).

(35) For hydrolysis of cyanamides via *O*-methyl isoureas, see A. Donetti, A. Omodei Sale, and A. Mantegani, *Tetrahedron Lett.*, 3327 (1969).

Table III

<i>N</i> -Methoxycarbonylmethyltropanium bromide	g	Mol	Water, ml	Ni, g	K ₂ CO ₃ , g	H ₂ uptake, mmol	Carboxytropanium bromide, g (%)
3 β -Chloro, 14	4.0	0.013	50	6	1.0	1.1	2.6 (80)
3 α -Chloro, 13	1.0	0.032	30, MeOH	5	0.550 ^a	1.2	0.736 (82)
3 β ,6 β -Dichloro, 15	1.0	0.0032	50	5	0.5	2.1	0.65 (82)

^a Ba(OH)₂·8H₂O.

been chosen, for the methoxyl signal as singlet does not interfere with others, as do methylene protons of ethyl groups.

***N*-Methoxycarbonylmethyl-3 α -hydroxytropanium Bromide (3a).** Quaternization of 7.05 g (0.05 mol) of tropine, mp 62–64°, with 10 g (0.065 mol) of methyl bromoacetate in 30 ml of acetonitrile at 22° for 4 hr gave 13.53 g (93%) of salt, mp 192°, and a second crop, 0.62 g, mp 188–192°; total yield 97%. For analytical and spectroscopic data, see Tables I and II. No N-Me signal of the minor product could be detected by 100-Mcps nmr in the first crop.

***N*-Methoxycarbonylmethyl-3 β -hydroxytropanium Bromide (12a).** Quaternization of 1.41 g (0.01 mol) of pseudotropine with 2 g (0.013 mol) of methyl bromoacetate in 25 ml of acetonitrile at 22° afforded 2.9 g (98.5%) of the tropanium salt, mp 223° dec, with fitting analytical and spectroscopic data. Recrystallization from acetonitrile gave a product with only one N-Me signal, at 3.38 (100 Mcps), 3.39 (60 Mcps) ppm.

***N*-Methoxycarbonylmethyl-3 α ,6 β -dihydroxytropanium Bromide (7a).** Acetonitrile (100 ml) was used as a solvent, as before, in quaternizing 1.3 g (0.0083 mol) of 3 α ,6 β -tropanediol with 1.53 g (0.01 mol) of methyl bromoacetate; 15 hr, 22°. Evaporation *in vacuo* of the solvent and excess methyl bromoacetate at 40° gave 3 g (97%) of a crystalline residue that was recrystallized from acetonitrile-ether; mp 165°, after resolidification, second mp 263–265° of the lactone bromide **7f**. A very small amount of the "reverse" N stereoisomer with δ_{N-Me} 3.45 was found beside the major product, showing δ 3.31 (D₂O), in the first crop. However, product analysis by nmr of quaternization of 3 α ,6 β -tropanediol in DMSO had indicated a 92:8 ratio of N_b- and N_a-ethoxycarbonylmethyl derivatives.

