Syntheses with Isoxazoles. Part IV.[1] Ring-opening Reactions of 4,5,6,7-Tetrahydro-4-oxoisoxazolo[2,3-*a*]pyridinium Salts and Related Compounds under the Influence of Tertiary Amines

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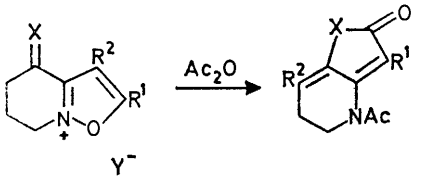
On treatment of the 4,5,6,7-tetrahydro-4-oxoisoxazolo[2,3-*a*]pyridinium salts (1) and (3) with triethylamine in methanol, methyl 4-(2-formyl-1-methoxyvinylamino)butyrate (7) and its homologue (9), respectively, are formed. The oxime (13) and the phenylhydrazone (14), under similar conditions, give the methyl piperidin-2-ylideneacetates (16) and (17). The mechanisms of the ring-opening reactions are discussed. Compound (7) is converted spontaneously into *N*-(*trans*-3-methoxyacryloyl)-2-pyrrolidone (12), which has been synthesised.

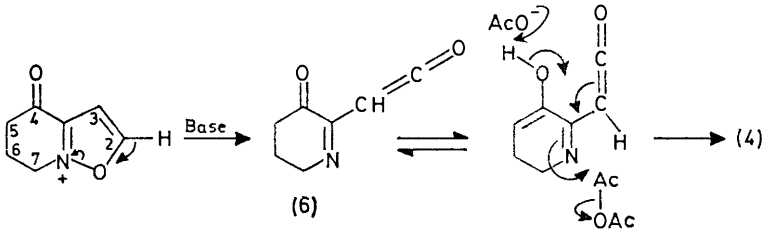
WE have reported [1-3] that the isoxazolopyridinium salts (1) and (2), treated with boiling acetic anhydride for a few minutes, are converted into the reduced furopyridinones (4) and (5); pyrrolopyridinones were similarly



(1) $R^1 = R^2 = H, X = O, Y = Br$ (4) $R^1 = R^2 = H, X = O$
(2) $R^1 = H, R^2 = Me, X = O, Y = Br$ (5) $R^1 = Me, R^2 = H, X = O$
(3) $R^1 = Me, R^2 = H, X = O, Y = Br$

formed from the oximes (X = NOH). The failure of the isoxazolopyridinium salt (3) to undergo a similar reaction we have ascribed to the absence of a hydrogen atom at position 2, essential to the conversion in either of the mechanisms which we have suggested. Since analogies exist for both mechanisms among the reactions of isoxazolium salts, we have attempted to form and trap the keten intermediate (6) required by Scheme 1, and thus establish the reaction pathway.

In our first attempts, the salts (1) and (3) were treated with triethylamine in boiling methanol. Surprisingly, both salts gave non-quaternary products in satisfactory yields, but the spectral data left little doubt that a more drastic change had occurred than had been observed in the acetic anhydride reaction. The compound from the salt (1) showed in the ^{1}H n.m.r. spectrum a pair of widely spaced doublets (both 1 H, J 4.0 Hz) at δ 8.85 and 4.55, whereas that from the salt (3) showed no signal near δ 8.85, but a singlet (1 H) at δ 4.7. The product from the salt (1) showed two 3 H singlets at δ 3.60 and 3.75 assigned to methyl ester (or vinylogous ester) groups,



