Tetrahedron Letters No. 2, pp 145 - 148, 1973. Pergamon Press. Printed in Great Britain.

6-SUBSTITUTED PENICILLIN DERIVATIVES, VI

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(Received in USA 13 October 1972; received in UK for publication 11 December 1972)

In the course of work directed toward preparing 6α-substituted penicillins and 7α-substituted cephalosporins[1-3] it was found that a reactive nucleophilic site can be generated at these positions by base treatment of the nitrobenzaldehyde Schiff base of 6-APA (6-aminopenicillanic acid) or 7-ACA (7-aminocephalosporanic acid) esters.[1,2] This nucleophilic center can be induced to undergo alkylation or aldol condensation to give after subsequent reactions the corresponding unsubstituted[1] or mono-substituted[2] alkyl APA or ACA derivatives. We here report the preparation of additional 6-substituted penicillin derivatives in which the side-chain contains a carbon atom in a more highly oxidized state.

The Schiff base Ia when reacted with an excess of acrylonitrile in t-butanol using N,N-diisopropylethylamine as a catalyst gave an initially blue-green solution which turned yellow after 15 minutes. The reaction product upon fractional chromatography (silica gel) afforded three isomeric nitrile containing compounds. The major isomer isolated (18%) was a glass and was assigned structure Ib (nmr, T-60, δ, $CDCl_3$: 2.77s, $\underline{CH}_2\underline{CH}_2CN$; 4.58s, 3-H; 5.68s, 5-H and 8.92s, -$\underline{CH}$=N-; M^+. 492, ir and other nmr peaks consistent with structure Ib). This material when carried through the previously described[1,2] steps of Schiff base reversal,[4] phenoxyacetylation to give IIa[4,5] and then hydrogenolysis of the benzyl ester afforded sodium 6α-cyanoethyl Pen-V, IIIa [nmr, D_2O, ppm from DOH: 0.77s downfield, 5-H; 2.38m downfield, aromatic; 0.44s upfield, 3-H; 2.05s upfield, $\underline{CH}_2\underline{CH}_2CN$; 3.19s and 3.21s upfield, $C(\underline{CH}_3)_2$]. The other isomeric materials which were eluted from the column immediately before (14% yield) and after (8% yield) the expected Michael addition product Ib were crystalline (m.p. 188-191° and 231-233°, respectively) and were found to have nearly identical mass spectra. The nmr ($CDCl_3$) spectra of these compounds lack the absorption characteristic of the vinyl hydrogen of the Schiff base but have new absorption near 4.6 ppm as well as complex absorption in the region

2.5-3.5 ppm. For both compounds the hydrogen absorbing in the region of 4.6 ppm (partially obscured by the 3-H singlet) was found to be coupled with both an NH and another single proton (at ~3.0 and 3.36 ppm, respectively) by spin decoupling and deuterium exchange experiments.[6] These data suggest the spiro-pyrrolidine structure IV. Inasmuch as there is only a small difference in the nmr position of the 5-H (5.54 and 5.37 ppm, respectively) and gem-dimethyl groups (1.43, 1.56; 1.42, 1.57 ppm; each pair, respectively) for each compound they probably do not differ in the orientation of the 6-nitrogen[1,2,7] but only in the orientation of the two substituents on the pyrrolidine ring. The major crystalline product when subjected to hydrogenolysis afforded the zwitterionic V [nmr, D_2O-$NaHCO_3$, ppm from DOH: 2.59d and 2.10d downfield, aromatic; 0.85s downfield, 5-H; 0.43s+m upfield, 3-H + N-CH-; 1.3-2.4m upfield, CH_2CH and 3.15s upfield, $C(CH_3)_2$; bis-trimethylsilyl derivative had $M^{+\cdot}$ of 516; ir, mull: 4.43 and 5.16μ].

As 6-methoxypenicillins and 7-methoxycephalosporins show highly interesting antibiotic activity we were led to prepare additional compounds in which the added functionality was electron withdrawing. The oxidation of alcohols obtained via aldol condensation of formaldehyde[2] and acetaldehyde with the Schiff base Ia afforded the corresponding formyl and acetyl derivatives. Thus, oxidation of 6-hydroxy methyl Pen-V (IIIb)[2] with dimethyl sulfoxide (DMSO) in the presence of pyridine-sulfur trioxide and triethylamine[8] afforded 6-formyl Pen-V, IIIc, [nmr, δ, $CDCl_3$: 9.62s, -CHO; 5.87s, 5-H; 4.65s, $-CH_2O$]. The analogous product VIb has been obtained by the corresponding oxidation of the 7α-hydroxymethylcephalosporin VIa.[2] Condensation of Ia with acetaldehyde has given the crude α-hydroxyethyl derivative Ic[5] which was converted in two steps[2] to the intermediate IIb[4,5] which could be purified by chromatography. Hydrogenolysis of the benzyl group of IIb in the presence of one mole of sodium bicarbonate[2] gave sodium 6α-(α-hydroxyethyl) Pen-V, IIId, [nmr, D_2O, ppm from DOH: 0.81s downfield, 5-H; 0.42s upfield, 3-H; 3.22s upfield $C(CH_3)_2$ and 3.39d, J = 7Hz, $CHCH_3$]. DMSO oxidation of IIId failed, but the chromium trioxide-pyridine complex in methylene chloride[9] oxidized IIb in near quantitative yield to give IIc.[4,5] Hydrogenolysis as described above then gave sodium 6α-acetyl Pen-V, IIIe, [nmr, D_2O, ppm from DOH; 1.18s downfield, 5-H; 0.13s downfield, $CH_2OØ$; 0.35s upfield, 3-H; 2.29s upfield, CH_3CO; 3.17s and 3.23s upfield,

$C(CH_3)_2$]. The corresponding steps have been carried out in the cephalosporin series to give compound VIc.

