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THE REACTION OF 1-METHYLTRICYCLO[4.4.0.$0^{2,6}$]DECAN-3-ONE AND RELATED COMPOUNDS WITH HYDROGEN BROMIDE IN ACETIC ACID[1]

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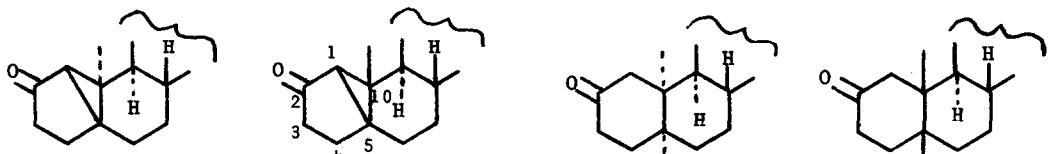
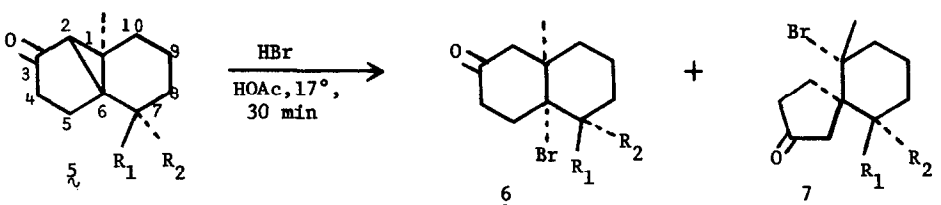
In recent years there has been considerable interest in the mode of cleavage of conjugated cyclopropyl ketones with electrophilic reagents.[2] 1-Methyltricyclo[4.4.0.$0^{2,6}$]decan-3-one (5c) and derivatives which have both β carbons of the cyclopropane ring fully substituted in principle can give spiro or fused-ring halo ketones upon reaction with electrophilic reagents such as halogen acids. However, ketones 1 and 2 which have a tricyclo[4.4.0.$0^{2,6}$]decan-2-one moiety fused to the C ring of a steroid system have been found to yield only fused-ring products 3[3] and 4[4] upon reaction with hydrogen chloride or hydrogen bromide in acetic acid.[5] In order to learn more about



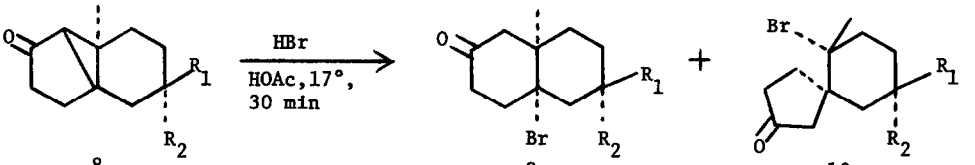
1 2 3 4

the factors which determine the mode of cleavage of 1-methyltricyclo[4.4.0.$0^{2,6}$]decan-3-ones by halogen acids, we have investigated the reactions of ketones 5a-c[6] and 8a-b[6] with hydrogen bromide in acetic acid. The results show that in these tricyclic systems both possible modes of cleavage may be involved and that the location and stereochemistry of substituents can have a profound influence upon the course of the reaction.



5 6 7

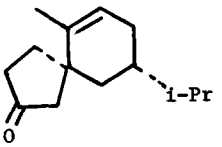
a. R_1 = H, R_2 = CH_3	83%	17%
b. R_1 = CH_3, R_2 = H	~1%	~99%
c. R_1 = R_2 = H	~35%	~65%