SCHEME 1

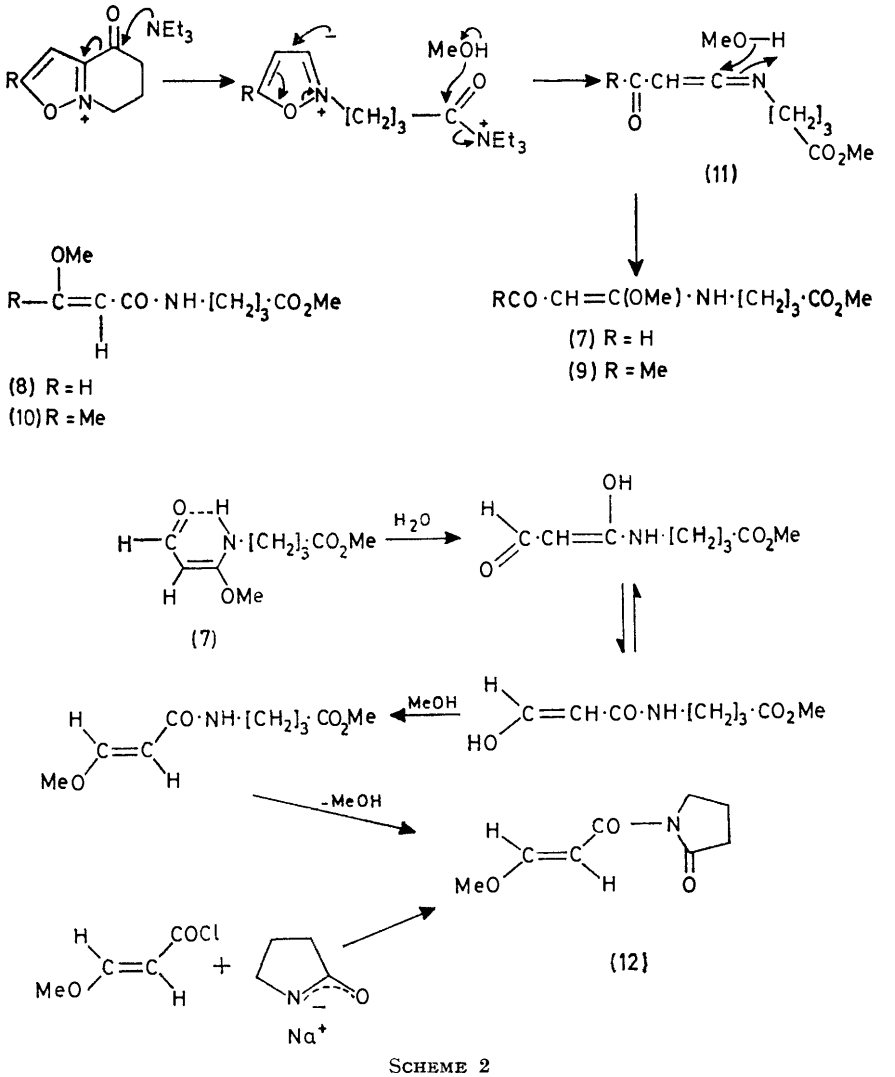
and the rest of the spectrum showed a broad NH absorption (vinylogous amide) at δ 10.5 and a trimethylene grouping. The spectrum of the product from the salt

[1] Part III, G. Jones and J. R. Phipps, *J.C.S. Perkin I*, 1974, 158.

[2] R. H. Good, G. Jones, J. R. Phipps, G. Ferguson, and W. C. Marsh, *Tetrahedron Letters*, 1972, 609.

[3] R. H. Good, G. Jones, and J. R. Phipps, *J.C.S. Perkin I*, 1972, 2441.

(3) was very similar; two satisfactory formulae can be written for each product: (7) and (8), and (9) and (10), respectively. The i.r. and u.v. absorptions agree equally well with either; thus $\nu_{max.}$ at 1 575 and 1 625 cm^{-1} and $\lambda_{max.}$ at 289.5 nm (log ε 5.3) are comparable to those reported for enamino-ketones [$\nu_{max.}$ 1 575 and 1 635 cm^{-1}, $\lambda_{max.}$ 278 (4.12)].[4] The ^{13}C n.m.r. spectrum showed three signals, at 183.9, 173.5, and 169 p.p.m. (from Me_4Si), in the low-field region expected for carbonyl carbon atoms, the signal at lowest field being shown by



SCHEME 2

off-resonance decoupling to be due to a formyl group. The small coupling constant between the low-field signals in the ^1H n.m.r. spectrum, combined with the observation that the ^{13}C n.m.r. signal at lowest field is due to a formyl group, led us to prefer formulae (7) and (9) for the two products, and a synthesis of compound (12) (see below) confirmed this preference. A satisfactory mechanism for the formation of the enamino-aldehyde (7) and the enamino-ketone (9) can be envisaged by consideration of the base-catalysed elimination of 3-acyl substituents from isoxazolium salts. The intermediate ketenimine (11) is then analogous to that involved in the Mumm–Woodward–Olofson synthesis of peptides.[5]

