Syntheses with Isoxazoles. Part III.[1] Rearrangement of 4,5,6,7-Tetrahydro-4-hydroxyiminoisoxazolo[2,3-*a*]pyridinium Salts into Derivatives of Pyrrolo[3,2-*b*]pyridin-2-one

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When 4,5,6,7-tetrahydro-4-hydroxyiminoisoxazolo[2,3-*a*]pyridinium chloride (5) or bromide (6) was heated with acetic anhydride, rearrangement to the corresponding 4-acetyl-7-halogeno-5,6-dihydro-4H-pyrrolo[3,2-*b*]-pyridin-2(1*H*)-one (9) or (8) occurred. The bromo-derivative (8) was hydrogenated to give a debrominated dihydro-derivative (10), and hydrolysed to the deacetylated derivative (11). Mechanisms for the rearrangement are suggested.

WE have reported[1,2] that brief treatment of the isoxazolo[2,3-*a*]pyridinium salts (1) and (2) with boiling acetic anhydride gave the furo[3,2-*b*]pyridin-2-ones (3) and (4). We report here a similar rearrangement of the oxime of compound (1) into pyrrolo[3,2-*b*]pyridin-2-ones.

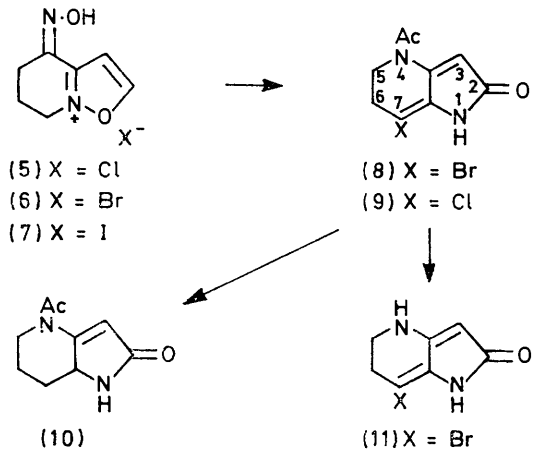
(1) $R^1 = R^2 = H$
(2) $R^1 = H, R^2 = Me$

(3) $R^1 = H$
(4) $R^1 = Me$

The ketone (1) reacted with a solution of hydroxylamine in absolute ethanol to give a crude oxime mixture; passage of the mixture through Amberlite columns loaded with the appropriate ion gave pure samples of the oxime chloride (5), bromide (6), and iodide (7). A similar oxime[3,4] undergoes Wolff aromatisation to give the acetylated aromatic amine when heated with acetic anhydride (with or without added hydrogen halide). Brief treatment of the oxime bromide (6) with boiling acetic anhydride gave a major product which was non-ionic; the analytical figures and spectral data (see later) indicated the formula $C_9H_9BrN_2O_2$. A comparison of the properties and the spectral data for this compound with those of the furo[3,2-*b*]pyridin-2-one (3) leaves no doubt that the former is a derivative of pyrrolo[3,2-*b*]-pyridin-2-one, of formula (8); the chloride (5) similarly gave compound (9), but the iodide (7) gave only decomposition products on heating with acetic anhydride.

The pyrrolopyridinone (8) showed i.r. maxima at 3430, 1690, and 1590 cm^{-1}, and a u.v. maximum at 291·5 nm [comparable figures for compound (3) are 1778 and 1684 cm^{-1} and 264 nm]. The n.m.r. spectrum of compound (8) established that the bromine atom was at position 7. The signals for the methylene groups at positions 5 and 6 were simple triplets (δ 3·98 and 2·82) and that for the acetyl methyl group was a singlet at δ 2·31. A comparison with the spectrum of compound (3) showed that both compounds gave an alkene proton signal near δ 6·0 but that compound (3) showed a second alkene signal at δ 5·8. The small coupling between H-3 and H-7, present in compound (3) but absent in compound (8) confirmed the presence of a 7-substituent in the latter.

Reduction of compound (8) over palladium–charcoal led to the uptake of 2 mol. equiv. of hydrogen, with no perceptible break, the product being the debrominated dihydro-compound (10). The spectral data were similar to those of the dihydro-derivative of compound (3). Addition of a drop of base to an ethanolic solution of the pyrrolopyridinone (8) produced an instantaneous, irreversible change in the u.v. absorption with the develop-



(5) X = Cl
(6) X = Br
(7) X = I

(8) X = Br
(9) X = Cl

(10)

(11) X = Br

[1] Part II, R. H. Good, G. Jones, and J. R. Phipps, *J.C.S. Perkin I*, 1972, 2441.
[2] R. H. Good, G. Jones, J. R. Phipps, G. Ferguson, and W. C. Marsh, *Tetrahedron Letters*, 1972, 609.
[3] A. R. Collicutt and G. Jones, *J. Chem. Soc.*, 1960, 4101.
[4] A. Fozard and G. Jones, *J. Chem. Soc.*, 1964, 2763.

