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CYCLOPROPANONE CHEMISTRY. V. β-LACTAM FORMATION AND OTHER REACTIONS OF CYCLOPROPANONE PRECURSORS IN THE BICYCLO[4.1.0] SERIES

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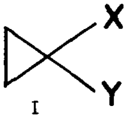
We have previously described[1] reactions of 1,1-disubstituted cyclopropane derivatives of type I which appear to take place through cyclopropanone or its iminium salts. We now report studies on cyclopropanone derivatives in the bicyclo[4.1.0] series, and provide evidence for the intermediacy of the species II.

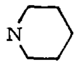
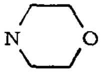


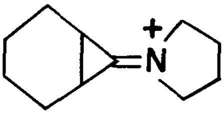
I

a, X = OH; Y = OEt

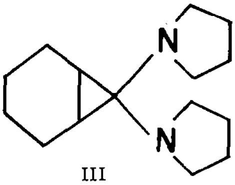
b, X = OH; Y = 

c, X = Y = 

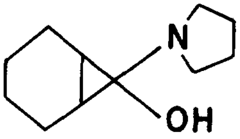
d, X =  ; Y = 



II



III



IV

The starting materials for this investigation were 7,7-dipyrrolidinobicyclo[4.1.0]heptane(III)and the corresponding carbinol amine(IV)prepared from 2-chlorocycloheptanone by the elegant method of Szmuszkovicz and coworkers.[2] On standing in methanol for 18 hr. at 25°, III underwent almost complete conversion (89%) to 7-methoxy-7-pyrrol-

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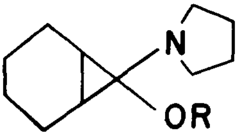
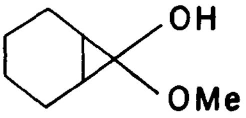
+ Department of Organic Chemistry, University of Newcastle upon Tyne, Newcastle upon Tyne, NEI 7RU, England idinobicyclo[4.1.0]heptane (Va)*: ν_{max}^{film} 3025, 2995, 2975, 2865, 2840, 1090 cm^{-1}; $\tau_{CDCl_3}^{TMS}$ 6.72 (s, 3H), 7.0 (t, J = 10Hz, 4H), 8.25 (m, 8H), 8.8 (m, 6H); mol. wt.,** 195. With ethanol, conversion to Vb* similarly took place (82%): ν_{max}^{film} 3050, 2975, 2900, 2860, 1075 cm^{-1}; $\tau_{CDCl_3}^{TMS}$ 6.4 (q, J = 10Hz, 2H), 7.05 (m, 4H), 8.35 (m, 8H), 8.85 (m, 7H); mol. wt., 209. When Va was allowed to stand in ethanol for two weeks, essentially complete conversion to Vb took place.



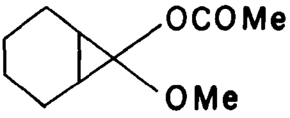
V

a, R = Me

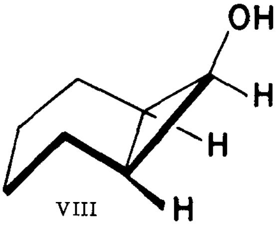
b, R = Et



VI



VII



VIII

The carbinol amine(IV) reacted only slowly with methanol, but on treatment with excess methyl iodide in methanol for 18 hr., at 25°, it was converted nearly quantitatively (95%) to the methyl hemiketal (VI). Product VI was a practically pure yellow oil, stable for several weeks at 0°: ν_{max}^{film} 3380, 3050, 2950, 2860, 1100 cm^{-1}; $\tau_{CDCl_3}^{TMS}$ 6.6 (s, 3H), 8.4 (m, 4H), 8.8 (m, 6H); mol. wt., 142. It was further characterized as the acetate (VII)* prepared by reaction with ketene in the presence of a trace of acid at -40°, and purified by molecular distillation (90°/1mm) (68%): ν_{max}^{film} 3040, 2940, 2870, 1765, 1630; $\tau_{CDCl_3}^{TMS}$ 6.56 (s, 3H), 7.80 (s, 3H), 8.30 (m, 4H), 8.7 (m, 6H); mol. wt., 184.

The methyl hemiketal, VI, underwent ring opening to form cyclohexane carboxylic acid methyl ester as the only volatile product on G. L. C. or on heating to reflux in n-hexane

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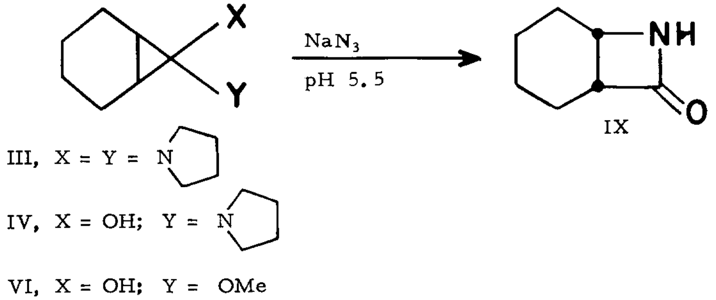
* Satisfactory elemental analyses were obtained.