Conversion of the Hydroxytropanium Salts 3a, 11a, and 7a into Chlorotropanium Salts 13, 14, and 15. Replacement of hydroxyl by chlorine has been (i) attempted by thionyl chloride alone, or (ii) catalyzed by DMF at various temperatures. Finally, the second combination in acetonitrile and at room temperature gave best results. Phosphorous pentachloride in POCl₃ as a solvent led to a less pure product. As an example, 4 g (0.0137 mol) of tropine derivative **3a** was dissolved in 20 ml of acetonitrile, then 15 ml of carefully purified SOCl₂ and 0.4 ml of DMF were added and allowed to stand for 24 hr at 20°. Evaporation of excess reactant and solvent followed by two more evaporations with methanol gave a solid. Recrystallization from acetonitrile gave 3.40 g (81%) of 3 β -chloro-*N*-methoxycarbonylmethyltropanium bromide (**14**), mp 183°, that showed correct analytical figures. Pseudotropine derivative **12a** (2.55 g, 0.00875 mol) was converted into 3 α -chloro-*N*-methoxycarbonylmethyltropanium bromide on heating to 80° with 10 ml of thionyl chloride and 1 ml of DMF for 20 hr, followed by recrystallization from acetonitrile; yield, 1.5 g, mp 189°. Nmr (100 Mcps) indicated a 96:4 ratio of two N stereoisomers. Details are in Table II. Treatment of 1.5 g (0.005 mol) of tropanediol derivative **7a**, in 20 ml of acetonitrile with 20 ml of thionyl chloride and 0.4 ml of DMF at 20°, afforded after 24 hr **15a** as a foam-like residue. Dissolution in 15 ml of water, extraction with 200 ml of ether, and evaporation gave a colorless material with appropriate spectral data. Apparently, some ion exchange took place but the product was adequate for hydrogenation. For microanalysis this product was, however, redissolved in 20 ml of water and treated with Permutite ion exchange resin (bromide form). Evaporation *in vacuo* then afforded a crystalline material, mp 232°. Based on ir and nmr data, this is *N*-carboxymethyl-3 β ,6 β -dichlorotropanium bromide (**15d**) further corroborated by analytical figures. Configurations of the chlorine(s) are tentatively given.

Hydrogenolysis of Chlorotropanium Salts 13, 14, and 15. As a general technique, reductive dehalogenation has been carried out in aqueous solution, over Raney-Ni W2 catalyst at atmospheric pressure in the presence of baryta or potassium carbonate. Filtering off the catalyst followed by acidification with aqueous 2 *N* hydrobromic acid to pH 7, evaporation *in vacuo* at 25°, and ex-

traction with acetonitrile yielded *N*-carboxymethyltropanium bromide (**16d**), mp 260° dec in all three cases. Identification was done by nmr and ir. Treatment of the carboxymethylammonium salt with wet silver oxide and filtration then gave *N*-carboxymethyltropanium betaine (**16e**) (Table III). The products had been carefully analyzed and spectroscopically compared with each other and with an ammonium salt prepared from 1.8 g (0.0145 mol) of tropane and 4 g (0.026 mol) of methyl bromoacetate in 10 ml of acetonitrile at 20° for 3 hr; after having evaporated the solvent on a Rotavapor, the residue was dissolved in 20 ml of water, 3 g of silver oxide was added, it was shaken for 30 min, filtered, acidified with aqueous HBr, and water was removed at 1 mm to give the crystalline *N*-carboxymethyltropanium bromide (**16d**). Evaporation without acidification gave the betaine **16e**. The carboxymethyl derivative from tropanediol gave at 60 Mcps 3.34 (s) for N-Me in D₂O and 4.13 (s) for N⁺-CH₂; that from tropine had 3.35 (s) and 4.15 (s). Comparison of the betaine at 100 Mcps showed: from tropine, 3.24 (s, 3, N-Me), 3.70 (s, 2, N⁺-CH₂); from pseudotropine, 3.24 (75%) and 3.34 (25%) (s, 3, N-Me); 3.70 (major), 3.75 (minor) (s, 2, N⁺-CH₂); from tropane, 3.34 (s) and 3.70 (s) (98%). In acetone-*d*₆, the latter betaine shows δ 3.26 (s) and 3.75 (s) for N-Me and N-CH₂. In consequence there is no doubt about the identity of major products of direct quaternization with methyl bromoacetate obtained from different tropane alkalines.

***N*-Methoxycarbonylmethyl-3 α -hydroxy-*d*-tropanium Bromide.** (a) To a solution of 1.9 g (0.0034 mol) of *N*-methoxycarbonylmethyl-3 α -hydroxytropanium bromide in 30 ml of methanol-*d*, 5 mg of sodium methoxide was added and stirred at room temperature for 36 hr. It was then neutralized by DBr and the solvent evaporated *in vacuo*. The ester showed mp 190° and an ir band at 2530 cm⁻¹ for CD₂, while in the nmr there was but little indication at δ 3.39 ppm, characteristic of N⁺-CH₂ in **3a**. (b) The same compound was obtained from tropine and methyl bromoacetate-*d*₂, that had been prepared according to Schwenk and Papa,³⁶ from acetic acid-*d*₄, via the acid chloride.

