Synthesis of Chloroisoxazoline Amino-acids

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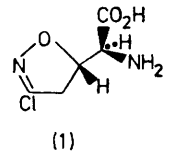
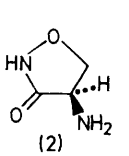
Summary The addition of chloronitrile oxide to the nitronate salts of $\alpha\beta$-unsaturated-α-nitrocrotonic esters yields the 3-chloroisoxazoline adducts, in an efficient reaction; further transformations convert these into the free amino-derivatives which are members of a class of biologically interesting amino-acids.

THE recent discovery of the unusual amino acid (**1**) as a fungal metabolite of *Streptomyces sviceus*, its antitumour activity, and the difficulty of obtaining it in quantity[1] led us to consider synthetic routes to this general class of compounds, which includes cycloserine (**2**)[2] and tricholomic acid (**3**).[3]

It seemed reasonable that (**1**) could be made by a 1,3-dipolar addition of chloronitrile oxide[4] to vinyl glycine,[5] as (**4**). As a test of this idea we showed that styrene added chloronitrile oxide, generated *in situ* from phosgene oxime, to give a poor yield (6%) of the adduct (**5**),† δ ($CDCl_3$) 3·2—3·9 (ABX, J 9 and 3 Hz, 2H), 5·7 (t, J 10 Hz, 1H) and 7·17 (s, 5H); ν_{max} 3200, 2950, and 1595 cm^{-1}; *m/e* 181 (M^+). However, chloronitrile oxide could not, in our hands, be added to vinyl glycine, as the zwitterion or as its ester and *N*-acyl derivatives; apparently the rate of the 1,3-dipolar reaction was too slow to compete with furoxan formation.



(1)



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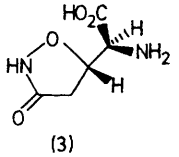

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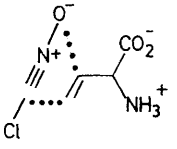

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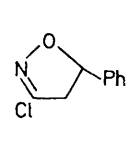
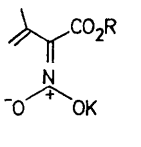
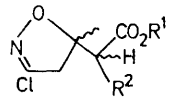


(5)



(6) R = Me
(7) R = CH_2CCl_3



(8), R^1 = Me, R^2 = NO_2
(9) R^1 = Me, R^2 = NH_2•$MeC_6H_4SO_3H$-*p*
(10) R^1 = CH_2CCl_3, R^2 = NO_2
(11) R^1 = H, R^2 = NH_2

In connection with our total stereocontrolled synthesis of penicillin,[6] we had prepared the nitronate salt (**6**), and it

† All new compounds have given adequate analytical and spectral data.

was found to add smoothly in aqueous solution to chloronitrile oxide to yield (99%) the adduct (**8**) as a mixture of diastereoisomers, δ ($CDCl_3$) 1·67, 1·72 (2× s, 3H total), 3·00, 3·20, 3·71, 3·91, 4·02 (2× AB q, *J* 17 Hz, 2H total, one peak obscured by the methyl ester), 3·84 (s, 3H total), 5·33, and 5·42 (2× s, 1H total); ν_{max} 2950, 1750, 1595, 1560, and 1340 cm^{-1}; *m/e* 237 (M^+).

Reduction of (**8**) with zinc amalgam in dioxan–HCl gave the amino-ester which was isolated as its toluene-*p*-sulphonic acid salt (**9**), m.p. 167—169 °C; δ (D_2O) 1·40, 1·53 (2× s, 3H total), 2·26 (s, 3H), 3·00, 3·32, 3·42, 3·54, 3·82 (AB q, *J* 18 Hz, 2H), 3·73, 3·77 (2× s, 3H total), 4·32, 4·42 (2 × s, 1H total) 7·17—8·0 (m, 4H); ν_{max} 1740 and 1601 cm^{-1}, which resisted all attempts at selective hydrolysis of the methyl ester. Repetition of this sequence with the trichloroethyl ester (**7**) gave (**10**), 85%; δ ($CDCl_3$) 1·75, 1·78 (2× s, 3H total), 3·0, 3·33, 3·7, 3·83, 4·0, 4·15 (2× ABq, *J* 17 Hz, 2H total), 4·9, 4·92 (2× s, 2H total), 5·58, and 5·62 (2× s, 1H total); ν_{max} 2950, 1760, 1560, 1440, and 1370 cm^{-1}.

Reduction of (**10**) with zinc in acetic acid at 0 °C gave in one step the diastereoisomeric mixture (**11**), δ (D_2O) 1·43 (s, 3H total), 2·83, 3·13, 3·16, 3·53, 3·55, 3·83, and 3·86 (2× AB q, *J* 17 Hz, 2H total); ν_{max} 3300, 2950, and 1720 cm^{-1}, chromatographed on Dowex 50×4 cation exchange resin (H^+ cycle). One of the isomers, of unknown relative configuration, was separated by crystallization from acetone, m.p. 228—230 °C; δ (D_2O) 1·43 (s, 3H), 2·83, 3·16, 3·55, and 3·86 (AB q, *J* 17 Hz, 2H), ν_{max} 3300, 2950, and 1720 cm^{-1}.

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[1] D. G. Martin, D. J. Duchamp, and C. G. Chidester, *Tetrahedron Letters*, 1973, **27**, 2549; D. A. Cooney, H. N. Jayaram, J. A. Ryan, and V. H. Bono, *Cancer Chem. Rep.*, 1974, **58**, 793.

[2] Pl. A. Plottner, A. Boller, H. Frick, A. Fürst, B. Hegedüs, H. Kirchensteiner, St. Majnoni, R. Schläpfer, and H. Spiegelburg, *Helv. Chim. Acta*, 1957, **40**, 1531.

[3] T. Takemoto and T. Nakajima, *Yakugaku Zasshi*, 1964, **84**, 1183.

[4] G. Endres, *Ber.*, 1932, **65**, 65; L. Birkenbach and K. Sennewald, *Annalen*, 1931, **489**, 7; *Ber.*, 1932, **65**, 546.

[5] P. Friis, P. Helboe, and P. O. Larsen, *Acta Chim. Scand.*, 1974, **28**B, 317; R. Rando, *Biochemistry*, 1974, **13**, 3859; *Accounts Chem. Res.*, 1975, **8**, 281.

[6] J. E. Baldwin, M. A. Christie, S. B. Haber, and L. I. Kruse, *J. Amer. Chem. Soc.*, 1976, **98**, 3045.