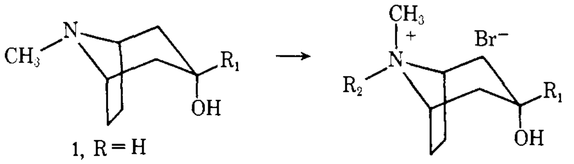
Stereochemistry of Quaternization of Tropidines

Sir:

Fodor and his coworkers have recently demonstrated that the preferred steric course for the quaternization of tropane derivatives is that in which the entering group approaches from the equatorial direction.[1] For example, ethylation of tropine (**1**) produces mostly tropine ethobromide (**2**), the structure of which has been unambiguously demonstrated.[1,2] It was suggested that the interaction of the incoming alkylating agent with the two axial hydrogens of the tropane ring raises the energy of the transition state for axial quaternization. An alternate interpretation is that the energy required to compress the group already on the nitrogen against the proximate hydrogens on the 2-carbon bridge is greater than that required to fix that same group in the axial position. In the first hypothesis, the incoming group is the determining factor, while in the second it is the group already on the nitrogen that determines the course of the reaction.

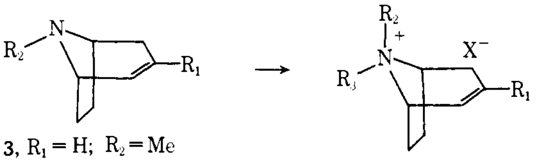


1, R = H
5, R = Ph

2, $R_1 = H$, $R_2 = Et$
6, $R_1 = Ph$, $R_2 = PhCH_2$

We report here a study of the stereochemistry of quaternization of four tropidine derivatives. In the tropidine series, the pathway for the axial approach of the alkylating agent might be less hindered by axial hydrogens, whereas the equatorial pathway should suffer essentially the same interactions as in the tropanes. If interaction of the incoming group is the determining factor, we would expect to observe more axial quaternization in the tropidines than in the tropanes.

Tropidine (**3**),[3] on treatment with benzyl bromide in ether solution, gave a quantitative yield of a salt mixture. The major *N*-methyl signal (92%) was observed in the nmr spectrum of the reaction product at 3.304,[4] while the *N*-methyl signal of the minor component (8%) appeared at 3.209. The major peak for the benzyl methylene protons appeared as a singlet at 5.107, but the minor benzyl signal was not clearly observable.



3, $R_1 = H$; $R_2 = Me$
4, $R_1 = Ph$; $R_2 = Me$
9, $R_1 = H$; $R_2 = PhCH_2$
10, $R_1 = Ph$; $R_2 = PhCH_2$

7, $R_1 = H$; $R_2 = Me$; $R_3 = PhCH_2$; X = Br
8, $R_1 = Ph$; $R_2 = Me$; $R_3 = PhCH_2$; X = Br
11, $R_1 = H$; $R_2 = PhCH_2$; $R_3 = Me$; X = I
12, $R_1 = Ph$; $R_2 = PhCH_2$; $R_3 = Me$; X = I

Similarly, 3-phenyltropidine (**4**),[5] on treatment with benzyl bromide in dry ether, rapidly gave a white solid with the major (91%) methyl signal at 3.342 and the minor (9%) one at 3.265. Only one benzyl methylene singlet was observed at 5.169.

In order to assign the structure of these salts, 3-phenyltropine (**5**)[6] in ether was treated with benzyl bromide and the salt which formed was dehydrated with 48% HBr. After recrystallization from acetonitrile a salt was obtained, mp 242–243°,[7] which was identical in every respect with the major product from the direct benzylation of 3-phenyltropidine after recrystallization from acetonitrile. Since 3-phenyltropine should quaternize principally by equatorial attack of reagent to give **6**,[1] and since benzyl salts of tropanes are resistant to equilibration,[8] we can describe the major product of the benzylation of 3-phenyltropidine as N_b-benzyl-3-phenyl-2-tropidinium bromide (**8**). By analogy, N_b-benzyl-2-tropidinium bromide (**7**) is assigned as the structure of the major product from the benzylation of tropidine.