Compound (7) proved unstable to strong bases and to acid. The liquid compound (7) [but not compound (9)] showed signs of slow crystallisation. A crystalline compound was isolated in 20—30% yield and shown by analysis and mass spectral data to have been formed by elimination of methanol. The lowest field signal (1 H) in the ^1H n.m.r. spectrum of the new compound was at δ 7.98, and showed a coupling to a signal at δ 5.12 (14 Hz); the i.r. absorptions in the carbonyl region were at 1 724, 1 690, and 1 620 cm^{-1}. A ^{13}C n.m.r. spectrum showed two similar carbonyl carbon absorptions at 174.3 and

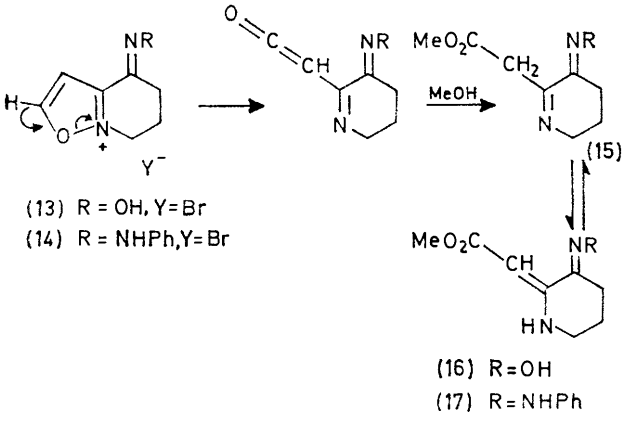
[4] E. J. Cone, R. H. Gamer, and A. W. Hayes, *J. Org. Chem.*, 1972, **37**, 4436.

[5] R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, 1961, **83**, 1007.

167.6 p.p.m., two widely separated alkene carbon absorptions at 100.2 and 137.5 p.p.m., a methoxy-group and three saturated methylene groups.

These data agree with only one reasonable formula, (12), and this was confirmed by synthesis from the sodium salt of 2-pyrrolidone and *trans*-3-methoxyacryloyl chloride. The transformation of compound (7) into compound (12) is formally similar to that observed in the peptide synthesis [5] with the important difference that an alkyl rather than acyl group is migrating. We suppose that hydrolysis of the methoxy-group in compound (7) is followed by methylation of the terminal carbonyl group and cyclisation of the γ-aminobutyrate ester to give the pyrrolidone, but we have not been able to confirm any of these stages, nor, as yet, to accelerate the transformation (Scheme 2). A referee has suggested that a 1,5 methyl shift is possible, but not probable, in the light of the preferred H-bonded stereochemistry of compound (7), as shown in Scheme 2.

Our first attempts to obtain a keten intermediate were thus frustrated by the highly electrophilic carbon atom at position 4 of the original isoxazolopyridinium salt (1). The electrophilic activity of this carbon atom was expected to be much less in the corresponding oxime or hydrazone. We have already reported [1] the preparation of an oxime (13) from compound (1), and we have now prepared a phenylhydrazone (14). When the oxime (13)



SCHEME 3

was treated with triethylamine in boiling methanol a compound was obtained whose spectral characteristics were those expected for the tetrahydropyridine (16). The presence of a methyl ester was shown by carbonyl absorption ($\nu_{max.}$ 1 640 cm^{-1}; enamino-ester) and by a 3 H ^1H n.m.r. singlet at δ 3.6. A sharp singlet (1 H) at δ 5.18 (=CH) and broad singlets at δ 8.8 and 9.3 were all removed in D_2O. The exchange of the alkene proton provides evidence for the tautomeric equilibrium (15) ⇄ (16), shown in Scheme 3. The product (17) obtained after treatment of the phenylhydrazone (14) with triethylamine in boiling methanol showed similar characteristics; a singlet due to an exchangeable proton at δ 5.42, and two broad NH signals at δ 7.55 and 8.95 (tentatively assigned to the phenylhydrazone NH and to H-1, by comparison with similar systems [6]). We feel that the isolation of these two products confirms the intermediacy of a keten in the opening of the isoxazole ring. When the ring opening reagent is acetic anhydride, the acetylation of the piperidine nitrogen atom increases the electron deficiency at the keten carbon atom and possibly enhances also the contribution from 'enol' tautomers which can cyclise to give the lactone or pyrrolidone ring.