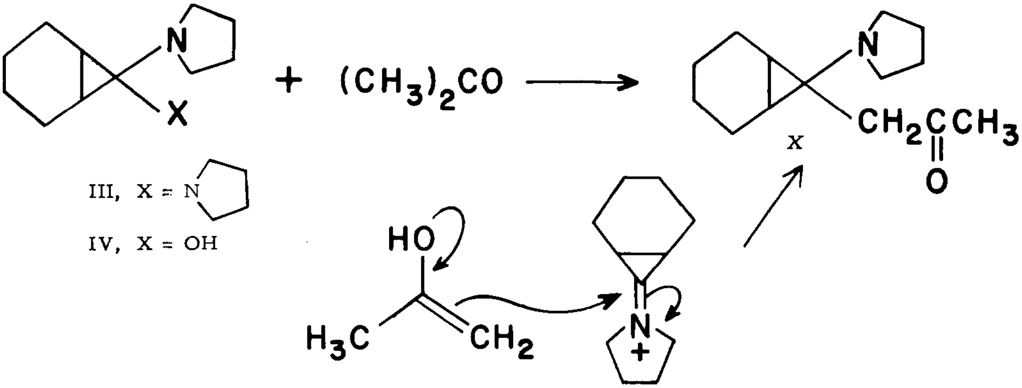
** All molecular weight values were determined by mass spectrometry.

for 18 hr. Compound VI could be reduced readily with lithium aluminum hydride in ether at 25° to give endo-bicyclo[4.1.0]heptan-7-ol (VIII) identical with an authentic sample.[2,6] This reaction is analogous to the reduction (LiAlH$_4$) of cyclopropanone ethyl hemiketal (I, X = OH, Y = OEt)[3,5] to cyclopropanol (I, X = OH, Y = H). When VI was heated in acetone at reflux with sodium azide (pH 5.5) for 12 hr., the β-lactam (IX)* m.p. 52-54° was obtained in excellent yield (95%): ν_{max}^{film} 3500, 3370, 2955, 2885, 1750 cm^{-1}; $\tau_{CDCl_3}^{TMS}$ 2.80 (br. s, 1H), 6.15 (m, 1H), 6.75 (m, 1H), 8.25 (m, 8H). With HCl in ether, the β-lactam (IX) could be readily converted to cis-hexahydroanthranilic acid.[7]

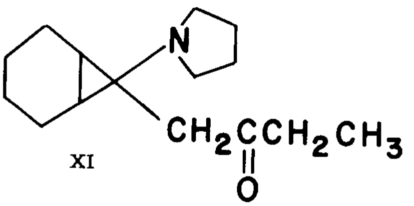


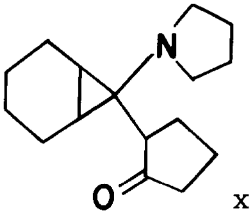
Formation of the β-lactam (IX) also took place if either III (63%) or IV (67%) was heated in buffered aqueous tetrahydrofuran with sodium azide.

Both III and IV underwent remarkably ready reaction with acetone in the presence of aqueous pH 5.5 buffer to form the addition product(X*) (60%), most probably through the



iminium ion shown: $\nu_{\text{max}}^{\text{film}}$ 3010, 2975, 2940, 2900, 2860, 2830, 1725, 1710; $\tau_{\text{CDCl}_3}^{\text{TMS}}$ 7.34 (m, 4H), 7.55 (s, 2H), 7.80 (s, 3H), 8.35-8.70 (m, 12H), 9.15 (m, 2H); mol. wt., 221.


XI


XII

Under the same conditions,[8] the bis-pyrrolidino derivative (III) reacted with methyl ethyl ketone to form the addition product (XI)* (44%): $\nu_{\text{max}}^{\text{film}}$ 2950, 2925, 2830, 2800, 1703 cm^{-1}; $\tau_{\text{CDCl}_3}^{\text{TMS}}$ 7.25 (m, 4H), 7.50 (m, 4H), 8.25-9.2 (m, 17H); mol. wt., 235. Compound III also underwent addition to cyclopentanone, to form XII (24%): $\nu_{\text{max}}^{\text{film}}$ 2950, 2920, 2850, 2800, 1740; $\tau_{\text{CDCl}_3}^{\text{TMS}}$ 7.3 (m, 4H), 7.5-8.4 (m, 15H), 8.75 (m, 4H) 9.18 (m, 2H); mol. wt. 247.

Acknowledgement: This work was supported by Grant GM-07874 from the National Institutes of Health.

1. Cyclopropanone Chemistry, IV., H. H. Wasserman and M. S. Baird, Tetrahedron Letters, 1729 (1970).
2. J. Szmuszkovicz, D. J. Duchamp, E. Cerda, and C. G. Chidester, Tetrahedron Letters, 1309 (1969).
3. H. H. Wasserman, R. E. Cochoy and M. S. Baird, J. Am. Chem. Soc., **91**, 2375 (1969).
4. H. H. Wasserman and D. C. Clagett, J. Am. Chem. Soc., **88**, 5368 (1966).
5. With Grignard reagents neither VI nor VII underwent smooth reactions to form 7-substituted cyclopropanols as was observed in the case of cyclopropanone hemiketal and its acetate.[3,4] Instead, complex products were obtained.
6. Formation of the endo product, VIII does not prove the stereochemistry of VI since the reaction may occur through a symmetrical cyclopropanone intermediate. In fact, VI, in solution may well exist in rapid equilibrium with the cyclopropanone and methanol as has been postulated for the cyclopropanone hemiketals.[4]
7. E. J. Moriconi and P. H. Mazzocchi, J. Org. Chem., **31**, 1372 (1966).
8. Under these conditions, 3-pentanone failed to undergo the addition reaction.