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FORMATION AND 6α-SUBSTITUTION OF 6β-(2-CARBOXY) KETENIMINO PENICILLINS

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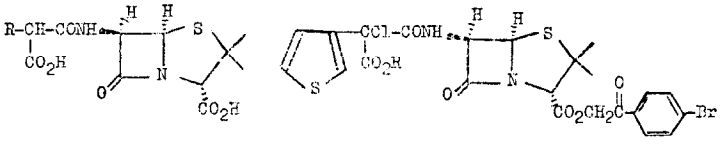
Although various methods for the synthesis of 6α-substituted penicillins are now available,[1] only the acyl imine procedure used by both Koppel[2] and Firestone[3] describes the direct conversion of a preformed acetamido penicillin ester (e.g., penicillin G benzyl ester) into its 6α-methoxy analogue. However, this method is unsuitable in certain cases where the acetamido side chain possesses an acidic proton besides that attached to the amide nitrogen.[4] Such a situation arises with (2-carboxy) acetamido penicillin diesters of type (IV) which derive from the pharmaceutically important free acids (I;(i),(ii)).[5] Our attempts to convert a diester of this type, e.g. (IVa), to its 6α-methoxy analogue (VIIIa) using the method of Koppel[2] produced instead a mixture of (2-chloro) acetamido esters (II(i);(ii)).

The following describes the successful conversion of preformed (2-carboxy) acetamido penicillin diesters (IV) to their 6α-methoxy analogues (VIII) by a method which is facilitated by the acidity of the side chain proton.

The key intermediates in this conversion are ketenimines (V), prepared in high yield directly from their acetamido analogues (IV). For example, (IVb) (1.50g) in benzene at 5°, treated sequentially with excess pyridine (1.7ml.) and, dropwise, phosphorus pentachloride (1.32g.) in benzene and stirred for three hours at 5° gave almost pure 6β-ketenimine (Vb)(1.23g.), υ_{max} ($CHCl_3$) 2030cm^{-1}, δ ($CDCl_3$) 1.36, 1.42 (3H, 3H, 2s), 4.56 (1H,s), 5.43 (2H,s), 5.77 (2H,s), 7.1 - 7.9 (12H, complex), 8.37 (2H,d, J 8Hz). Hydrolysis of (Vb) at pH 4 (moist T.H.F.: phosphoric acid) for 24 hours afforded starting 6β-acetamido ester (IVb) and thus confirmed the configuration at C-6 shown (Vb). Although unstable to chromatography, ketenimines (V) may be stored at 0°C for several weeks without deterioration.



(I)(i) R = phenyl;(ii) = thien-3-yl (II)(i) R = p-methylphenyl;(ii) R = methyl

Carroll and co-workers[6] have prepared an epimeric mixture of ketenimines (XII) on treating the imino chloride (XI) with triethylamine, but in our case no intermediate imino chlorides were observed and there is no requirement for a base stronger than pyridine, such as triethylamine. In fact, exposure of (Vc) to triethylamine (1 molar equivalent in CH_2Cl_2, 30min) caused removal of the ketenimine band (2030cm^{-1}) from the infrared spectrum.[7]

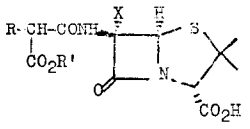
6α-Methoxylation of ketenimines (V) was preferably carried out as follows:-

Chlorination (1 molar equivalent Cl_2) of (Vc) (T.H.F.; -70°) presumably proceeded regioselectively at the olefinic portion of the ketenimine[8] to give the unstable dichloro-compound (VIc) which is not isolated but treated *in situ* with a methanolic solution of lithium methoxide (2.7 molar equivalents) at -70° to give, after quenching with acetic acid and chromatography on silica, the 6α-methoxy ketenimine (VIIc) (39% overall from IVc), υ_{max} ($CHCl_3$) 2010cm^{-1}, δ ($CDCl_3$) 1.34 (6H,s), 2.23 (3H,s), 3.58 (3H,s), 4.36 (1H,s), 5.23 (2H,s), 5.53 (1H,s), 6.8 - 7.7 (9H, complex), 8.16 (2H, d, J 8Hz).

