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RAPIDLY EQUILIBRATING KETOLS

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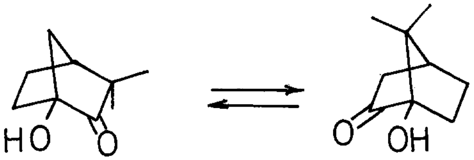
Rapid rearrangements, in bicyclic systems and especially in bicyclo[2.2.1]heptanes, are usually associated with carbonium ions. Several recent reports, describing interconverting ketols[1] and bridgehead ketols in particular have appeared.[2,3,4] These reports prompt us to report our observations of rapid inconversion of bridgehead ketols on a n.m.r. time scale. During the course of another study[5] we observed an equilibrium mixture of 3,3-dimethyl-1-hydroxybicyclo-[2.2.1]heptan-2-one (1) and 7,7-dimethyl-1-hydroxybicyclo[2.2.1]heptan-2-one (2) under a variety of conditions. Treatment of the mixture of 1 and 2 with acetic anhydride gave predominately the the acetate 3.[5] Benzylation with sodium hydride and benzylchloride in dimethylformamide[6,7] gave predominately benzylether 4. If the mixture of 1 and 2 in acetone was treated with ketene, two acetates were formed in approximately equal amounts and could be separated by gas or liquid chromatography. One was identified as the previously known 3 and the second was identified as 5 by



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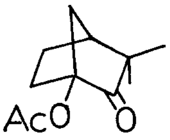

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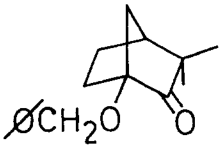

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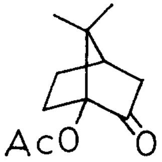

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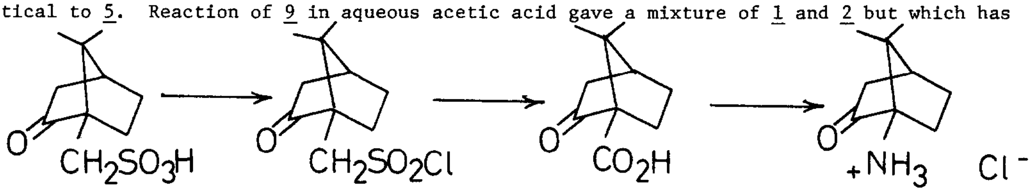
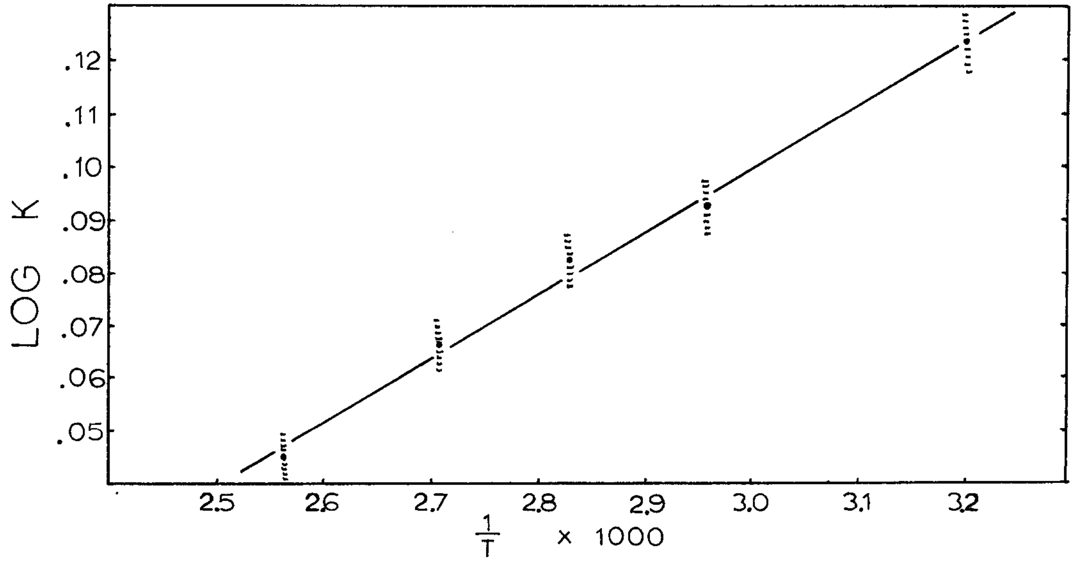
following sequence of reactions. 10-Camphorsulfonic acid (6) was converted to the sulfonyl chloride 7 and oxidized to the ketopinic acid 8.[8,9] The acid 8, on treatment with thionyl chloride and sodium azide, rearrangement at 60° in dry benzene and hydrolysis in concentrated hydrochloric acid gave 1-amino-7,7-dimethylbicyclo[2.2.1]heptan-2-one hydrochloride (9)[10] in 79% yield based on 8. Treatment of 9 in glacial acetic acid with solid sodium nitrite gave an acetate identical to 5. Reaction of 9 in aqueous acetic acid gave a mixture of 1 and 2 but which has been reported previously as a single compound 2[10] and more recently separated by thin layer chromatography.[4]



6 7 8 9

Treatment of the acetates 3 or 5 with sodium methoxide in methanol gave identical mixtures of 1 and 2. The n.m.r. spectrum of 1 shows a singlet (CCl_4) at $\delta=1.06$ while 2 shows two singlets at $\delta=0.83$ and 1.10. When 50% by volume benzene was added, the signals for 1 were $\delta=0.93$ and for 2 at 0.72 and 0.99. These chemical shifts are in complete agreement with those reported in the literature.[4]

