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7 SUBSTITUTED 2,3-DIAZABICYCLO [2.2.1] HEPTANE DERIVATIVES

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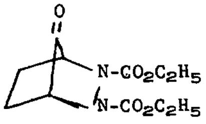
Several groups of workers have in recent years attempted to synthesize a 2,3-diazabicyclo [2.2.1] heptyl ring system with a keto function at the 7-position. All such attempts have failed. The reason for this was that the synthetic sequence involved preparation of the readily available corresponding ketals which were subsequently found to be completely inert toward hydrolysis (1-4).

The availability of this ketone is important since it would make possible the preparation of a variety of derivatives monosubstituted at the 7-position and thereby permit a comparison of the chemistry of the 7-substituted 2,3-diazabicycloheptyl system with that of the exhaustively studied all carbon ring system. Furthermore, these 7-substituted compounds should be valuable as precursors for the synthesis of endo 5-substituted bicyclo [2.1.0] pentanes for which an extremely fast solvolysis rate has been predicted (5) and which as yet have not been successfully prepared (6).

We now report the preparation of the 7-keto compound 1, the corresponding alcohol 2, (7) and tosylate 3 as well as some of their unusual properties.



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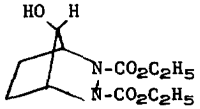

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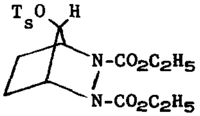

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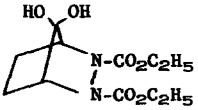

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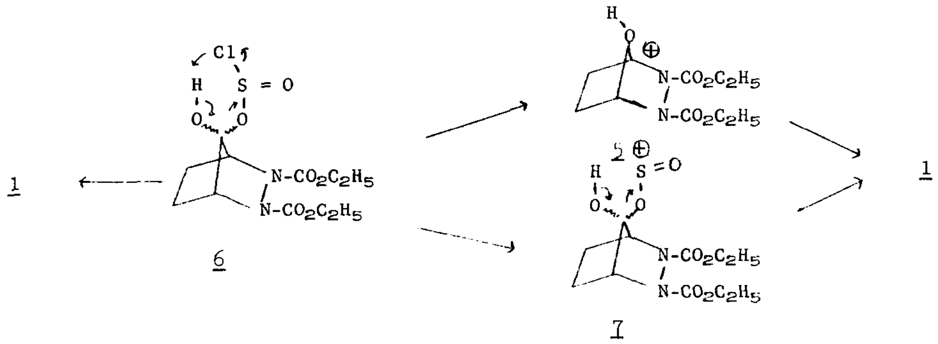
Warming of 4, the preparation of which has been previously described (2), with thionyl chloride gave 1 in 90% yield as a colorless liquid, bp 120-121 (0.2 mm). The infrared spectrum showed strong carbonyl stretching at 5.6 microns which is characteristic of 7-keto-bicycloheptanes (8) and no hydroxyl absorption; δ 1.30 (triplet 6H), 2.08 (broad singlet 4H), 4.25 (quartet 4H), 4.07 (singlet 2H). Anal. Calcd. for $C_{11}H_{16}O_5N_2$: C, 51.54; H, 6.22; N, 10.93. Found: C, 51.74; H, 6.50; N, 10.82.

Although the reaction of secondary or tertiary alcohols with thionyl chloride is thought to proceed via a rate determining carbon-oxygen bond cleavage (9), for reasons which will be discussed later formation of 5 which bears a positive charge at the 7-position is considered unlikely. It is therefore suggested that 1 is formed via 7 or directly from 6.

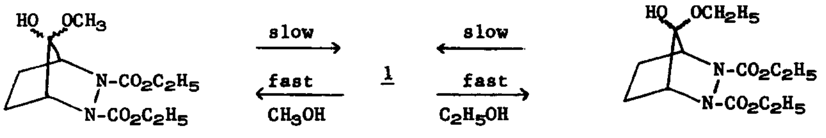


Reduction of 1 with sodium borohydride gave a 95% yield of 2 as a colorless viscous liquid. Anal. Calcd for $C_{11}H_{18}O_5N_2$: C, 51.16; H, 7.02; N, 1085. Found: C, 50.90; H, 6.87; N, 10.63. The crude reduction product consisted almost exclusively of 2 as evidenced by tlc and is tentatively assigned the anti configuration on the basis of the absence of any observable intramolecular hydrogen bonding vibration in its near infrared spectrum (10). Comparison of the nmr spectrum of 2 with that of 4 and 2,3-dicarboethoxy-2,3-diazabicyclo [2.2.1] heptane (8) also supports an anti configuration for 2. The ethano bridge hydrogens of 4 consist of a broadened quartet centered at 1.95 (2) whereas those of 8 are a singlet at 1.76.

