Mass Spectra of Some Tropane and Tropidine Derivatives

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Fragmentation patterns of tropane and tropidine derivatives have been shown to depend on the nature of the substituents. Unsaturation in the 6-membered ring leads to preferential fragmentation of the two carbon bridge. When the 6-membered ring is saturated and substituted with poor leaving groups (OH and CN) fragmentation of the 6-membered ring is preferred.

The tropane ring system can fragment under electron impact by two different pathways involving α-cleavage of either the 1,7-bond (pathway *a* Scheme I) or the 1,2-bond (pathway *b*) of the tropane ring. The first pathway leads to a dihydropyridinium ion and potentially to the stable *N*-methylpyridinium ion (**1**), m/e 94. Pathway *b* follows cleavage of the 6-membered ring with loss of a three carbon fragment forming the stable *N*-methyl-3*H*-pyrrolinium ion (**2**), m/e 82.

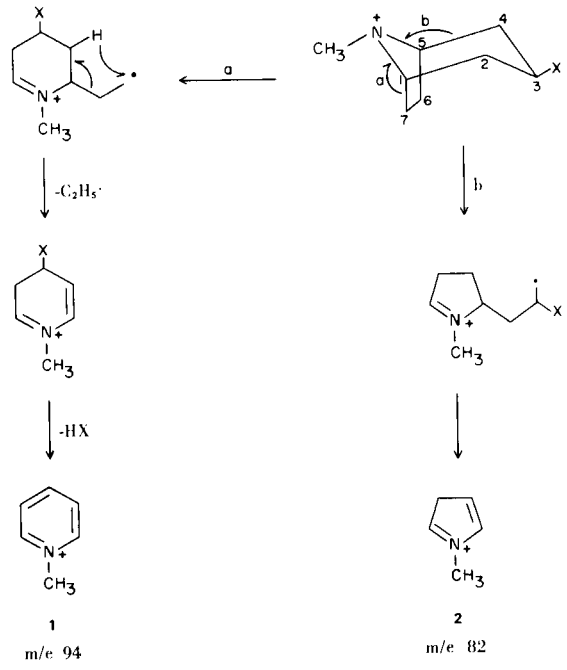
Most tropane derivatives studied previously have had an oxygen attached to the tropane ring as a ketone, alcohol, or esterified alcohol functionality (2-5). In such instances, fragmentation by pathway *a* has been of little significance, pathway *b* being much more important. For example the base peak in the spectrum of tropinone (**3**) (3) is that appearing at m/e 82 (**2**). A peak, 20% of base, at m/e 83 attributed to ion **4** is also cited as evidence of initial cleavage of the 5-membered ring. Although this is undoubtedly correct in the instance of tropinone, the m/e 83 peak cannot be taken as generally characteristic of 1,7-cleavage. In tropanes it can also result from cleavage of the 6-membered ring by a process similar to that shown in Scheme II which may or may not involve the tricyclic ion **5** (5).

Similarly, the mass spectrum of tropine (**6**) (5) is characterized by the ions **2** (100%) and **4** (86%) both resulting from cleavage of the 6-membered ring. A peak at m/e 96 (30%) was shown to result, at least in part, from cleavage of the 5-membered ring and assigned the structure **7** (3). The *N*-methylpyridinium ion at m/e 94, however, appears only to the extent of 9%. In fact, a survey of the literature indicates that initial fragmentation of tropane derivatives in the 1,7-(5,6-) bond is predominant only when a stabilizing substituent appears in the 5-membered ring, as in 6-methoxytropane (3) or in one instance when a double bond was present in the 6-membered ring (4).

We have investigated the mass spectra of several tropane and tropidine derivatives in order to assign structures to the major fragment ions and to determine the effect of substituents on the fragmentation process. In particular, we wished to determine which factors favor fragmentation leading to pyridinium ions. The results are summarized in Table I.

In the tropidines 8, 9, 13 and 17 fragmentation by pathway *c* (Scheme III) leads to a dihydropyridinium ion radical which can form pyridinium ions (**1**, **10**, **14**, **18**) by

SCHEME I



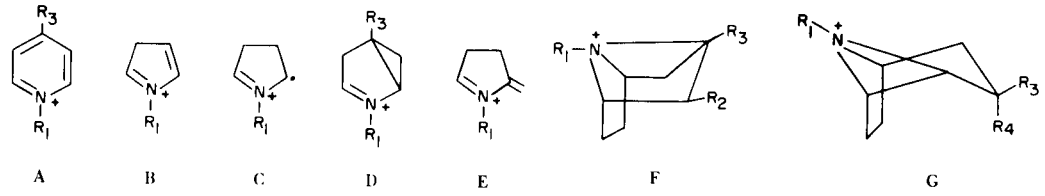
X = OH, Br, OAc, etc.