	8	9	10
a. R_1 = i-Pr, R_2 = H		∿90%	∿10%
b. R_1 = H, R_2 = i-Pr		∿5%	∿95%

The cyclopropyl ketones were reacted with excess hydrogen bromide in acetic acid at 17° for 30 min and the products were isolated in the usual way. The structures of the bromo ketone products, except for the configurations at the carbons bearing bromine, were readily assigned from the ir and nmr spectral properties. Previous work[2,3] indicates that in general the ring opening reaction involves inversion of configuration at the β carbon of the cyclopropane ring. This was confirmed in the case of the bicyclic ketone 6a by a single crystal x-ray structure.[7] The assignments of the configurations of the other bicyclic and spirocyclic bromo ketones are by analogy. The percentages of each bromo ketone in the mixtures are given beneath the structures. Total yields were in the 80-90% range in each case. Compounds 6a[8] [mp 104-105°; ir(CCl_4) 1720 cm^{-1}; nmr (CCl_4) δ 1.10 (d, J=6Hz, 3H) and 1.17 ppm (d, J=∿1Hz, 3H)], 7a[8] [mp 89-90°; ir (CCl_4) 1744 cm^{-1}; nmr (CCl_4) δ 0.85 (d, J=6.5Hz, 3H) and 1.79 ppm (s, 3H)], and 9a[8] [mp 81.5-83.0°; ir (CCl_4) 1714 cm^{-1}; nmr (CCl_4) δ 0.93 (d, J=6Hz, 6H) and 1.13 ppm (s, 3H)] were purified by recrystallization. Spiro ketone 10b [ir (CCl_4) 1745 cm^{-1}; nmr (CCl_4) δ 0.95 (d, J=6Hz, 6H) and 1.80 ppm (s, 3H)] was subjected to distillation but a sample sufficiently pure for elemental analysis could not be obtained. Therefore the product was subjected to dehydrobromination with tetra-n-butylammonium bromide in acetone containing 2,6-lutidine[9] to yield the pure spiro enone 11[8] [bp 95-105° (bath temperature)/0.1 mm; ir (CCl_4) 1747 and 1692 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J=5.6Hz, 6H), 1.68 (bs, 3H), and 5.44 ppm (mult., 1H)]. Bromo ketone 7b was dehydrobrominated in a similar manner to give the known spiro enone 12b.[10]

Attempted isolation of the pure bromo ketones 7a, 6c, and 7c by chromatographic methods failed. The ratios of the products derived from cleavages of 5a and 5c were estimated from the nmr and ir spectra of the crude mixtures and were confirmed by GLC analysis[11] of the spiro and fused-ring enone mixtures produced by dehydrobromination.[9] Thus the mixture of 6a and 7a obtained from 5a produced a 17:83 mixture of the known enones 12a[12] and 13[13] and the mixture of 6c and 7c obtained from 5c gave a ca. 65:35 mixture of 12c[8] [ir (CCl_4) 1737 cm^{-1}, nmr (CCl_4) δ 1.67 (bs, 3H) and 5.48 (m, 1H)] and 14a[8] [ir (CCl_4) 1724 cm^{-1}; nmr (CCl_4) δ 1.03 (s, 3H), 2.73 (m, 2H), and 5.27 ppm (m, 1H)]. Enone 14a was readily isomerized into a conjugated enone which had ir and nmr spectral properties which were consistent with structure 14b upon treatment with potassium hydroxide in methanol. Spectroscopic analysis on the crude products derived from 8a and 8b indicated that small amounts (5-10%) of the spiro bromo ketone 10a and the bicyclic bromo ketone 9a, respectively, were produced along with the major products. However, these compounds were not produced in sufficient quantities to permit isolation.



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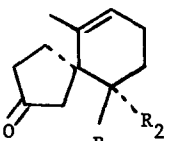
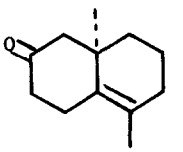
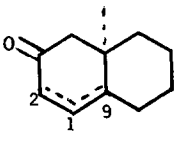