***N*-Carboxymethyl-*d*₃-3 α -hydroxy-*d*-tropanium Bromide (3d-*d*₁).** The ester **3a-d**₂ was hydrolyzed by 1 g of silver oxide suspended in 2 ml of D₂O at 20°, with stirring for 30 min, and then the solution was acidified with DBr and evaporated on a Rotavapor at 25° to dryness. The acid showed: mp 244° dec; ir 2520 cm⁻¹ (C-D); no CH₂ signal around 4.18 ppm, and no hydroxyl or carbonyl protons that would be exchangeable by D₂O. The betaine has mp 280° dec, close to that of the nondeuterated species,³⁶ mp 284°.

Decarboxylation. To a warm solution of 0.5 g (0.00175 mol) of the acid-*d*₁ in 30 ml of quinoline, 0.3 g of cupric bromide was added and the mixture was refluxed in a nitrogen atmosphere for 90 min. Carbon dioxide was trapped by baryta whereby 0.340 g (96%) of barium carbonate was obtained. After cooling to 20°, the reaction mixture was extracted twice with a total of 100 ml of water, the aqueous solution of the tropanium salt was washed several times with ether to remove quinoline and some colored by-products, and then it was evaporated to dryness at 0.1-mm pressure. The viscous residue containing tropine methobromide-*d*₃ could not easily be crystallized; therefore it became converted into the hexafluoroantimonate. Dissolved in 25 ml of nitromethane, a solution of 0.8 g of silver hexafluoroantimonate in 10 ml of nitromethane was added and the whole was stirred at 25° for 30 min. Removal of AgBr by filtration followed by evaporation at 30° *in vacuo* and two subsequent evaporations with acetonitrile afforded a crystalline material. This was recrystallized from hot chloroform (30 ml) to deposit 0.59 g of *N*-methyl-*d*₃-3 α -hydroxytropanium hexafluoroantimonate (**20**), mp 351° dec. An authentic specimen was prepared on direct methylation with methyl bromide-*d*₃ from tropine and ion exchange by AgSbF₆ in order to have an identical cation and anion for spec-

(36) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 362 (1948).

tral comparison. Both ir and 100-Mcps nmr spectra were superimposable; for details see the tables.

A control experiment was carried out to see whether heating could or could not have caused N inversion of the methobromide-*d*₃. No change of the positions of methyl and H-1,5 signals could be observed under these conditions.

*N*₅-Methoxycarbonylmethyl-*d*₂-3 α ,6 β -dihydroxy-*d*₂-tropanium bromide (7a-*d*₄) was prepared in a completely analogous manner from 7a as the tropine derivative. Hydrolysis to the betaine 7e-*d*₄ by silver oxide in D₂O proceeded normally. However, evaporation of the carboxylic acid bromide 7a-*d*₃ had to be carried out with freeze drying in order to avoid spontaneous lactonization. This way the yield was quantitative. Decarboxylation of 0.5 g (0.0015 mol) of acid 7d-*d*₃ was carried out in 35 ml of quinoline, by refluxing under N₂ with 0.4 g of cupric bromide for 2.5 hr. 84% of the calculated amount of CO₂ was trapped as BaCO₃ and the mixture worked up as given for the tropine derivative. Precipitation with 0.52 g of AgSbF₆ in 10 ml of nitromethane afforded 0.462 g of *N*₅-methyl-*d*₃-3 α ,6 β -dihydroxytropanium hexafluoroantimonate (69% over-all yield), mp 263–265°.