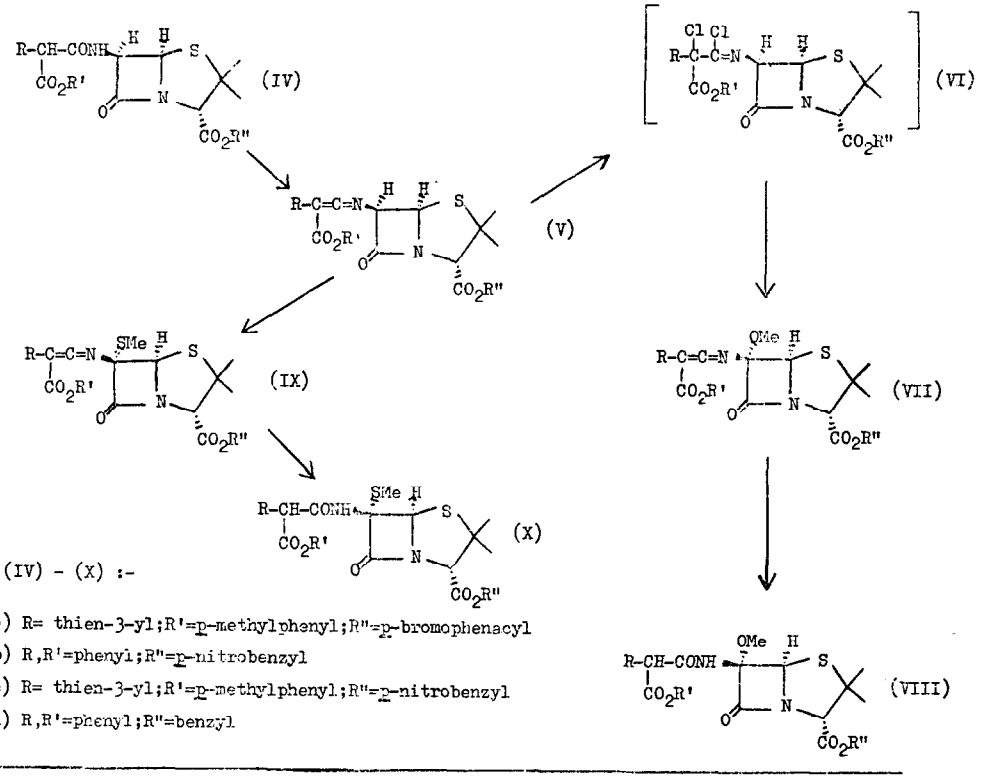
The intermediacy of (VIc) is assumed because this species is analogous to the isolable dichloro-compound (XIV) prepared by Hiroaka *et al.* from the (2-chloro) acetamido penicillanate (XIII), and subsequently converted by them to the 6α-methoxy ketenimine (XV).[9] During the course of our work, Hiroaka *et al* also described the preparation of 7β-ketenimino-7α-methoxy cephalosporins, e.g., obtaining (XVI(i)) on treating an epimeric mixture of ketenimines (XVI (ii)), prepared by the method of Carroll,[6] with bromine and methanolic lithium methoxide.[10] However, in our case substitution of bromine in place of chlorine as described above gave inferior results.

Hydrolysis of 6α-methoxy ketenimine (VIIc) at pH 2.6 (T.H.F.: H_2O (30:1); H_3PO_4) cleanly afforded the acetamido diester (VIIIc), hydrogenated in good yield to the biologically active free acid (III(i)), identical to material prepared by the appropriate side-chain acylation of benzyl 6β-amino-6α-methoxy penicillanate[11] and subsequent hydrogenation. The 6α-methoxy penicillins (III(i); (ii)) showed much enhanced activity against a number of Gram-negative β-lactamase producing organisms compared with their unsubstituted analogues (III (iii);(iv)). Such an enhancement caused by the 6α-methoxy group is unusual in penicillins.

6β-Ketenimines (V) may also undergo direct electrophilic substitution at C-6. For example, ketenimine (Vd) and methyl methanethiosulphonate (1 molar equivalent) in D.M.F. were treated with anhydrous potassium carbonate (1 molar equivalent) at 0°, and the mixture stirred for forty-five minutes. Chromatography on silica gave the 6α-methylthio derivative (IX)(28% overall from (IVd)), υ_{max} ($CHCl_3$) 2010cm^{-1}, δ ($CDCl_3$) 1.37, 1.40 (3H, 3H, 2s), 2.44 (3H,s),



(III) (i) R = thien-3-yl; R' = p-methylphenyl; X = OMe
(ii) R,R' = phenyl ; X = OMe
(iii) R = thien-3-yl;R' = p-methylphenyl; X = H
(iv) R,R' = phenyl ; X = H