Reaction of Ia with methyl chloroformate in acetonitrile with N,N-diisopropylethylamine as base resulted in a crude mixture from which impure Id[5] could be isolated by chromatography. Subsequent transformations of Id gave IId[4,5] which could be further purified by chromatography. Hydrogenolysis then gave after acidification 6α-carbomethoxy Pen-V, IIIf, [nmr, δ, $CDCl_3$: 7.1m, aromatic; 5.58s, 5-H; 4.55s, CH_2O; 3.92s, CH_3O; 1.75s and 1.64s, $C(CH_3)_2$; $M^{+\cdot}$ 408]. A similar series of reactions starting with Ia and benzyl chloroformate gave the corresponding Ie,[4,5] IIe[4,5] and final product, disodium 6-carboxy Pen-V, IIIg [nmr, D_2O, ppm from DOH: 2.10 to 2.90m downfield, aromatic; 0.52s upfield, 5-H, 1.31s upfield, 3-H and 3.13s upfield, $C(CH_3)_2$].

The orientation of all introduced substituents in the cases cited above has been assumed to be α- based on the arguments presented elsewhere.[1,2,7] No other isomers were found in the examples above although the low isolated yields experienced with the preparation of IIIf and IIIg could possibly have resulted in the separation of the less favored β-isomers. However, the fact that the final products have some bioactivity supports the supposition of α-side attack.

The penicillins III have all been tested against B. subtilis by the agar diffusion disc assay. The relative activity of the compounds is IIIc ≈ IIIe > IIIa ≈ IIIb > IIIf ≈ IIIg > IIId. Compound V is inactive. The cephalosporin derivatives VIb and VIc are slightly more active than the corresponding penicillins IIIc and IIIe.

References

1. R. A. Firestone, N. Schelechow, D. B. R. Johnston and B. G. Christensen, Tetrahedron Letters, 375 (1972).
2. Paper V; D. B. R. Johnston, S. M. Schmitt, R. A. Firestone and B. G. Christensen, Tetrahedron Letters, submitted for publication.
3. L. D. Cama, W. J. Leanza, T. R. Beattie and B. G. Christensen, J. Am. Chem. Soc., 94, 1408 (1972).
4. The materials isolated at this stage exhibited satisfactory nmr and ir spectra. They were also uniformly pure as judged by thin layer chromatography.

5. These materials gave the appropriate molecular ion in the mass spectrometer and showed fragmentation characteristic of penicillin derivatives. High resolution mass spectrographic analysis of the molecular ions of Ib-c, IIa-e and both isomers of IV verified the elemental composition of these materials.
6. Data were obtained on a HR-100 Varian spectrometer. We are indebted to Dr. B. Arison for carrying out and interpreting these experiments.
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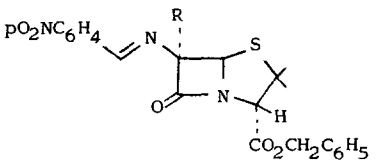
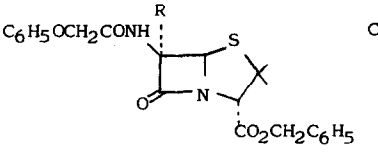
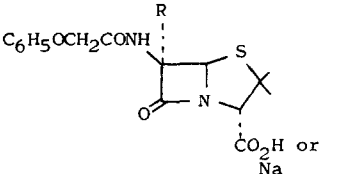


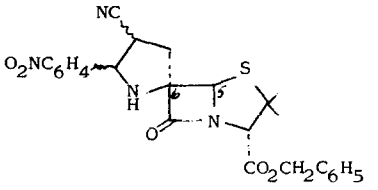
Ia R = H
b R = CH_2CH_2CN
c R = $CHOHCH_3$
d R = CO_2CH_3
e R = $CO_2CH_2C_6H_5$



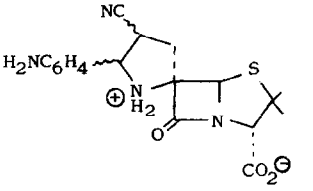
IIa R = CH_2CH_2CN
b R = $CHOHCH_3$
c R = $COCH_3$
d R = CO_2CH_3
e R = $CO_2CH_2C_6H_5$



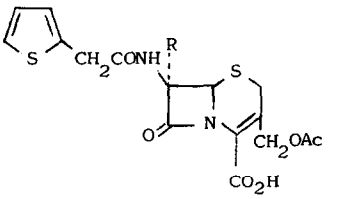
IIIa R = CH_2CH_2CN
b R = CH_2OH
c R = CHO
d R = $CHOHCH_3$
e R = $COCH_3$
f R = CO_2CH_3
g R = CO_2Na



IV



V



VIa R = CH_2OH
b R = CHO
c R = $COCH_3$