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RE-ARRANGEMENTS OF ISOXAZOLIUM SALTS. THE CONVERSION OF AN ISOXAZOLO[2,3-a]PYRIDINIUM SALT INTO A REDUCED FURO[3,2-b]PYRIDONE

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Isoxazoles and isoxazolium salts undergo a number of useful fragmentations; they have been intermediates in annelation[1] and in peptide synthesis.[2] We are investigating a series of isoxazolium salts, such as (1), in which the normal mode of fragmentation is suppressed; we have reported[3] that the isoxazolo[2,3-a]pyridinium salt (1) can be aromatised by a bromination-dehydrobromination sequence to give compound (2).

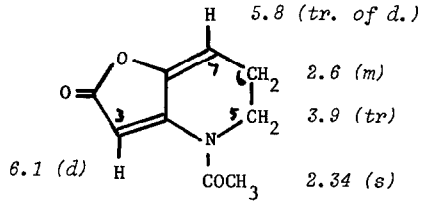
(1) $R^1 = R^2 = H$

(7) $R^1 = Me$, $R^2 = H$

(8) $R^1 = H$, $R^2 = Me$

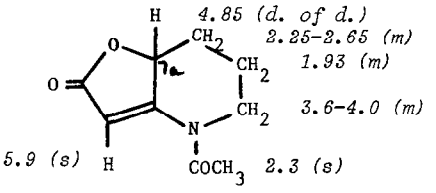
(2) $R^1 = R^2 = H$

An attempt to aromatise the salt (1) by the use of boiling acetic anhydride[4] led to rapid re-arrangement (2 min. optimum) giving a compound, $C_9H_9NO_3$, m.p. 110-112° (47%); the physical and chemical properties of this compound, in particular a single crystal X-ray structure analysis, show that it results from a novel cleavage of the isoxazole ring, followed by re-cyclisation to give the furopyridone derivative (3).



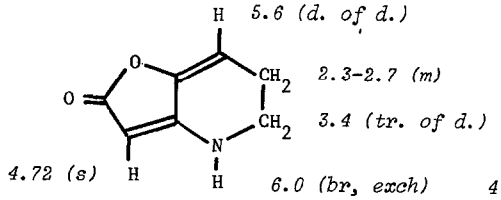
(3)

$J_{3,7}$ 1; $J_{5,6}$ 6; $J_{6,7}$ 5 Hz



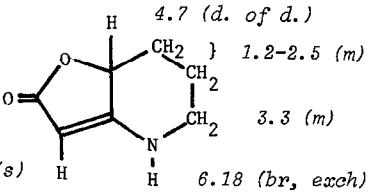
(4)

$J_{7,7a}$ 6 and 1 Hz



(5)

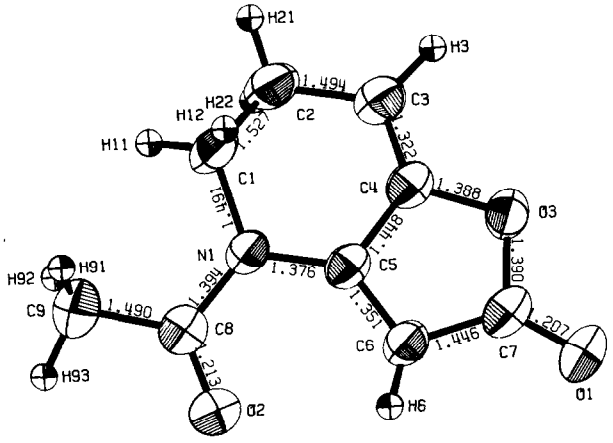
$J_{3,7}$ 1 Hz



(6)

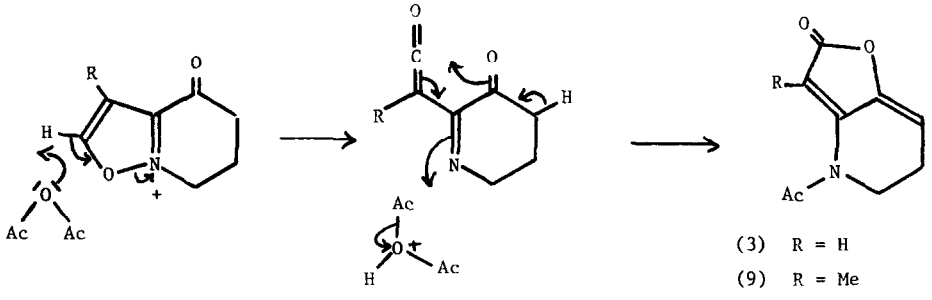
N.m.r. shifts in δ (p.p.m. from TMS)

The compound (3) had $\nu_{max.}$ ($CHCl_3$) 1778, 1684 and 1590 cm^{-1}, $\lambda_{max.}$ (EtOH) 276 nm (log ε 4.24); the n.m.r. data for compounds (3) - (6) are shown with the structures. Reduction of compound (3) with a palladium catalyst gave a dihydro-derivative (4), m.p. 99-100°, $\nu_{max.}$ ($CHCl_3$) 1740, 1687, and 1610 cm^{-1}, $\lambda_{max.}$ (EtOH) 264 nm (log ε 4.18). The most striking property of the re-arrangement product (3) was an instantaneous, irreversible change in the ultraviolet absorption on addition of dilute alkali; the isolated hydrolysis product (5) m.p. 110-111°, lacked the acetyl group, and had $\nu_{max.}$ ($CHCl_3$) 3420, 1750, and 1620 cm^{-1}, $\lambda_{max.}$ (EtOH) 260, 312 (log ε 3.82, 4.03). A similar hydrolysis of the dihydro-derivative (4) gave the de-acetylated compound (6), m.p. 119-120°, $\nu_{max.}$ ($CHCl_3$) 3395, 1720, and 1625 cm^{-1}. Vigorous reduction of the hydrolysis products (5) or (6) (PtO_2 and ethanol with added base) gave piperidine-2-acetic acid identified by comparison of the picrate of its ethyl ester with a synthetic specimen.[5] Only a few structures accord with this evidence; a single crystal structure analysis of crystals of the re-arrangement product (3) unambiguously established its structure. A view of the molecule showing bond distances and the conformation is in the Figure.



FIGURE

We suggest that the re-arrangement proceeds by abstraction of the hydrogen atom at position 2 in the isoxazolopyridinium salt (1) forming a ketene which cyclises as shown in the SCHEME. This suggestion is supported by the observation that the 2-methyl derivative (7) fails to undergo the re-arrangement, although the 3-methyl derivative (8) does, giving the substituted furopyridone (9).



SCHEME

Crystals of compound (3) are monoclinic, space group $P2_1/n$ with 4 molecules in a unit cell of dimensions $\underline{a}$ = 7.476, $\underline{b}$ = 6.853, $\underline{c}$ = 16.363 Å, β = 91.81°. Some 850 independent observed structure amplitudes were obtained with a Hilger and Watts computer controlled four circle diffractometer. The structure was solved by "direct methods" procedures and refined by full-matrix least squares methods. All hydrogen

atoms were located and R at the conclusion of refinement is 4.3%.

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