The ethano bridge hydrogens of 2 are essentially identical with those of 4 and consist of a broadened quartet centered at 1.93.

Compound 2 was converted into 3 in 85% yield, mp 80-82°. Anal. Calcd. for $C_{18}H_{24}O_7N_2$: C, 52.43; H, 5.87; N, 6.79. Found: C, 52.15; H, 5.72; N, 6.77.

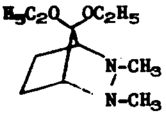
The carbonyl function of 1 is remarkably active toward addition of nucleophiles. For example, when a thin film of 1 is exposed to the atmosphere for less than one second it is completely converted to the gem diol 4. Also, the addition of methanol to 1 results in its complete and immediate conversion to the hemiketal 9. As is apparently the case for the hydride reduction of 1, the addition of methanol to 1 also appears to be highly stereoselective to give almost exclusively a single epimer as evidenced by tlc, sharp melting point (118-119°) of the crude product and the nmr spectrum of the methoxyl protons consists of a highly symmetrical sharp singlet at 3.37. Similarly the ethyl hemiketal 10, is formed by addition of ethanol to 1. Furthermore, 9 and 10 can be converted into each other by standing at room temperature for several days with the corresponding alcohol. This behavior is analogous to that found for the hemiketals of cyclopropanone (11).



9 10

These reactions, particularly since no ketals seem to be formed, provide good evidence that generation of a cationic center at the 7-position is very unfavorable. This conclusion is supported by the unreactivity of 3 toward acetolysis. No measureable titer was obtained when 3 was heated at 118° with sodium acetate in acetic acid for 11 days (12). Even if it is assumed that 3 underwent 1% acetolysis, a maximum rate constant can be calculated which is 10 times less than that of 7-norbornyl tosylate at 118° (13).

The thermal stability of 4 (2), hydrolytic stability of ketals, interconversion of hemiketals, solvolytic stability of 3 and exceptional reactivity of 1 toward nucleophilic addition demonstrate that the 7-position of the 2,3-diazabicycloheptyl ring is chemically similar to cyclopropyl carbon. Nitrogen atoms at the 2,3-positions must be partially responsible for this unusual behavior since the norbornanes do not behave anomolously (14). Since the N-N single bond length is intermediate between that of C-C and C=C, this behavior cannot be due solely to bond angle effects at the 7-position. Therefore it is suggested that this behavior is due to the inductive electron withdrawal by nitrogen, superimposed on the unfavorable bond angle at the 7-position of bicycloheptanes. Type of substitution on nitrogens or even their hybridization do not appear to be very important since the ketals **11** and **12** (1) as well as **13** (3) are all inert toward hydrolysis.



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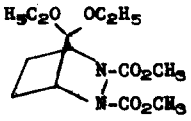

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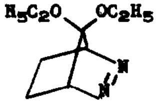

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References

1. E. L. Allred and C. Anderson, *J. Org. Chem.*, **32**, 1874 (1967).
2. N. P. Marullo and J. A. Alford, *J. Org. Chem.*, **33**, 2368 (1968).
3. W. Pirkle, private communication.
4. J. Tufariello, private communication.
5. P. von R. Schleyer, National Organic Chemistry Symposium, p. 21, 1967.
6. P. von R. Schleyer, private communication.
7. J. Tufariello has prepared the N-carbomethoxy analog of **2** by a different procedure. However, he has been unable to generate the corresponding ketone from the alcohol. We are grateful to him for supplying us with this information prior to publication.
8. F. H. Allen, *J. Am. Chem. Soc.*, **82**, 653 (1962).
9. E. S. Lewis and C. E. Boozer, J. Am. Chem. Soc., 76, 794 (1954) and references therein.
10. P. G. Gassman and J. L. Marshall, *J. Am. Chem. Soc.*, **88**, 2822 (1966).
11. H. H. Wasserman and D. C. Clagett, *J. Am. Chem. Soc.*, **88**, 5368 (1966).
12. Attempted acetolysis at higher temperatures resulted in extensive darkening of the reaction mixture.
13. S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955).
14. P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964); P. E. Eaton and R. A. H. Hudson, *J. Am. Chem. Soc.*, **87**, 2769 (1965).