ment of a long-wavelength band (345 nm). The hydrolysis product was isolated and shown to be the deacetylated enamide (11), which was also obtained in a reductive cleavage of compound (8) with sodium in ethanol. Compound (11) showed a broad n.m.r. absorption at δ 9·6, with further signals at δ 4·2 (3H) and 3·3 (2H). A number of attempts to remove the bromine atom from compound (8) reductively, notably with tri-n-butyltin hydride, were unsuccessful. Attempts to interconvert the furopyridine with the pyrrolopyridine series, by treatment of compound (3) with boiling aniline, were unsuccessful.

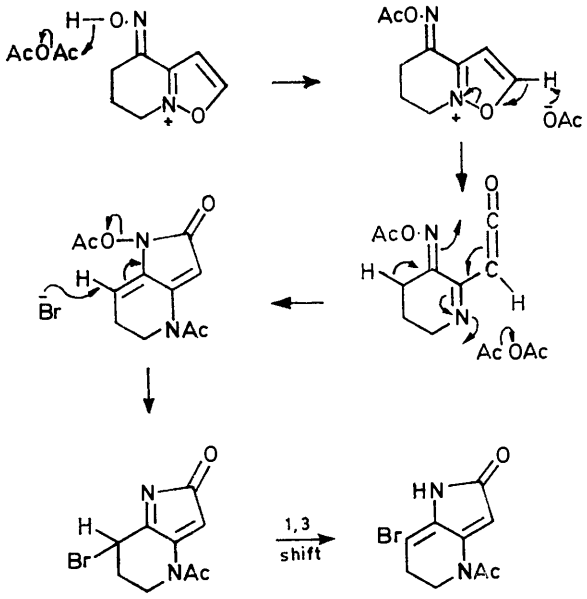
We have suggested [1] that conversion of the isoxazolopyridinium salt (1) into the furopyridinone (3) proceeds by abstraction of H-2 and cyclisation of the keten intermediate so obtained. A similar route (Scheme 1) could account for the corresponding reaction of the oxime. An alternative mechanism (Scheme 2), also applicable to the conversion (1) ⟶ (3), involves a mixed anhydride (12). We have no evidence which distinguishes between these routes. The similarity of the yields of compounds (8) and (9) indicates that the nucleophilicity of the counter-ion has no effect on the yield and that the nucleophilic attack cannot be rate-determining.

EXPERIMENTAL

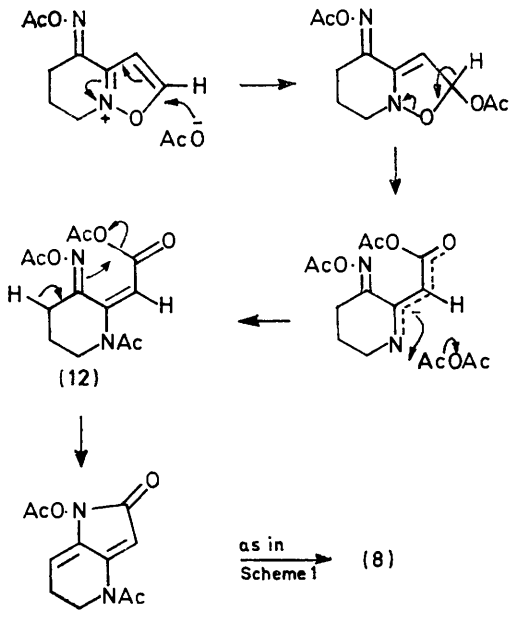
M.p.s were determined on a Kofler hot-stage apparatus. Thick-layer chromatography was carried out on 40 cm plates coated with Merck silica gel PF_{254}; alumina chromatography was performed on Woelm alumina (activity indicated).

4,5,6,7-Tetrahydro-4-hydroxyiminoisoxazolo[2,3-a]*pyridinium Salts*.—Solutions of hydroxylamine hydrochloride (3 g) and sodium acetate (3 g) in absolute ethanol were mixed and cooled, and sodium chloride was filtered off. The salt (1; X = Br) (3 g) was added and the solution was boiled (0·5 h), evaporated to small volume, and cooled. The precipitated salt was filtered off, dissolved in ethanol, and passed through an Amberlite IRA400 column loaded with the appropriate anion; evaporation of the eluate gave the corresponding salt, which was recrystallised from ethanol. The *oxime chloride* (5) had m.p. >300° (Found: C, 43·4; H, 4·9; N, 14·3. $3C_7H_9ClN_2O_2,H_2O$ requires C, 43·2; H, 5·0; N, 14·4%). The *oxime bromide* (6) had m.p. >300° (Found: C, 36·2; H, 4·3; N, 12·0. $C_7H_9BrN_2O_2$ requires C, 36·1; H, 3·9; N, 12·0%). The *oxime iodide* (7) had m.p. 199—200° (Found: C, 30·6; H, 3·3; N, 9·5. $C_7H_9IN_2O_2$ requires C, 30·0; H, 3·2; N, 10·0%).