[6] G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, 1963, **85**, 3624 give δ 6.8 for acetophenone phenylhydrazone.

EXPERIMENTAL

I.r. spectra were measured on a Perkin-Elmer 257 spectrometer and ^1H n.m.r. spectra on a Perkin-Elmer–Hitachi R24 instrument; ^{13}C n.m.r. spectra were determined by JEOL (U.K.) Ltd., with an FT-60 spectrometer. M.p.s were determined on a Kofler hot-stage apparatus. Column chromatography was performed on Woelm alumina, activity 4.

Methyl 4-(2-*Formyl*-1-*methoxyvinylamino*)*butyrate* (7).—The isoxazolium bromide (1) (1 g) was dissolved in boiling methanol (30 ml) and triethylamine (1.5 ml, *ca.* 2 equiv.) was added. After further boiling (3—5 min) the solvent was removed under reduced pressure and the residue extracted with dry acetone (5 ml) and filtered from precipitated triethylamine hydrobromide. Evaporation of the filtrate gave an oil which was adsorbed on alumina and eluted with chloroform. The first band eluted (pale yellow) was almost pure *ester* (7) (0.51 g, 56%). The ester could be further purified by preparative layer chromatography, but gave inconsistent analyses (Found: M^+, 201.1003. $C_9H_{15}NO_4$ requires M, 201.1001), $\lambda_{max.}$ 292 nm (log ε 4.31), $\nu_{max.}$ (film) 1 739, 1 625, and 1 575 cm^{-1}, $\delta_H(CCl_4)$ 1.9 (2 H, q), 2.28 (2 H, m), 3.30 (2 H, q), 3.60 (3 H, s), 4.55 (1 H, d, J 4 Hz), 8.85 (1 H, d, J 4 Hz), and 10.5br (1 H), $\delta_C(CDCl_3)$ 25.29, 31.15, 39.28, 51.64, 56.03, 78.0, 169.15, 173.47, and 183.88.

Methyl 4-(1-*Methoxy*-3-*oxobut*-1-*enylamino*)*butyrate* (9).—Prepared in 67% yield as described for compound (7), from the isoxazolium salt (3), the *ester* (9) had b.p. 100—115° at 0.1 mmHg (bulb-tube) (Found: C, 55.5; H, 7.7; N, 6.4. $C_{10}H_{17}NO_4$ requires C, 55.8; H, 7.95; N, 6.5%), $\lambda_{max.}$ 289.5 nm (log ε 5.3), $\nu_{max.}$ (film) 1 735 and 1 625 cm^{-1}, $\delta_H(CDCl_3)$ 1.9 (2 H, m), 2.02 (3 H, s), 2.3 (2 H, m), 3.3 (2 H, q), 3.65 (3 H, s), 3.75 (3 H, s), 4.72 (1 H, s), and 10.75br (1 H), *m/e* 215 (M^+), 200, 172, 142, 128, 116, 101, 99, and 59.

N-(trans-3-*Methoxyacryloyl*)*pyrrolidin*-2-*one* (12).—(*a*) The ester (7), kept (>4 weeks) in the dark, gave a mixture; the *pyrrolodinone* (12), isolated by p.l.c., had m.p. 78—78.5° [from petroleum (b.p. 40—60°)] (Found: C, 57.0; H, 6.7; N, 8.45. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.55; N, 8.3%), $\lambda_{max.}$ 271 nm (log ε 4.34), $\nu_{max.}$ (Nujol) 1 724, 1 690, and 1 620 cm^{-1}, $\delta_H(CDCl_3)$ 2.32 (4 H, m), 3.5 (2 H, t), 3.67 (3 H, s), 5.12 (1 H, d, J 14 Hz), and 7.98 (1 H, d, J 14 Hz), $\delta_C(CDCl_3)$ 17.46 (t), 30.94 (t), 44.99 (t), 51.41 (q), 100.22 (d), 137.5 (d), 167.63 (s), and 174.3 (s) (off-resonance decoupled multiplicity in parentheses), *m/e* 169 (M^+), 138, 110, 82, and 41.

