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SUBSTITUTED PENICILLINS AND CEPHALOSPORINS V.[1] 6(7)-SUBSTITUTED ALKYL DERIVATIVES

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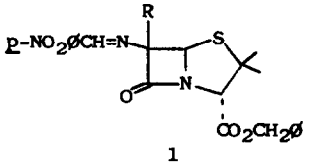
Long standing theoretical interest in C-6 and C-7 substituted penicillin and cephalosporin derivatives has been stimulated by recent reports of isolation from natural sources and/or synthesis of such compounds.[2] While preparation of a 6-phenylhydroxymethyl penicillin (4f) has been reported, efforts to obtain the simple hydroxymethyl compound itself (4b) were unsuccessful.[3] We would like to report our synthesis of this compound and some others derived from it, as well as our synthesis of the corresponding 7-hydroxymethyl cephalosporin (8b).



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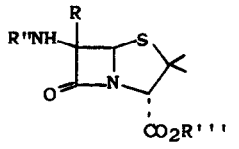
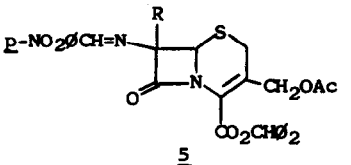


2 R"=H, R'''=$CH_2Ø$
3 R"=$ØOCH_2CO$, R'''=$CH_2Ø$
4 R"=$ØOCH_2CO$, R'''=H



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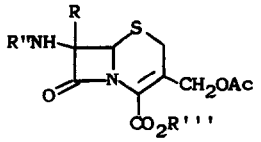

6 R"=H, R'''=$CHØ_2$

7 R"=  $-CH_2CO$, R'''=$CHØ_2$

8 R"=  $-CH_2CO$, R'''=H

For All Structures:

a R=H
b R=CH_2OH
c R=CH_2O_3SR'
d R=CH_2X
e R=CH_2O_2CR'
f R=$CHØOH$

Gaseous formaldehyde reacts with a DMF solution of Schiff base 1a[2] giving crude 1b which, upon stirring with an equivalent of preformed 2,4-dinitrophenylhydrazine tosylate salt in ethanol affords the crystalline tosylate salt of 2b (mp. 168-169°; Calcd. for $C_{23}H_{27}N_2O_7S_2$: C, 54.31; H, 5.55; N, 5.51; S, 12.61. Found: C, 54.01; H, 5.59; N, 5.42; S, 12.54. Nmr[4] (δ, DMSO-d_6) 7.56, 7.43, 7.18, 7.04 (4H), 7.42 (5H), 5.50 (1H), 5.23 (2H), 4.57 (1H), 3.88 (2H), 2.30 (3H), 1.62 (3H), and 1.38 (3H). Ir (Nujol) NH-OH (2.85, 2.99, 3.7-4.3μ), β-lactam (5.63μ), ester (5.77μ))[8]. Treatment of this salt with aqueous K_2HPO_4 and phenoxyacetyl chloride in methylene chloride affords 3b which is hydrogenolyzed with an equal weight of 10% Pd/C in aqueous methanol containing one equivalent of $NaHCO_3$, over one hour under 40 psi H_2, giving the sodium salt of 4b (nmr (δ, D_2O) 7.54-6.84 (complex 5H; major peak at 7.04), 5.50 (1H), 4.65 (HDO; obscures ϕOCH_2CO peak), 4.20 (1H), 4.04 (2H), and 1.40 (6H). Ir (Nujol) NH-OH (2.8-3.2μ), β-lactam (5.68μ), amide (5.96μ), and carboxylate (6.26μ)).

An alternate preparation of 3b entails phenoxyacetylation of chromatographically purified 1b to give 1e (R'=$CH_2O\phi$). Treatment as above gives the tosylate salt of 2e (R'=$CH_2O\phi$); upon neutralization, rapid O → N acyl migration takes place giving 3b. When R'=CH_3 or $CH_2\phi$, the O → N acyl migration is slow enough to permit purification of the O-acyl compound.

By an analogous series of reactions 5a, 5b, 6b[9], and 7b have been prepared; treatment of 7b with CF_3CO_2H/anisol gives 8b (mp 144-145° (dec.); Calcd. for $C_{17}H_{18}O_7N_2S_5$: C, 47.86; H, 4.25; N, 6.57; S, 15.04; Found: C, 47.94; H, 4.43; N, 6.01; S, 14.92. Nmr (δ, as the sodium salt in D_2O) 7.35, 7.30, 7.25, 7.02 and 6.95 (3H), 4.94 (1H), 4.77, 4.73 (complete pattern being obscured by HDO at 4.67), 4.10 (2H), 3.87 (2H), 3.78, 3.48, 3.33, 3.03 (2H), and 2.10 (3H). Uv (aqueous pH 7 buffer) λ_{max} 237 (ε 13,600), λ_{infl} 257.5 (ε 9,750). Ir (Nujol) shows a strong β-lactam (5.61μ), along with other peaks consistent with the acetate, amide, and carboxyl groups).