To confirm the assignments, we synthesized the iodide salts of opposite configuration, N_a-benzyl-2-tropidinium iodide (**11**) and N_a-benzyl-3-phenyl-2-tropidinium iodide (**12**). Both tropidine and 3-phenyltropidine were demethylated with ethyl chloroformate followed by hydrolysis to the nor compounds.[9] Benzoylation of these with benzoyl chloride in benzene for 3 days, followed by lengthy (5 days) reduction with excess $LiAlH_4$, gave *N*-benzylnortropidine (**9**) and *N*-benzyl-3-phenylnortropidine (**10**), respectively. Treatment of **9** in ether with methyl iodide resulted, after 8 hr, in formation of a pale yellow methiodide mixture. The nmr spectrum showed a major methyl singlet (84%) at 3.188 and a minor one (16%) at 3.296. The major absorption of the benzyl methylene appeared as an AB quartet (5.354, 5.230, 4.922, 4.797) which explains why it was not observed previously as the minor component in the mixture. The minor component in this mixture appeared as a singlet at 5.014. The nmr spectrum of the methiodide of **10** showed a methyl singlet at 3.252 and an AB quartet (5.489, 5.359, 4.881, 4.757) for the benzyl methylene protons. It was not possible to observe signals for the minor components.

That these iodides have the structures **11** and **12** as a result of equatorial methylation is corroborated by the nonequivalence of the benzyl protons in the nmr spectra. Theoretically, the benzyl methylene protons in **7** and in **8** should also be nonequivalent. Because of the distance of the double bond from the equatorial benzyl methylene hydrogens, however, the nonequivalence is not apparent. The nonequivalence of these protons in **11** and **12** then is a direct result of their proximity to the chiral portion of the molecule, *i.e.*, the double bond, and demonstrates their axial orientation.

To rule out any unusual influence of the anions involved, spectra of mixtures of **7** and **11** as well as **8** and **12** were obtained. They showed no effects of mixing

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[1] G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gordon, *J. Amer. Chem. Soc.*, **93**, 403 (1971).

[2] P. Benci, C. H. Stam, and C. H. MacGillavry, *Tetrahedron Lett.*, 243 (1971).

[3] W. L. Archer, C. J. Cavalitto, and A. P. Gray, *J. Amer. Chem. Soc.*, **78**, 1227 (1956).

[4] All nmr spectra were determined at 100 MHz in $CDCl_3$, and data are reported in parts per million from TMS. The actual chemical shifts were measured with a frequency counter on a 250-Hz expanded spectrum, but the positions of absorption are very sensitive to solvent and concentration.

[5] R. E. Lyle and C. R. Ellefson, *J. Amer. Chem. Soc.*, **89**, 4363 (1967).

[6] A. C. Cope and A. A. D'Addieco, *ibid.*, **73**, 3419 (1951).

[7] All new compounds gave satisfactory analytical values.

[8] D. R. Brown, J. McKenna, and J. M. McKenna, *J. Chem. Soc. B*, 1195 (1967).

[9] E. Jucker and A. Lindenmann, Swiss Patent 442,318 (1968); *Chem. Abstr.*, **69**, 35974*x* (1968).

other than minor shifts in peak positions. Consistent with the results in the tropane salts,[1] the axial methyl groups appear at lower field than the equatorial methyls.

If the factors that determine the steric preference in the tropanes and the tropidines are similar (as is suggested by the similar results in both series), it is unlikely that interference with the axial approach of the quaternizing reagent is the dominant factor. If this is so, the interaction of the nitrogen substituent with two of the hydrogens of the ethane bridge must be greater than the interaction it suffers when being fixed in the axial position in the transition state. This is a reasonable interpretation in the tropidine series.

In view of the flattened nature[10–13] of the six-membered ring in tropanes, the interpretation may be reasonable there as well. The flattening of the ring should cause the axial hydrogens to twist away from one another, thus reducing their steric influence. Substantial axial quaternization in the piperidine series[14] further establishes the importance of the rigid ethane bridge in giving an equatorial bias to the reaction. Further work on the nature and extent of these interactions is in progress.

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(10) H. Schenk, C. H. MacGillavry, S. Skolnik, and J. Laan, *Acta Crystallogr.*, **23**, 423 (1967).