Table I

Percent Abundance of Diagnostic Fragment Ions

					Ion Type							
Compound	R1	R2	R3	R4	M^+	A	B	C	D/E	F/G	$HC{=}\overset{+}{N}CH_3$	Other
6	Me	H	H	OH	17	9	100	86	72(D/E)	20(F)	56	
8	Me		H		43	100	18	<1	------	----	45	
9	H		H		30	100	14	19	------	----		
13	COOEt		H		99	89	2	1	------	----		100(ion **10**)
17	Me		Ph		12	100	6	1	------	----		
19	Me	H	Ph	OH	25	16	64	100	3(D), 42(E)	13(F)	29	
21	Me	H	H	OAC	--	39	79	100	29(D/E)	25(F)	72	57($CH_3C{=}\overset{+}{O}$)
23	Me	H	H	CN	3	7	100	52	42(D/E)	----	35	24(M^+–HCN)
25	Me	H	CN	OH	10	2	100	60	73(E)	22(F)		25(M^+–HCN) 13(ion **28**)
26	Me	Br	OH	H	2	30	100	15	60(E)	49(G)		
29	Me	Br	H	Br	--	67	25	25	10(E)	100(F/G)		

1. Ion Types are



A B C D E F G

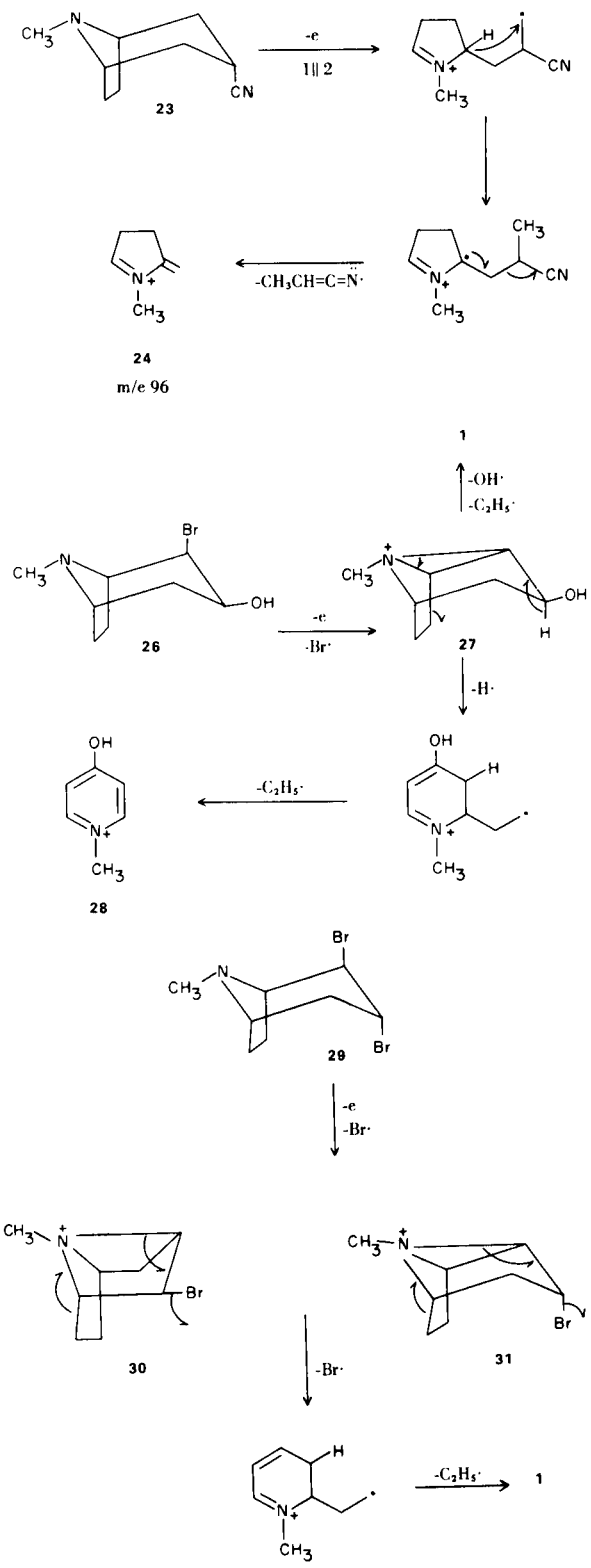
the loss of an ethyl radical. On the other hand, fragmentation by pathway *d* would give a stabilized allylic radical ion as the initial product followed by formation of 5-membered ring ions.