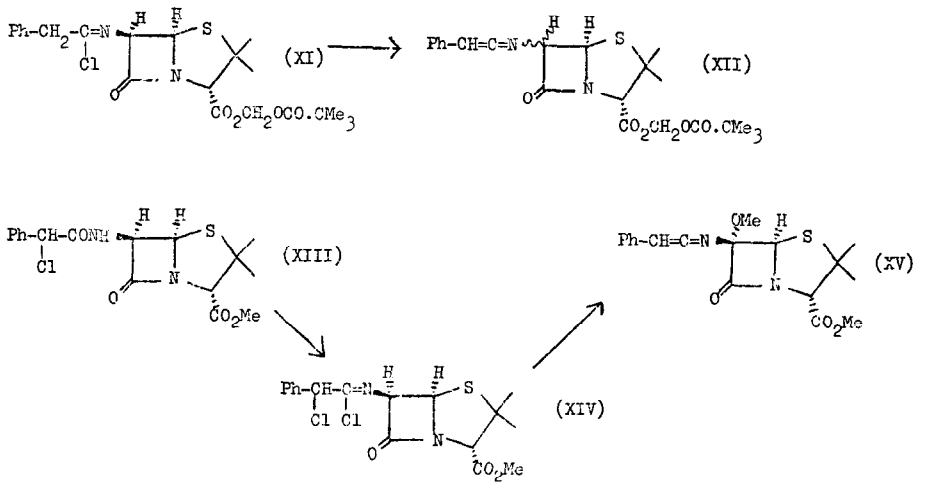
(IV) - (X) :-

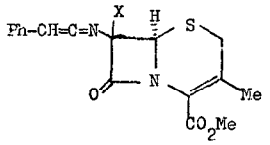
(a) R= thien-3-yl;R'=p-methylphenyl;R"=p-bromophenacyl

(b) R,R'=phenyl;R"=p-nitrobenzyl

(c) R= thien-3-yl;R'=p-methylphenyl;R"=p-nitrobenzyl

(d) R,R'=phenyl;R"=benzyl





(XVI)(i) X = ····OMe
(ii) X = ∿∿H

4.51 (1H,s), 5.22 (2H,s), 5.50 (1H,s). 7.0 - 7.8 (15H, complex). Hydrolysis in the usual way gave the acetamido analogue (Xd), identical to material prepared by the appropriate side-chain acylation of benzyl 6β-amino-6α-methylthio penicillanate.[11]

Thus ketenimines have been found to be useful intermediates in the 6-substitution of penicillins possessing an acidic side-chain hydrogen as described above. In particular, their use in 6α-methoxylation of such compounds provides a complement to the procedure of Koppel et al.[2,3]

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REFERENCES

1. L.D. Cama, W.J. Leanza, T.R. Beattie and B.G. Christensen, J.Amer.Chem.Soc., 94, 1408 (1972); W.A. Slusarchyk, H.E. Applegate, P. Funke, W. Koster, M.S. Puar, M. Young and J.E. Dolfini, J.Org.Chem., 38, 943 (1973), L.D. Cama and B.G. Christensen, Tetrahedron Lett., 3505 (1973); W.A. Spitzer and T. Goodson, ibid., 273 (1973); P.H. Bentley and J.P. Clayton, J.C.S. Chem.Comm., 278 (1974), D.H. Bremner, M.M. Campbell and G. Johnson J.C.S. Perkin I, 1918 (1976), O. Hirai, Y. Iwano, T. Saito, T. Hiraoka and Y. Kishida Tetrahedron Lett., 1303 (1976); H. Yanagisawa, M. Fukushima, A. Ando and H. Nakao, J.Antibiotics, 29, 969 (1976). See also references 2,3,9,11.
2. G.A. Koppel and R.E. Koehler, J.Amer.Chem.Soc., 95, 2403 (1973).
3. R.A. Firestone and B.G. Christensen, J.Org.Chem., 38, 1436 (1973).
4. W.H.W. Lunn and E.V. Mason, Tetrahedron Lett., 1311 (1974).
5. M.J. Basker and R. Sutherland, Chemotherapy, 5, 51 (1976); R. Sutherland and P.J. Wise, Antimicrob.Ag.Chemother., 402 (1970).
6. R.D. Carroll, E.S. Hamanaka, D.K. Pirie and W.M. Welch, Tetrahedron Lett., 1515 (1974).
7. c.f. R.D. Carroll and L.M. Smith, J.Het.Chem., 445 (1975).
8. C.L. Stevens and J.C. French, J.Amer.Chem.Soc., 75, 657 (1953).
9. Y. Sugimura, K. Iino, Y. Iwano, T. Saito and T. Hiraoka. Tetrahedron Lett., 1307 (1976); T. Hiraoka and Y. Sugimura, Ger.Patent 2512670 (1975).
10. T. Saito, Y. Sugimura, Y. Iwano, K. Iino and T. Hiraoka, J.C.S. Chem.Comm., 516 (1976).
11. T. Jen, J. Frazee and J.R.E. Hoover, J.Org.Chem., 38, 2857 (1973).