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SUBSTITUTED PENICILLINS AND CEPHALOSPORINS II. C-6(7)-ALKYL DERIVATIVES (1)

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The theory that penicillins and cephalosporins are D-alanyl-D-alanine surrogates led Strominger and Tipper (2) to predict that placing a methyl group in the same position as is found in the D-alanyl residue, i.e. α to the lactam carbonyl, would increase antibacterial effectiveness. Interest in 6-alkyl penicillins (3,4,5,6) dates from that time, and a recent report (7) describes the preparation of 6α-methyl penicillin G methyl ester, an inactive compound, and a 7α-methyl cephalosporin, slightly active. We now report the preparation of 6α-methyl (and -ethyl) penicillin G sodium, which has appreciable antimicrobial activity, and also the corresponding cephalothin derivatives.

The Schiff base Ia (m.p. 90-92°; nmr, T-60, δ, $CDCl_3$: 4.44s, 3-H; 5.24q, J=4,2, 6-H; 5.69d, J=4, 5-H; 8.75d, J=2, -CH=N-; ir, analysis, other nmr peaks correct) was prepared from 6-APA benzyl ester and p-nitrobenzaldehyde by azeotropic drying in benzene for 1 hour. In a typical alkylation, 110 mg (.00025 mole) Ia was treated at -78° under N_2 in 4 ml THF with 0.109 ml 2.3M phenyllithium (.00025) to give inky blue Ib. Addition of 0.2 ml CH_3I in 5 ml DMF and warming to 25° over 20 minutes afforded Ic quantitatively (nmr, δ, $CDCl_3$: 1.78s, 6-CH_3; 4.35s, 3-H; 5.35s, 5-H; 8.80s, -CH=N-; ir, other nmr peaks correct).

Removal of the p-nitrobenzylidene group by exchange with aniline·HCl in MeOH (45%) or, better, with 2,4-DNPH·HOTs in EtOH (90%) afforded IIc (nmr, δ, $CDCl_3$: 1.53s, 6-CH_3 and one 2-CH_3; 4.32s, 3-H; 5.11s, 5-H; ms, ir, other nmr peaks correct). This was acylated (74% crude, 25% crystalline) with phenylacetyl chloride-pyridine in

CH_2Cl_2 to IIIc (m.p. 143-5°; nmr, δ, $CDCl_3$: 1.72s, 6-CH_3; 4.32s, 3-H; 5.32s, 5-H; ms, ir, analysis, other nmr peaks correct), which was hydrogenolyzed quantitatively, using an equal weight of 10% Pd/C and equimolar $NaHCO_3$ in 4:1 MeOH-H_2O for 1 hour at 40 psi, to 6α-methyl pen G IVc (nmr, D_2O, ppm from HOD: 0.67s downfield, 5-H; 0.26s upfield, 3-H; 2.91s upfield, 6-CH_3; ir, other nmr peaks correct). Preparation of 6α-ethyl pen G IVd was achieved via the same sequence of reactions; the product and all intermediates exhibited the expected physical characteristics.

The Schiff base Va (oil; nmr, δ, $CDCl_3$: 5.09d, J=5, 6-H; 5.41q, J=5,2, 7-H; 8.60d, J=2, -CH=N-; ir, other nmr peaks correct) was prepared in similar fashion to Ia. Methylation of Vb as before afforded Vc (nmr, δ, $CDCl_3$: 1.78s, 7-CH_3; 4.81s, 6-H; 8.66s, -CH=N-; ir, other nmr peaks correct), which was converted to VIc (nmr, δ, $CDCl_3$: 1.60s, 7-CH_3; 4.61s, 6-H; ms, ir, other nmr peaks correct) with DNPH·HOTs in 36% yield after chromatography. Acylation with 2-thienylacetyl chloride-pyridine in CH_2Cl_2 afforded VIIc, 77% after chromatography (nmr, δ, $CDCl_3$: 1.80s, 7-CH_3; 4.78s, 6-H; ir, other nmr peaks correct). The benzhydryl ester was cleaved with 5:1 trifluoroacetic acid-anisole for 4 minutes at 0°, extracted with aqueous bicarbonate and lyophilized to produce 7α-methyl cephalothin VIIIc in 74% yield (nmr, D_2O, ppm from HOD: 2.90s upfield, 7-CH_3; 0.21s downfield, 6-H; ir, other nmr peaks correct). The 7α-ethyl analog VIIId was made in parallel fashion, except that the reaction with ethyl iodide and Vb was too sluggish in THF-DMF, and 5:1 HMPA-THF was used instead. The product and all intermediates were identified by spectral data.