That 1,7-cleavage predominates is clear from the appearance of the *N*-methylpyridinium ion (**1**) at m/e 94 as the base peak in the spectrum of tropidine (**8**). The 5-membered ring fragment **2** is formed to the extent of 18% and **4** is immeasurably small. Similarly, nortropidine (**9**) gives the protonated pyridinium ion **10** as the base peak and ions **11** and **12** in abundances of 14% and 19% respectively. Further corroboration is given by the appearance of the ions **14** (89%), **15** (2%), and **16** (<1%) from *N*-ethoxycarbonylnortropidine (**13**) and ions **18** (100%), **2** (6%), and **4** (1%) from 3-phenyltropidine (**17**). The carbamate **13** has its base peak at m/e 80 which is best rationalized as forming *via* rearrangement of the pyridinium ion **14** with loss of carbon dioxide and ethylene (6). Other fragment ions characteristic of the carbamate functionality are also observed.

With substituted tropanes containing no unsaturation in the 6-membered ring, the results are less conclusive. For example, 3-phenyltropine (**19**) fragments predominantly in the 6-membered ring as expected. However, the ion **20**, analogous to ion **7** which gives a major peak in the tropine (**6**) spectrum, is weak (3%). Similarly, 3-α-acetoxytropane (**21**) favors the formation of ions **2** (79%) and **4** (100%) but a significant amount of **1** (39%) is also formed. The ester gives no observable molecular ion but exhibits a peak at m/e 124 (25%) which may be assigned the tricyclic structure **5** (or the monocyclic analog **5'**). The same peak is also found in the spectrum of tropine (**6**) and an analogous one (**22**; 13%) in the spectrum of 3-phenyltropine (**19**).

There seems, then, to be a tendency for a group at the 3-position to be lost as a neutral species with direct or indirect assistance from the nitrogen atom. The process also appears to depend on the nature of the leaving group. The spectrum of 3-α-cyanotropane (**23**) shows negligible intensity at m/e 124 (**5**), principal peaks appearing at m/e 82 (**2**; 100%), m/e 83 (**4**; 52%) and m/e 96 (42%). The last peak may be due to the bicyclic species **7**, or the 5-membered ring fragment **24**.

Support for structure **24** is found in its appearance in the spectrum of tropinone cyanohydrin (**25**) to the extent of 73%. It is unlikely that ion **7** would be an important fragment of **25**. The spectrum of the cyanohydrin, **25**, also shows the direct loss of ·OH (22%) but not ·CN. This is probably due to inherent differences in leaving ability rather than to stereochemical factors, although the importance of the latter cannot be ruled out at this time. Pyridinium ions are observed in the spectrum of **25**, but the



predominant fragmentation occurs in the 6-membered ring.

When a bromine atom is introduced into the molecule, as in the *cis*-bromohydrin **26**, there is no evidence of the hydroxyl radical being displaced. Instead a bromine atom is lost to give M^+-Br (49%). A reasonable formulation of this ion is the tricyclic species **27** which can fragment to give the pyridinium ions **1** (29%) and **28** (30%). The base peak in the spectrum appears at m/e 82 (**2**) indicating that cleavage of the 6-membered ring still predominates.

Incorporation of one more bromine into the molecule, however, changes the situation. In the spectrum of the *trans*-dibromide, **29**, the pyridinium ion **1** (67%) is more abundant than ions **2** (25%) and **4** (25%). No molecular ion is observable for **29**; the base peaks comprise a doublet at m/e 202, 204 corresponding to M^+-Br. Either one of the possible tricyclic ions (**30** or **31**) can collapse to the pyridinium ion **1**. The only other peaks in the spectrum of particular interest appear at m/e 172 and 174 (16%) and correspond to the *N*-methyl-3-bromopyridinium ion (**32**) and/or the 4-bromo isomer (**33**). The peak at m/e 96 in the spectra of **26** and **29** is best assigned the structure **24**.