The axial N-Me signal is at 3.01 ppm at 60 Mcps (in acetonitrile-*d*₃) of this authentic specimen; its position is same as that of the major product of deuteriomethylating 3 α ,6 β -tropanediol. For more spectral and analytical data see the tables. Control experiments have shown no change in N-Me chemical shift when 21 (bromide) was heated in quinoline under the same conditions under which decarboxylation of 7d-*d*₃ (bromide) had previously been carried out.

Thus it was definitely proven that deuteriomethylation of tropine and of 3 α ,6 β -tropanediol has taken the same steric course as other N alkylations.

Conversion of Tropine Ethobromide 2 and of Pseudotropine Ethobromide 22 into Tropane Ethobromide 23. (a) Following procedures used for conversion of 3a, 7a, and 12a into 16d, 1.45 g (0.0058 mol) of tropine ethobromide in 10 ml of benzene with 5 ml of thionyl chloride and 0.12 ml of DMF gave 0.927 g of 3 β -chlorotropane ethobromide, mp 210°. Hydrogenolysis of 0.537 g (0.002 mol) of the same specimen in 15 ml of water over 2 g of Raney-Ni and 0.414 g (0.002 mol + 10% excess) of potassium carbonate led to 0.735 g of tropane ethobromide, mp 350° dec; for analysis and spectral data see the tables.

(b) Pseudotropine ethobromide (22), 2.3 g (0.0094 mol), 9 ml of SOCl₂, and 0.4 ml of DMF as catalyst gave by refluxing, 5 hr, 0.529 g of 3 α -chlorotropane ethobromide, mp 182°, that by hydrogenolysis led to 240 mg of tropane ethobromide (23), mp 346° dec; ir and nmr spectra were superimposable with those obtained from 3 α -tropanol ethobromide. Tentative configurations at C-3 had been ascribed to the chloro derivatives based upon relative chemical shifts^{29,30} of H-3 (3.43 ppm for α and 4.30 for β).

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Vinyl Ether Hydrolysis. III. Some Brønsted Relations and Transition State Structure¹

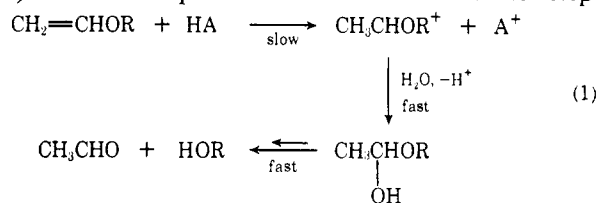
A. J. Kresge,* H. L. Chen, Y. Chiang, E. Murrill,^{2a} M. A. Payne,^{2b} and D. S. Sagatys

Contribution from the Department of Chemistry,
Illinois Institute of Technology, Chicago, Illinois 60616. Received June 18, 1970

Abstract: Brønsted relations for the acid-catalyzed hydrolysis of seven vinyl ethers are constructed using a homogeneous set of carboxylic acid catalytic coefficients. Small but real systematic deviations from these relationships by electronegatively substituted carboxylic acids are detected, and these are attributed to intermolecular interactions between catalyst and substrate in the transition state. The presence of these interactions implies that the exponents of these Brønsted relations overestimate the extent of proton transfer at the transition state of these reactions by at least 0.1; this conclusion is consistent with the result of isotope effect studies. Additional evidence for intermolecular effects in proton transfer reactions is adduced from other deviations from Brønsted relations, and it is suggested that some of the large negative deviation usually found for the hydronium ion in rate-determining proton transfer to a substrate is the result of such effects.

Proton transfer from catalyst to substrate is an essential component of all acid-catalyzed reactions. In most cases, however, this elementary reaction step takes place in a rapidly established equilibrium preceding the rate-determining step; this makes it inaccessible to direct kinetic investigation by ordinary methods. In the acid-catalyzed hydrolysis of simple vinyl ethers, on the other hand, proton transfer from catalyst to substrate is itself rate-determining

(eq 1).^{1b,3-8} Since proton transfer is also the first step



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