(*b*) A solution of 2-pyrrolidone (4.3 g) in benzene (100 ml) with sodium hydride (50% dispersion; 2.4 g) was boiled

(2 h). To the cooled mixture was added, dropwise, *trans*-3-methoxyacryloyl chloride [7] [5.5 g; prepared from *trans*-3-methoxyacrylic acid [8,9] and thionyl chloride in boiling ether; b.p. 77—79° (20 mmHg)]. The mixture was stirred at room temperature (2.5 days), treated with ice–water, and filtered, and the benzene layer was separated, dried, and evaporated. Chromatography on alumina (elution with benzene) gave first an unidentified methoxyacryloyl compound, and secondly the pyrrolidinone (12), identical with that obtained as in (*a*).

Methyl (3-*Hydroxyiminopiperidin*-2-*ylidene*)*acetate* (16).—To the oxime bromide [1] (13) (0.5 g) in hot methanol (30 ml; dry) was added triethylamine (0.7 ml). The solution was allowed to cool to room temperature (*ca.* 0.5 h), then evaporated under reduced pressure, and the residue was treated with chloroform and filtered from triethylamine hydrobromide. The chloroform extract was evaporated on to alumina, and the coated alumina was added to a column. Elution with benzene gave the *piperidinylideneacetate* (16), m.p. 138.5—139.5° (0.2 g, 52%) (Found: C, 51.6; H, 6.45; N, 14.7. $C_8H_{12}N_2O_3$ requires C, 52.15; H, 6.55; N, 15.2%), $\lambda_{max.}$ 230 and 338 nm (log ε 5.15 and 4.90), $\nu_{max.}$ (Nujol) 3 290, 3 220, 1 640, 1 610, and 1 570 cm^{-1}, $\delta_H(CDCl_3)$ 1.9 (2 H, m), 2.7 (2 H, t) 3.3 (2 H, m), 3.6 (3 H, s), 5.18 (1 H, s exch.), 8.8br (1 H, exch.), and 9.3br (1 H, exch.).

4,5,6,7-*Tetrahydro*-4-*oxoisoxazolo*[2,3-a]*pyridinium Bromide Phenylhydrazone* (14).—A solution of phenylhydrazine hydrochloride (0.36 g) in absolute ethanol (10 ml) was added to a solution of the isoxazolium bromide (1) (0.5 g), also in absolute ethanol (10 ml). The mixture was boiled (20 min) and evaporated; the residue was crystallised from ethanol, and the salt so obtained passed through a column of Amberlite IRA 400 resin (Br^-). The eluate was crystallised from ethanol to give the *phenylhydrazone bromide* (14), m.p. >300° (Found: C, 50.95; H, 4.6; N, 13.5. $C_{13}H_{14}BrN_3O$ requires C, 50.65; H, 4.6; N, 13.65%), $\lambda_{max.}$ 245, 300sh, and 380 nm (log ε 4.13—4.27), $\delta_H(CF_3{\cdot}CO_2H)$ 2.5 (2 H, m), 2.8 (2 H, m), 4.55 (2 H, t), 7.4 (6 H, m, Ph + isoxazolium H), and 8.52 (1 H, d, *J* 2 Hz).

Methyl (3-*Phenylhydrazinopiperidin*-2-*ylidene*)*acetate* (17).—The phenylhydrazone (14) (1 g) was treated as described for compound (13), and gave the *piperidinyl acetate* (17), m.p. 122—124° (0.05 g, 6%) (Found: C, 64.55; H, 6.55; N, 16.15. $C_{13}H_{17}N_3O_2$ requires C, 64.85; H, 6.6; N, 16.2%), $\nu_{max.}$ (film) 3 280, 1 620, and 1 595 cm^{-1}; $\lambda_{max.}$ 242, and 330 nm (log ε 4.15 and 4.22), $\delta_H(CDCl_3)$ 1.92 (2 H, m), 2.4 (2 H, m), 3.22 (2 H, m), 3.62 (3 H, s), 5.42 (1 H, s, exch.), 7.15 (5 H, m), 7.55br (1 H, exch.), and 8.95br (1 H, exch.), Other products were formed but were not characterised, decomposing during chromatography.

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[8] E. Winterfeld and H. Preuss, *Chem. Ber.*, 1966, **99**, 450.

[9] K. Bowden, *Canad. J. Chem.*, 1966, **44**, 661.