We next sought to modify the hydroxymethyl group by displacement reactions of the easily prepared sulfonate esters of the acylamino derivative (3c), but the results were not encouraging. When the sulfonate esters of the Schiff base (1c) were employed, however, satisfactory conversions could be obtained; thus, the Schiff base nosylate 1c (R'=p$NO_2\phi$) reacts with LiN_3, LiCl, or LiI in DMSO to give the azido-

methyl, chloromethyl or iodomethyl derivatives (1d, X=N_3, Cl, or I). The fluoromethyl derivative (1d, X=F) is best prepared using the triflate ester (1c, R'=CF_3) and Bt_4NF[5] in acetonitrile.[6] After straightforward conversion of the 1ds to the 3ds, hydrogenolysis affords the sodium salts of the aminomethyl, chloromethyl, methyl and fluoromethyl penicillins (4d, X=NH_2, Cl, H and F).

The stereochemistry of these molecules now remains to be discussed. Since the 2β-methyl overhangs the C-6 position, 6β-substituents might affect its chemical shift. The geminal methyl groups in compounds 2a, 2b, and 2e manifest themselves in the nmr spectra as two sharp singlets separated by 10-11 cps. Upon conversion to 3a, 3b, and 3b (R"=ϕCH_2CO) the methyl peaks are only separated by 2-4 cps; in contrast, the methyl peaks of 3a (R"=$C_6H_{11}CH_2CO$)or 3b (R"=CH_3CO) remained 11 cps apart. A similar trend towards coalescence of the geminal methyl groups upon phenylacetylation of 6-APA benzyl esters bearing methyl or methoxyl[2] groups at C-6 and assigned the normal configuration at that center has also been observed, whereas the N-phenylacetyl benzyl esters assigned the epi configuration show almost no sign of coalescence. We suggest that these results may be due to a shielding of the β-methyl group by the anisotropic aryl group in the normal series where the 6-amino and 2β-methyl groups point toward one another. Since in the epi series the amino group points away from the β-methyl group, the aromatic system would not be forced into its vicinity and hence the coalescence is not observed. The failure of the bulky cyclohexylacetyl group to bring about coalescence supports the argument that the effect is due to the aromatic ring and not merely due to steric compression. It should be noted, however, that this effect is influenced by the substituent on the C-3 carboxyl; while the differences are quite striking in the benzyl esters, they are rather small in the sodium salts and methyl esters.[7] They do appear, however, to be in the expected direction.

A still more compelling argument comes from a study of the nuclear Overhauser effect observed between the 6-methyl and C-5 protons in 2d (X=H, R"=ϕCH_2CO) prepared by direct methylation of 1a.[2] When 2d (X=I) was phenylacetylated and hydrogenolyzed, the identical compound was produced. Thus both alkylation and aldol condensation occur primarily from the α-face of the molecule.

By analogy the product similarly obtained in the cephalosporin series is assigned the normal configuration at C-7.

References

(1) For paper IV in this series see R. A. Firestone, N. Schelechow, and B. G. Christensen, Chem. Commun., (in press).

(2) For discussion and references, see paper II in this series: R. A. Firestone, N. Schelechow, D. B. R. Johnston and B. G. Christensen, Tetrahedron Lett., 375 (1972).

(3) R. Reiner and P. Zeller, Helv. Chim. Acta, 51, 1905 (1968).

(4) All nmr spectra were taken on a Varian T-60 spectrometer; nmr and ir spectra were consistent with all structures discussed. All mass spectra were consistent with the assigned structures.

(5) We are indebted to Dr. J. Kollonitsch for suggesting this reagent.

(6) J. Hayami, N. Ono and A. Kayi, Tetrahedron Lett., 1385 (1968).

(7) E. H. W. Bohme, H. E. Applegate, B. Toeplitz, J. E. Dolfini and J. Z. Gougoutas, J. Amer. Chem. Soc., 93, 4324 (1971).

(8) From 2.4 g of 1a, 2.4 g of crude crystalline tosylate salt of 2b were obtained.

(9) From 1.6 g of 5a, 0.48 g of 6b were obtained, after preparative tlc.