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POLYCYCLIC BASES-III

THE PREPARATION AND STRUCTURE OF A NOVEL SPIROOXAZINE

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DURING the course of a study on the total synthesis of aza-steroids, an unusual ring closure reaction was observed when α-(3-cyclopentenyl)tert-butanol (b.p. 74° (6mm); n_D^{30}, 1.4645) was heated with an excess of acetonitrile in cold concentrated sulfuric acid. The product, 2,4,4-trimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (I) was formed in 63% yield, b.p., 77-79° (4mm); n_D^{30}, 1.4694; $\lambda_{max}^{CCl_4}$ 6.01 (C=N). Found for $C_{11}H_{19}ON$: C, 73.12; H, 10.34; N, 7.75; picrate (EtOH), 154-155°; hydrobromide (EtOH-EtOAc), 173-175°. The use of α-(1-cyclopentenyl) t-butanol in place of the 3-substituted olefin gave the same product in somewhat lower yield (51%). This novel ring closure represents a further example of the nitrile-tertiary alcohol condensation which has, to date, led to a variety of heterocyclic systems.[1-5]

On the basis of the accumulated data for the preparation of heterocycles via this technique, the mechanism of this oxazine formation may be formulated in the manner described in Fig. 1. It is evident from the reaction scheme

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[1] E.J. Tillmanns and J.J. Ritter, J.Org.Chem. 22, 839 (1957).

[2] A.I. Meyers and J.J. Ritter, J.Org.Chem. 23, 1918 (1958).

[3] A.I. Meyers, J.Org.Chem. 25, 147, 1147, 2133 (1960).

[4] A.I. Meyers and W.Y. Libano, J.Org.Chem. 26, 1682 (1961).

[5] A.I. Meyers and W.Y. Libano, J.Org.Chem. 26. In press. (1961).

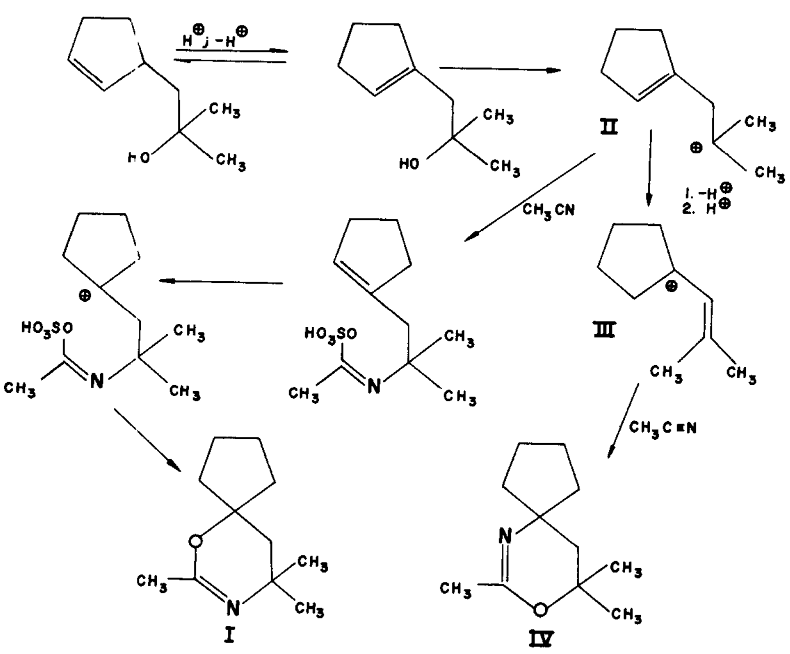

FIG. 1

that the simultaneous formation of the isomeric oxazine (IV) is possible through a rearrangement of the carbonium ion, II, to III. However, only a single product was obtained as indicated by vapor phase chromotography. That I was the product obtained in this reaction was supported by the sequence of reactions described in Fig. 2. Hydrolytic cleavage of the oxazine in 10% sodium hydroxide gave the hydroxyamide (V) as a viscous oil, $\lambda_{max}^{CCl_4}$ 2.76 (-OH), 2.91 (-NH), 5.89 (amide I), 6.61 (amide II). Found for $C_{11}H_2O_2N$: C, 70.12; H, 12.18; N, 7.90. Dehydration with iodine in benzene gave the unsaturated amide (VI) as a mixture of isomers, m.p. 84-92. Found for $C_{11}H_{19}ON$; C, 73.05; H, 10.41; N, 7.70. Reduction of the isomeric amides with rhodium-on-alumina at 3 atmospheres afforded the pure saturated amide (VII), m.p. 74-75°. Found for $C_{11}H_{21}ON$: C, 64.30; H, 11.12; N,