EXPERIMENTAL

Spectra of compounds **6**, **21**, **23**, **25**, **26**, and **29** were determined using a Finnigan model 1015 spectrometer. Spectra of compounds **8**, **9**, **13**, **17**, and **19** were run on a Hitachi RMU-6E spectrometer. Solids were run using direct insertion probes, liquids were leaked in through all glass inlet systems. All spectra were determined at 70 eV and heated to the minimum temperature necessary to produce a spectrum.

Tropine (**6**) was a commercial sample (Aldrich) purified by sublimation. Tropidine (**8**) (7), 3-phenyltropidine (**17**) (8), 3-phenyltropine (**19**) (8), 3-α-acetoxytropane (**21**) (9), 3-α-cyanotropane (**23**) (10,11), and 2-β-bromo-3-β-hydroxytropane (**26**) (12) were prepared as described in the literature. The sample of the 3-β-cyano-3-α-hydroxytropane (**25**) was kindly supplied by Dr. Robert E. Lyle of the University of New Hampshire. Infrared spectra were determined on Perkin-Elmer model 257 and 457 spectrometers, as neat liquids and in chloroform solution for solids. Nmr spectra were determined on Perkin-Elmer model R-12 and Hitachi-Perkin-Elmer model R-20A spectrometers in deuteriochloroform with TMS added. Melting points are uncorrected.

N-Ethoxycarbonylnortropidine (**13**) (13).

A solution of 12.9 g. of ethyl chloroformate in 35 ml. of anhydrous benzene was added dropwise to a stirred solution of 4.7 g. of tropidine (**8**) in 17 ml. of dry benzene at 70°. After the addition was completed the mixture was refluxed for 2 hours. The cooled reaction mixture was washed with 50 ml. of 10% hydrochloric acid and 50 ml. of water, dried (sodium sulfate) and evaporated under reduced pressure to give a nearly colorless oil. Distillation gave a colorless oil, b.p. 120° (13 mm): ir (cm^{-1}) 3040 (w), 1705 (s), 1320 (s), 1310 (m), 1105 (s); nmr (δ) 1.22 (t, 3H), 1.40-3.00 (complex, 6H), 4.10 (q 2H), 4.32 (broad, 2H), 5.30-6.15 (complex, 2H).

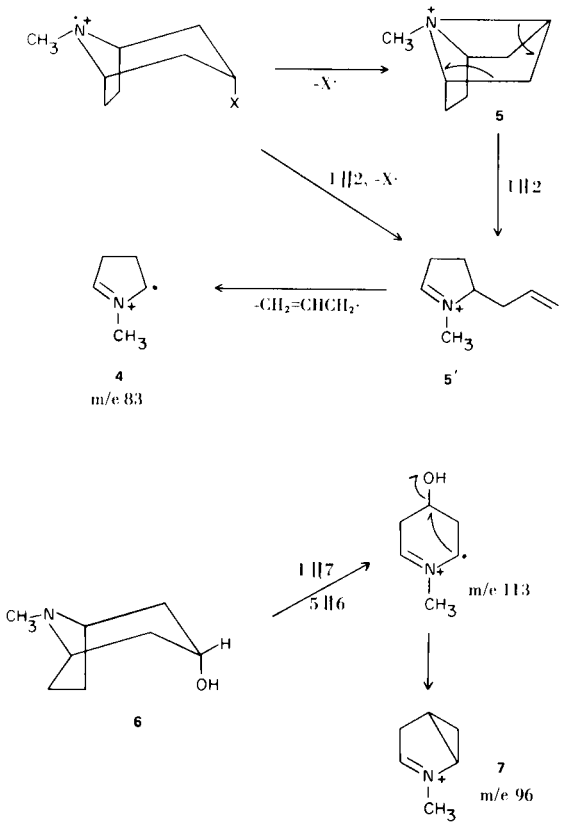
Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.36; H, 8.58; N, 8.13.

Nortropidine (**9**) (13).