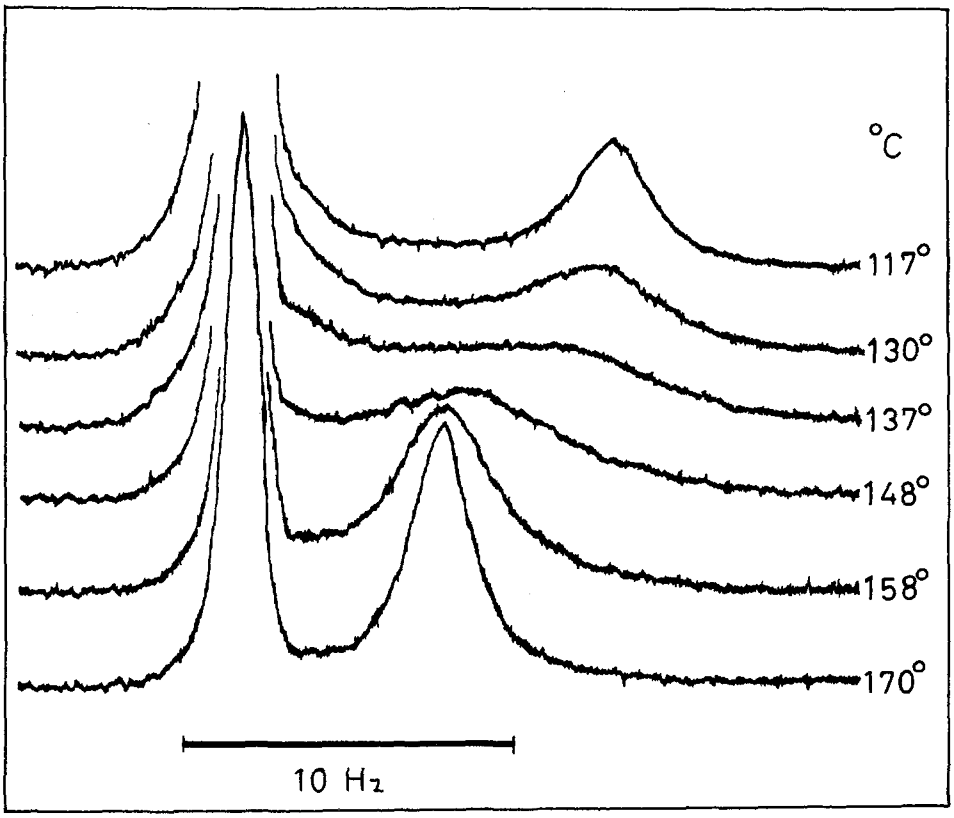
FIGURE 1



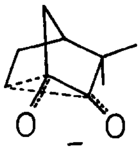
The good separation of the methyl signals in the two isomers allowed accurate determination of the equilibrium constant, K=2/1. We have examined the equilibrium in ethylene glycol containing an equivalent amount of base (Figure 1) and have found that at 39°, K=1.33; 61°, K=1.24; 80°, K=1.20; 96°, K=1.16; 117°, K=1.11 (all temperatures ±1°). The calculated values for $\Delta H°$, $\Delta G°$ and $\Delta S°$ at 312° were -550 calories, -180 calories and -1.2eu., respectively.

When the temperature was raised, noticable broadening of the methyl signals could be observed at 117°. Coalescence of the signals at δ=1.06 and 0.83 occurred at about 139° and the new signals at δ=1.03 and 0.93 did not become sharp until 180°. The changes in the spectrum are summarized in Figure 2.

FIGURE 2



A plot of log $(\frac{1}{\tau})$ vs 1/T gave $E_a = 24.1 \pm 1.0$ kcal and A=14.4.[11]



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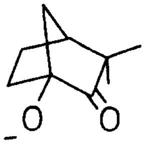

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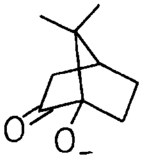

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Since three methyl signals corresponding to 11 and 12 could be observed until coalescence, 11 and 12 must be intermediates and 10 must be the transition state for their interconversion. This provides the first example of rapid interconversion of ketols in bicyclo[2.2.1]heptane. Rapid interconversion of other ketols have been observed and studies are in progress.[12]

REFERENCES

1. W. H. Urry, J. C. Duggan of M. H. Pai, J. Amer. Chem. Soc., 92, 5785 (1970) and references therein.
2. M. Nussim and Y. Mazur, Tetrahedron, 5337 (1968).
3. A. Nickon, T. Nishida and Y. Lin, J. Amer. Chem. Soc. 91, 6860 (1969), and references therein.
4. A. Nickon, T. Nishida, J. Frank and R. Muneyuki, J. Org. Chem. 36, 1075 (1971).
5. J. V. Paukstelis and B. W. Macharia, Tetrahedron Letters.
6. We wish to thank Mr. Benson Macharia for examining this reaction.
7. M. E. Tate and C. T. Bishop, Can. J. Chem. 41, 1801 (1963).
8. P. D. Bartlett of L. H. Knox, Org. Synthesis, 45, 14 (1965).
9. P. D. Bartlett of L. H. Knox, Org. Synthesis, 45, 55 (1965).
10. M. Ishidate and A. Kawada, Pharm. Bull. (Tokyo) 4, 483 (1956).
11. The rates were determined by a complete line shape calculation of the exchanging groups and by use of contour maps of the least squares fit of the experimental and calculated data with the rate constant and chemical shift as variables. The exact procedure for this method of obtaining rates with reliable confidence intervals will be published elsewhere. All of the calculations before coalescence were based on the signal at δ=0.83 ppm and after coalescence on the signal at δ=0.93 ppm.
12. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for partial support of this work and to the National Science Foundation for a RPCT Grant GY 6909 to DNS and Kansas State University.