12 a. R_1 = H, R_2 = CH_3
b. R_1 = CH_3, R_2 = H
c. R_1 = R_2 = H



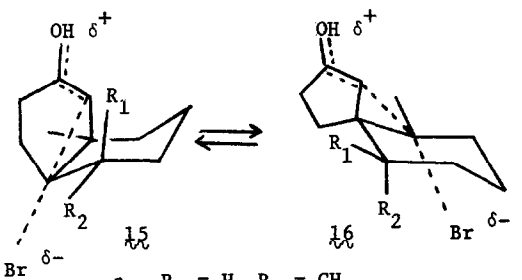
13



14

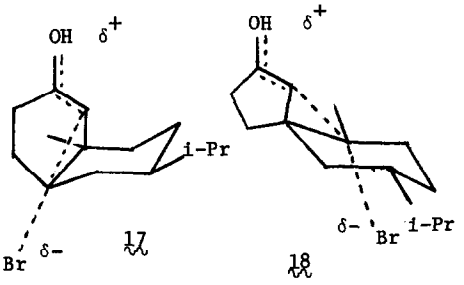
a. 1,9-double bond
b. 1,2-double bond

These results are consistent with a mechanism which involves a kinetically controlled concerted cleavage of the protonated cyclopropyl ketone by the halide ion,[2e] and indicate that the major pathway involves opening of the cyclopropane ring in a diaxial manner with respect to the most stable conformation of the six-membered ring. In ketone 5a a rather strong esclipsed interaction exists between the 7α-methyl group and the 5-methylene group in the conformation with the methyl group equatorial. This interaction is relieved when the methyl group is axial. However, in transition state 16a there is a 1,3-diaxial interaction between the axial methyl group and the approaching bromide ion. Thus transition state 15a leading to the bicyclic product is preferred by about 4:1. In the cleavage of 5b, transition state 16b, in which the 7β-methyl is equatorial, is clearly favored over 15b and ring opening occurs to give a spiro product essentially exclusively. In the cleavage of 5c, transition state 16c is slightly preferred, although the non-bonded interactions present in 15c and 16c appear to be about the same. Perhaps the slight preference for cleavage of the external cyclopropyl bond results from the fact that orbital overlap between the carbonyl group π-bond and the σ-bonds of the cyclopropane ring is much more favorable for the external than the internal bond.[5] In the cleavages of 8a and 8b transition states 17 and 18 which have the 8-isopropyl groups equatorial to the six-membered rings and lead to bicyclic and spiro bromo ketones, respectively, are strongly favored over the alternative transition states which would have the isopropyl groups axial. This accounts for the fact that each of these isomers gives essentially a single product. Product studies for certain cyclopropyl ketone openings have indicated that the reaction may be partially subject to thermodynamic control.[2e] However, this does not appear to be the case for the cleavages of the tricyclodecanones described above. For example, analysis of non-bonded interactions in compounds of the the type 9 and 10 provide no indication that thermodynamic factors would significantly favor a fused-ring ketone in one case and a spiro product in the other.



15 16

a. R_1 = H, R_2 = CH_3
b. R_1 = CH_3, R_2 = H
c. R_1 = R_2 = H



17 18

In the steroidal ketone 1 ring B is rigidly held in a conformation analogous to 15 or 17 and diaxial opening of the internal (1,5) bond results. In the case of the steroidal ketone 2 diaxial ring opening would be expected to lead to a spiro product, yet the fused-ring ketone 4 was actually isolated.[4] From examination of models of 2 it appears that β attack of bromide ion at C-10 at an angle of 180° with respect to the 1,10-bond would encounter steric interference involving C-11. This may possibly account for the preference for β attach of bromide ion at C-5 and diequatorial opening of the 1,5-bond.

References and Notes

1. This investigation was supported by Public Health Service Grant No. CA 12193 from the National Cancer Institute.
2. a. G. Stork and P. A. Grieco, Tetrahedron Lett., 1807 (1971), and refences therein; b. J. F. Ruppert and J. D. White, J. Chem. Soc., Chem. Commun., 976 (1976); c. S. K. Dasgupta and A. S. Sarma, Tetrahedron, 29, 309 (1973); d. W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, J. Org. Chem., 34, 2512 (1969); e. S. A. Monti, D. J. Bucheck, and J. C. Sheppard, ibid., 34, 3080 (1969); f. D. Caine and S. L. Graham, Tetrahedron Lett., 2521 (1976); g. G. Habermehl and W. Walz, Z. Naturforsch., 31b, 983 (1976).
3. B. A. Shoulders, W. W. Kwie, W. Klyne, and P. D. Gardner, Tetrahedron, 21, 2973 (1965).
4. S. B. Liang and P. J. Sykes, J. Chem. Soc. C, 937 (1968).
5. a. This mode of cleavage is in marked contrast to that observed in the lithium-ammonia cleavage of ketones such as 1,[5b] 2,[4] and related compounds such as 5a-c[5c,5d] and 8a-b[5d] which yields spiro ketones exclusively. Spiro products arise in the reductive process apparently because the geometry of these systems permits favorable overlap between the carbonyl group and the external bond of the cyclopropane ring; b. W. G. Dauben and E. J. Deviny, J. Org. Chem., 31, 3794 (1966); c. E. Piers and P. M. Worster, J. Am. Chem. Soc., 94, 2895 (1972); d. D. Caine, W. R. Pennington, and T. L. Smith, Jr., preceding communication.
6. For the method of synthesis of these compounds, see Ref. 5d, footnote 5.
7. The details of the x-ray crystallographic structure of 6a will be published later in a full paper. We are grateful to Professor J. A. Bertrand, Dr. H. Deutsch, and Dr. D. Van Deever for their assistance in carrying out this determination.
8. Correct elemental analysis and/or exact mass data have been obtained for all compounds for which spectral data are given with the exception of 10b.
9. G. Biale, D. Cook, D. J. Lloyd, A. J. Parker, I. O. R. Stevens, J. Takahashi, and S. Weinstein, J. Am. Chem. Soc., 93, 4735 (1971).
10. D. Caine, A. A. Boucugnani, and W. R. Pennington, J. Org. Chem., 41, 3632 (1976).
11. A 6 ft. x 1/8 in. stainless steel column containing 20% Carbowax K-20M on Chromosorb W HMDS was employed.
12. P. J. Kropp, J. Am. Chem. Soc., 87, 3914 (1965).
13. J. A. Marshall, N. Cohen, and R. A. Hochstetler, ibid., 88, 3408 (1966).