4-Acetyl-7-halogeno-5,6-dihydropyrrolo[3,2-b]*pyridin-2(1H)-ones* (8) *and* (9).—A suspension of the oxime halide (5) or (6) was heated in 10—20 times the weight of acetic anhydride just to the b.p.; the mixture was then cooled and evaporated under reduced pressure. The residue was dissolved in absolute ethanol and the solution was evaporated; the product was chromatographed on alumina in benzene. Recrystallisation of the eluted material from benzene gave *4-acetyl-7-bromo-5,6-dihydropyrrolo*[3,2-b]*pyridin-2(1H)-one* (8), m.p. 188—193° (decomp.) (33·6%) (Found: C, 42·2; H, 3·5; N, 10·7. $C_9H_9BrN_2O_2$ requires C, 42·0; H, 3·5; N, 10·9%), $\lambda_{max.}$ (EtOH) 291·5 nm (log ε 4·28); $\nu_{max.}$ ($CHCl_3$) 3430, 1690, and 1590 cm^{-1}; δ ($CDCl_3$) 2·31 (3H, s), 2·82 (2H, t), 3·98 (2H, t), 6·0br (1H, s), and 8·6br (1H, exchangeable with D_2O). *4-Acetyl-7-chloro-5,6-dihydro-4H-pyrrolo*[3,2-b]*pyridin-2(1H)-one* (9) (33%), had m.p. 215—217° (decomp.) (Found: C, 50·8; H, 4·4; N, 13·0. $C_9H_9ClN_2O_2$ requires C, 50·8; H, 4·3; N, 13·2%), $\lambda_{max.}$ (EtOH) 290 nm (log ε 4·1); $\nu_{max.}$ (Nujol) 3190, 1670, and



SCHEME 1



SCHEME 2

1575 cm^{-1}; δ ($CDCl_3$) 2·35 (3H, s), 2·75 (2H, t), 4·0 (2H, t), 6·0br (1H, s), and 8·4br (1H, exchangeable with D_2O).

4-Acetyl-5,6,7,7a-tetrahydro-4H-pyrrolo[3,2-b]*pyridin-2(1H)-one* (10).—A solution of the bromopyrrolopyridinone (8) (1 g) in 95% ethanol (100 ml) containing palladium–charcoal, was hydrogenated until no more hydrogen was absorbed at ambient temperature and pressure (2 mol. equiv.). The solution was filtered and evaporated, and the

residue crystallised from benzene to give the *tetrahydropyrrolopyridinone* (10), m.p. 182—184° (0·65 g, 93%) (Found: C, 59·7; H, 6·8; N, 15·4. $C_9H_{12}NO_4$ requires C, 60·0; H, 6·7; N, 15·6%), $\lambda_{max.}$ (EtOH) 234 and 266 nm (log ε 3·87 and 3·94); $\nu_{max.}$ (Nujol) 3200, 1680, and 1625 cm^{-1}, δ ($CF_3 \cdot CO_2H$) 1·5—3·0 (3H, m), 2·5 (3H, s), 4·0 (2H, t), 4·5—4·9 (1H, m), and 6·7 (1H, s).

5,6-*Dihydro*-4H-*pyrrolo*[3,2-b]*pyridin*-2(1H)-*one* (11).—Dilute sodium hydroxide solution was added to a solution of the bromo-compound (8) (0·5 g) in 95% ethanol (100 ml). When hydrolysis was complete (t.l.c. and u.v.) the solution was neutralised with hydrochloric acid, and evaporated. The solid residue was extracted with chloroform; the solution was filtered and evaporated. Crystallisation of the residue from methanol gave the *dihydropyrrolopyridinone* (11), m.p. >300° (0·17 g, 40%), which proved too unstable for satisfactory analysis (Found: M^+, 213·9744. $C_7H_7{}^{79}BrN_2O$ requires M, 213·9742); $\lambda_{max.}$ (EtOH) 283·5 and 345 nm (log ε 4·03 and 3·54); $\nu_{max.}$ (Nujol) 3170, 1660, and 1610 cm^{-1}; δ ($CF_3 \cdot CO_2H$) 3·3 (2H, m), 4·2 (3H, m), and 9·6br (1H).

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