Evidence that the alkylations occur from the α side is as follows. [1] Methylation of both Ia and its 6-epimer (8) gave the same product, Ic, indicating that the approach of methyl was controlled, not by the configuration of the anion, but by steric factors which should strongly favor attack on the α side (9). [2] The antibiotic activity of the final product IVc was too great for it to be epi-IVc (10). [3] The nmr spectra of all intermediates decisively favors the normal configuration. Thus, 3-H in Ia is at 4.44 δ, in Ic and Id at 4.35 δ, but at 4.61δ in epi-Ia. The gem. dimethyl resonances in IIIa occur 4 Hz apart; in IIIc, 3 Hz; in IIId, 4 Hz; but in epi-IIIa, 11 Hz. [4] Irradiation of IIc at 1.53δ resulted in an NOE with the 5-H. No NOE was observed when each 2-CH_3 of both IIa and 6-epi-IIa was individually irradi-

ated (11). The alkyl configurations in the cephalosporin series are assigned by analogy.

The prediction of enhanced bioactivity for IVc (2) was not fulfilled; neither, however, was the implication, from the behavior of the methyl ester (7), that IVc would be inactive, since the methyl ester showed no activity at the levels tested (<1.6% of pen G) (7). Minimum inhibitory concentrations for 79 organisms (12) ranged from <0.2% of pen G up to ca. 16% of pen G (2.5 γ/ml for Pasteurella multocida 1590 and Diplococcus pneumoniae 3377). Its antimicrobial spectrum was narrow and unlike that of pen G. The bulky 6-ethyl group in IVd reduced the activity markedly, but surprisingly, the less bulky CD_3 group in IVe also reduced the activity slightly, to ca. 20% of IVc. Full biological data for all compounds will be reported elsewhere. Further syntheses of substituted 6-alkyl penicillins and 7-alkyl cephalosporins will be reported shortly (13).

FOOTNOTES AND REFERENCES

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(8) Prepared by equilibration of Ia with its 6-epimer (ca. 1:3) in DMF at -18° with di-isopropylethylamine, DNPH·HOTs treatment, fivefold crystallization of pure epi-IIa, and reaction with p-nitrobenzaldehyde.

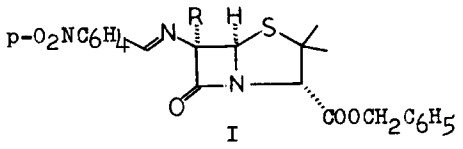
(9) Reaction of Ib with CH_3I occurs at about -10°. Under the same conditions, protonation of Ib is also steric-approach controlled, with Ia being obtained from both Ib and epi-Ib. In pure THF, in contrast, Ib and epi-Ib are protonated stereospecifically and with retention, and methylation goes very poorly if at all.

(10) We assume the same inhibitory mechanism for IVc and Pen G (2). We have prepared pure 6-epi-pen G and find its antimicrobial activity to be ≪1% of pen G, in agreement with the report of D.A. Johnson and D. Mania, Tetrahedron Letters, 267 (1969), but in disagreement with T. Sawai, T. Saito and S. Mitsuhashi, J. Antibiotics, 23, 488 (1970)

(11) We thank Dr. Byron H. Arison for the NOE study.

(12) We are grateful to Dr. E.H. Thiele for these measurements.

(13) D.B.R. Johnston, S.M. Schmitt, R.A. Firestone and B.G. Christensen, manuscript in preparation.



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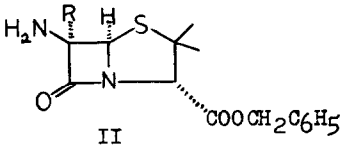

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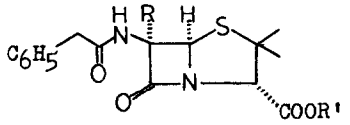
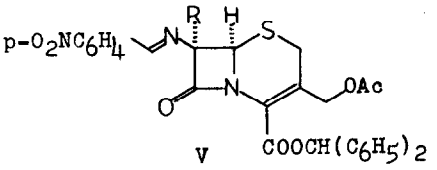
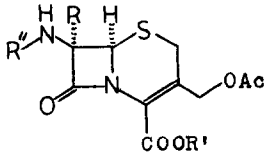


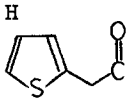
III R' = $CH_2C_6H_5$
IV R' = Na

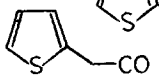


V



VI R' = $CH(C_6H_5)_2$, R'' = H
VII R' = $CH(C_6H_5)_2$, R'' =
VIII R' = Na, R'' =





a, R = H
b, R = Li
c, R = CH_3
d, R = C_2H_5
e, R = CD_3