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(12) J. H. Supple, L. N. Pridgen, and J. J. Kaminski, *Tetrahedron Lett.*, 1829 (1969).

(13) M. Ohashi, I. Morishima, K. Okada, T. Yonezawa, and T. Nishida, *Chem. Commun.*, 34 (1971).

(14) See, for example, D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc. B*, 1184 (1967).

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Protonation of Cyclopropane

Sir:

There has been much interest in the species formed by protonation of cyclopropane and in the fate of *n*-propyl cation;[1] we have studied these problems using the MINDO/2 method.[2]

As a preliminary we calculated the energies of several carbonium ions which are believed to have classical structures and are predicted to do so by MINDO/2. The geometries were optimized by the SIMPLEX method,[3] using a program written by Dr. A. Brown, and should correspond to true minima on the potential surface. The calculated heats of atomization were converted to heats of formation using experimental values for heats of atomization. The results are compared with experiment in Table I.

Table I. Heats of Formation of Carbonium Ions

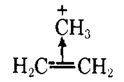
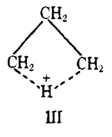
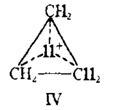
Ion	Heat of formation, kcal/mol, at 25° Calcd	Obsd[a]
CH_3^+	275.9	260
$CH_3CH_2^+$	225.2	219
$CH_3\overset{+}{C}HCH_3$	191.5	190
$CH_3CH_2\overset{+}{C}HCH_3$	183.4	183,[b] 192[c]
$(CH_3)_3C^+$	171.3	171.5,[d] 176[c]

[a] J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. J. Herron, K. Draxl, and F. M. Field, "Ionization Potentials, Appearance Potentials, and Heats of Formation of Gaseous Positive Ions," National Bureau of Standards, Washington, D. C., 1969. [b] From photoionization studies of F. A. Elder, C. F. Giese, and M. G. Inghram, *J. Chem. Phys.*, **36**, 3292 (1962). [c] Electron impact value. [d] From photoionization studies of B. Steiner, C. F. Giese, and M. G. Inghram, *J. Chem. Phys.*, **34**, 189 (1961).

The agreement is good, except for CH_3^+, for heats of formation calculated from photoionization data. The electron impact value for *sec*-Bu^+ is clearly too high, given that the corresponding values (Table I, footnote *a*) for *i*-Pr^+ and *n*-$BuCH^+CH_3$ are 190 and 173 kcal/mol, respectively.

Since the MINDO/2 method thus seems applicable to carbonium ions,[4] we calculated the various species that might be formed by protonation of cyclopropane. Only edge-protonated cyclopropane III was found to be stable, the other isomers, I, II, and IV, rearranging to III without activation. The values for I, II, and IV listed in Table II were calculated by assuming the CCC bond

Table II

Ion	Heat of formation, kcal/mol, at 25°
$CH_3CH_2\overset{+}{C}H_2$ I	216.0
 II	195.0
 III	187.6
 IV	247.5

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(1) (a) R. Hoffmann, *J. Chem. Phys.*, **40**, 2480 (1964); (b) C. C. Lee and J. E. Kruger, *Tetrahedron*, **23**, 2539 (1967); (c) J. D. Petke and J. L. Whitten, *J. Amer. Chem. Soc.*, **90**, 3338 (1968); (d) H. Fischer, H. Kollmar, and H. O. Smith, *Tetrahedron Lett.*, 5821 (1968); (e) L. Radom, J. A. Pople, V. Buss, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 1813 (1971).

(2) (a) M. J. S. Dewar and E. Haselbach, *ibid.*, **92**, 590 (1970); (b) N. Bodor, M. J. S. Dewar, A. Harget, and E. Haselbach, *ibid.*, **92**, 3854 (1970).

(3) J. A. Nelder and R. Mead, *Comput. J.*, 7, 308 (1964).

(4) It had already been shown that MINDO/2 gives good estimates of heats of formation of cation radicals formed by ionization of neutral molecules; see ref 2b and N. Bodor, M. J. S. Dewar, W. B. Jennings, and S. D. Worley, *Tetrahedron*, **26**, 4109 (1970).