5-Oxazolonium Perchlorates from α-Acylamino-acids

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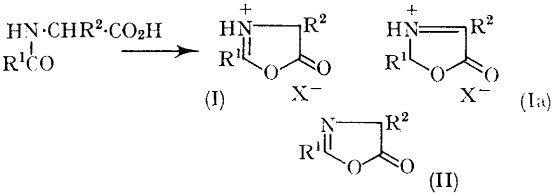
THE action of phosphorus halides on α-acylamino-acids[1] or of hydrogen halides on simple 5-oxazolones ("saturated azlactones")[2] results in the formation of highly reactive unstable compounds which have been extensively studied. The view[1] that they are 5-oxazolonium halides (I; X = Br or Cl) has been confirmed by cryoscopic measurements[3] and i.r. spectroscopy:[4] the presence of a strong absorption band near 1880 cm.$^{-1}$ is irreconcilable with the alternative acyl halide structure.

It has now been found that treatment of α-acylamino-acids with acetic anhydride and 70% perchloric acid at or below room temperature gives high yields of the corresponding 5-oxazolonium perchlorates:



(I) (Ia) (II)

Thus, hippuric acid affords the salt (I; R^1 = Ph, R^2 = H, X = ClO_4), 89%, m.p. 171° (decomp.)†

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† Satisfactory analytical and spectroscopic data have been obtained for all new compounds whose melting points are given.

ν_{max} 1880 cm.$^{-1}$, which is stable when kept dry. It rapidly reacts at room temperature with water, methanol, aniline, and sodium glycinate to yield, respectively, hippuric acid, methyl hippurate, hippuranilide, and benzoylglycylglycine. It is deprotonated by triethylamine with the formation of 2-phenyloxazol-5-one (II; R^1 = Ph, R^2 = H), from which perchloric acid regenerates the salt; cold aqueous sodium carbonate produces a mixture of the oxazolone and sodium hippurate. The latter does not arise from the azlactone since this is stable under these conditions. The perchlorate condenses with benzaldehyde in hot acetonitrile to yield the bright yellow benzylidene derivative (I; R^1 = Ph, R^2 = :CHPh, X = ClO_4), m.p. 198° (decomp.), which gives the labile geometrical isomer[5] of 4-benzylidene-2-phenyloxazol-5-one on treatment with water.

Cyclisation of *N*-benzoyl-L-phenylalanine gave the optically active salt (I; R^1 = Ph, R^2 = CH_2Ph, X = ClO_4), 76%, m.p. 132° (decomp.), i.r. 1880 cm.$^{-1}$, $[\alpha]_D^{25}$ − 37·8° (*c* 2·4, acetonitrile), from which the optically active oxazolone (II; R^1 = Ph, R^2 = CH_2Ph), $[\alpha]_D^{25}$ − 70·3° (*c* 0·37, dioxan) was obtained.‡ Water hydrolysed the salt to give the parent acid of 94% optical purity.

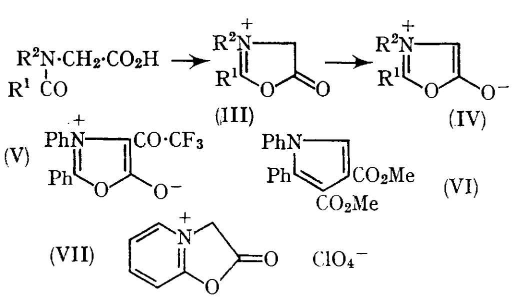
The formation of an optically active oxazolonium salt suggests strongly that these compounds exist in the Δ^2-form (I) rather than as the Δ^3-tautomers (Ia); conclusive evidence for structure (I) is provided by the n.m.r. spectra of the two salts: the first shows a methylene singlet at τ 4·98, and the second a methine triplet at 4·51 and a benzylic methylene doublet at 6·37. α-Acetaminophenylacetic acid was then used in the synthesis as it was thought that the 4-phenyl substituent might stabilise structure (Ia). However, the resulting oily perchlorate, i.r. 1885 cm.$^{-1}$, is clearly (I; R^1 = Me, R^2 = Ph, X = ClO_4) since its n.m.r. spectrum exhibits a methyl singlet (τ 7·30) and a methine doublet (due to coupling with N^+H) at 4·15.

N-Substituted oxazolonium salts have not been reported previously; the colourless hygroscopic perchlorates (III) are readily prepared from *N*-alkyl- and *N*-aryl-α-acylamino-acids:

N-*Substituted 5-oxazolonium perchlorates* (III)

Compound	R^1	R^2	Yield (%)	M.p. (decomp.)	ν_{max} (cm.$^{-1}$)	Chemical shift of CH_2-protons (τ) in $CF_3 \cdot CO_2H$
(a)	Ph	Ph	85	163°	1890	4·61
(b)	Ph	Me	82	167	1880	4·90
(c)	Me	Ph	90	143	1880	4·78
(d)	p-$NO_2 \cdot C_6H_4$	Ph	100	170	1887	5·01

Some of the salts are listed in the Table. They all show the characteristic high-frequency i.r. absorption, the appearance of methylene signals again confirms the Δ^2-structure (III). These salts are of current interest because they can be deprotonated to give mesoionic oxazolones, the "münchnones" (IV),[6] for which they are convenient precursors. The mesoionic compounds are too unstable to be isolated but their formation is manifest by the appearance of yellow or orange colours and they can be trapped by suitable reagents. Thus, when the diphenyl-compound (IIIa) is treated with triethylamine, or solid sodium carbonate, in the presence of trifluoroacetic anhydride the known[7] stable trifluoroacetyl-derivative (V) is obtained in 90% yield; dimethyl acetylenedicarboxylate yields the pyrrole (VI), 80%, m.p. 122·5°, by cycloaddition and subsequent loss of carbon dioxide,[6] and benzylamine gives the benzylamide of *N*-benzoyl-*N*-phenylglycine, 88%, m.p. 162°. The perchlorates (III) are instantly decomposed by cold water to the parent acylamino-acids without change of colour, but hydrolysis with aqueous sodium carbonate may proceed wholly or partly *via* the münchnones since transient colours are observed. *N*-*p*-Nitrobenzoyl-L-proline[8] yields an oily optically inactive perchlorate, i.r. 1890 cm.$^{-1}$, which gives the (±)-acid on treatment with water.



(III)

(IV)

(V)

(VI)

(VII)

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‡ The highest rotation recorded (M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, 1964, **86**, 2918.) for this azlactone is −71·2°.

The acetic anhydride–perchloric acid method when applied to 1-carboxymethyl-2-pyridone afforded the exceptionally stable condensed oxazolonium salt (VII), 94%, colourless prisms, m.p. 179° (decomp.), i.r. 1890 cm.$^{-1}$, CH_2-singlet at τ 4·35.

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