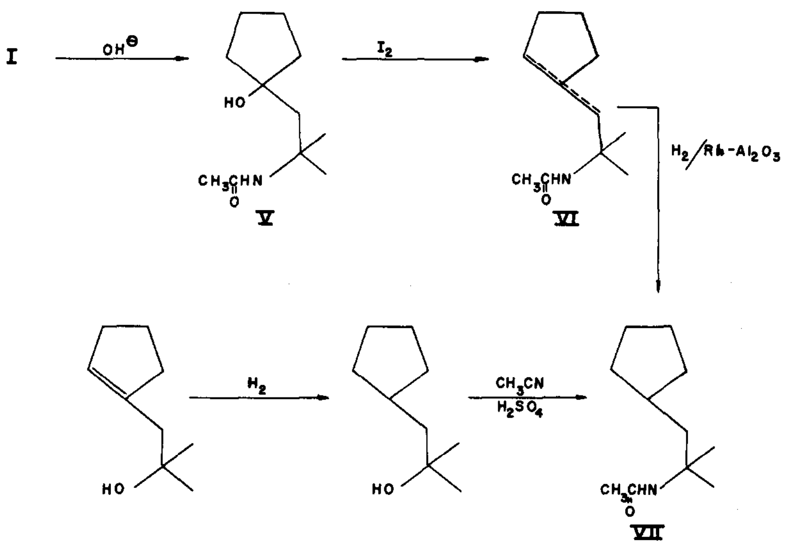

FIG. 2

7.40. This amide was alternately prepared via the Ritter reaction[6] from α-(cyclopentyl) t-butanol (b.p. 59-61 (0.5 mm); n_D^{30}, 1.4536) and acetonitrile in concentrated sulfuric acid. The amides obtained from both routes proved to be identical in every respect.

Although the degradative studies on the oxazine would, *a priori*, seem to eliminate the possibility of the product possessing structure IV, the results would prove to be inconclusive if a rearrangement occurred during the Ritter reaction preparation of VII through a bridged ion (VIII). The amide resulting from the rearranged carbonium ion (IX) would then support the structural assignment, IV. This possibility is not unlikely in view of the previous observation of a 1,3-hydride shift in norbornyl systems.[7]

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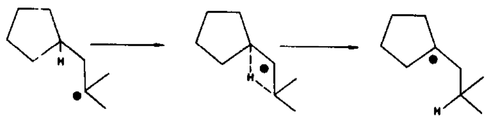
[6] J.J. Ritter and P.P. Minieri, J.Amer.Chem.Soc. 70, 4045, 4048 (1948).

[7] J.D. Roberts, C.C. Lee, and W.H. Saunders, J.Amer.Chem.Soc. 76, 4501 (1954).



VIII IX

FIG. 3

The structure of the oxazine was unambiguously confirmed as a result of a concurrent X-ray crystallographic study on the hydrobromide derivative. The lack of molecular parameters in the literature pertaining to a dihydro-1,3-oxazine system prompted this study by one of the authors (L.M.T.).

Suitable single crystals of the hydrobromide salt of the compound were grown from a solution of ethyl alcohol and ethyl acetate. Three-dimensional data were taken of the salt which was monoclinic, space group $P_{2_1/c}$ with four molecules per unit cell. The cell dimensions are $a=7.19_8$, $b=12.09_1$, $c=14.57_4$ Å and the monoclinic angle $\beta= 102^{\circ}10'$.

The heavy atom technique was used in determining the positions of the atoms. The bromine position was determined by vector-convergence maps of the three axial projections. The remaining atoms were found by Fourier methods utilizing the phases calculated from the bromine atom position.

The structure was refined isotropically by the least squares method utilizing the full matrix. The behavior of the temperature factors corroborated the differences in peak heights of the two heterocyclic atoms in the electron density maps and thus allowed the nitrogen and oxygen atoms to be unambiguously identified. The reliability index

$$R = \frac{\Sigma \big| |F_o| - |F_c| \big|}{\Sigma |F_o|}$$

was 0.118 for <u>all</u> of the observed data and $R_{hko} = 0.120$, $R_{okl} = 0.158$, $R_{hol} = 0.110$ for the three axial projections.

Although further anisotropic refinements (as indicated by the difference electron-density map) are planned, the structure (Ia) is essentially determined. The scope of this ring closure reaction as well as the completed X-ray study will be published separately at a later date.

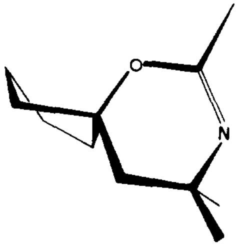


FIG. 4

Bond distances (Å)	Bond angles
$\overline{\mathrm{C{-}O}}$ $1.39 \pm .01_0$	$\underline{\angle \mathrm{CCC}}$ $107^\circ\ 30' + 3^\circ 30'$
$\overline{\mathrm{C{-}C}}$ $1.56 \pm .04_5$	$\underline{\angle \mathrm{COC}}$ 115°
$\overline{\mathrm{C{-}N}}$ 1.48_5	$\underline{\angle \mathrm{CNO}}$ 120°
$\overline{\mathrm{C{-}N}}$ 1.38_7	$\underline{\angle \mathrm{CNC}}$ 121°
$-NH^+ \ldots\ldots Br^-$ 3.24	

The bond lengths and bond angles are tabulated below with their average deviations as indicated. The bond distances and bond angles (except the C=N distance) correlate rather well with the predicted values,[8] with the angles very nicely corroborating the sp^3 hybridization for the carbon atoms

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[8] L. Pauling, <u>Nature of the Chemical Bond</u> Cornell University Press (1960).

[9] L. Merritt and E. Lanterman, <u>Acta Cryst.</u> <u>5</u>, 811 (1952).

[10] B. Penfold, <u>Acta Cryst.</u> <u>6</u>, 591 (1953).

(107° 30 ± 3° 30') and the sp^2 hybridization about the nitrogen atom (120° 30' ± 3°). The C=N distance is quite long at 1.38_7 Å as compared to the open chain C=N distance of 1.27 Å in dimethylglyoxime[9] and somewhat longer than the carbon nitrogen distance of 1.33_5 Å in a conjugated ring system such as 2-pyridone.[10] No heterocyclic C=N distances in unconjugated systems were found in the literature. Consequently, the anisotropic refinements will be of interest in indicating how statistically significant this variation will be.

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