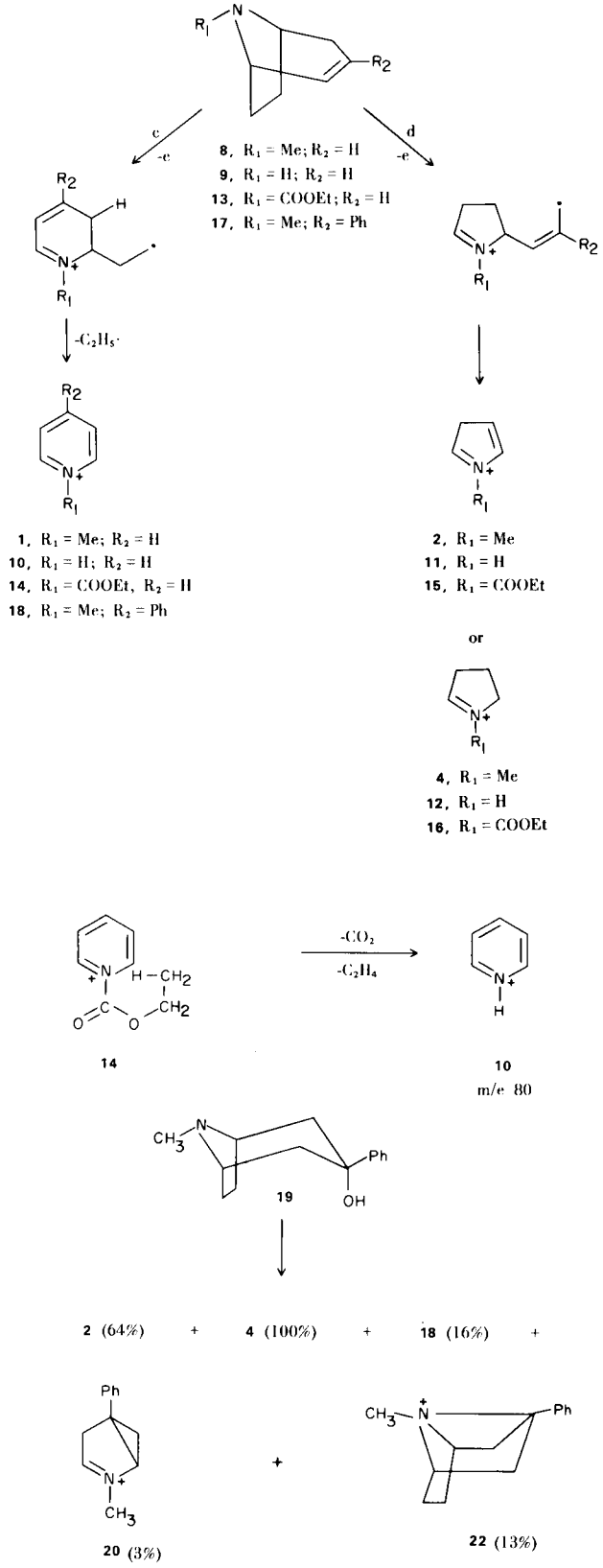
The carbamate **13** was refluxed for 15 hours in 20% hydrochloric acid and the mixture evaporated to dryness. The solid hydrochloride was recrystallized from 2-propanol, m.p. >285° dec.

Anal. Calcd. for $C_7H_{12}ClN$: C, 57.73; H, 8.31; Cl, 24.34; N,

SCHEME II



SCHEME III



9.62. Found: C, 57.53; H, 8.44; Cl, 24.36; N, 9.58.

The hydrochloride salt was dissolved in water, made basic with potassium carbonate and extracted with chloroform. The dried (potassium carbonate) extract was evaporated to give an oil which was distilled to give **9** as a colorless liquid, b.p. 160-167°: ir (cm^{-1}) 3400 (sh), 3250 (broad), 3030 (m), 1640 (w), 865 (m), 833 (m), 683 (m); nmr (δ) 1.35-2.80 (complex, 7H), 3.50 (broad, 2H), 5.25-6.25 (broad, complex, 2H).

2β-3α-Dibromotropane (**29**).

To a stirred solution of 3.59 g. (0.029 mole) of tropidine (**6**) in anhydrous ether was added dropwise 1.60 ml. of bromone. As insoluble material separated, the addition was stopped until a clear solution was obtained. After all of the bromine was added, the mixture was refluxed overnight. Removal of the ether afforded a viscous orange-red semi-solid which crystallized on treatment with acetone. Some bromination of acetone occurs, since a lachrymator is formed. Recrystallization of the solid from petroleum ether gave **29** as a white solid, m.p. 62.2-63.4°. The nmr spectral data have been published (14).

Anal. Calcd. for $C_8H_{13}Br_2N$: C, 33.93; H, 4.63. Found: C, 34.12; H, 4.77.

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