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SUBSTITUTED PENICILLINS AND CEPHALOSPORINS. VII.

A STEREOSPECIFIC INTRODUCTION OF THE C-6(7)α METHOXY GROUP

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Recently we reported a stereospecific general method for the introduction of a C-6(7) methoxy substituent on the penicillin and cephalosporin nuclei.[1] We now report a new method for the same transformation to these important β-lactam antibiotics.

The C-6 and C-7 aromatic aldimines of penicillanates and cephalosporanates and the C-6 and C-7 anions generated from these have been reported recently.[2] Treatment of benzyl 6-benzaliminopenicillanate (1): ir (film) 5.62μ, 5.72μ, 6.1μ; nmr ($CDCl_3$) τ: 1.50 (C=N H), 4.43 (C-5 H), 4.71 (C-6 H), 4.84 (C_6H_5-CH_2-O), 5.60 (C-3 H), 8.41 and 8.59 (gem dimethyl); with 1.2 eq. phenyl lithium at -78° in THF generated the 6-lithio derivative, which when treated with 1.2 eq. of NBS also at -78° gave benzyl 6-bromo-6-benzaliminopenicillanate (2) of undetermined stereochemistry at C-6, and limited stability at room temperature. Addition of a concentrated solution of 2 in CH_2Cl_2 to a suspension of excess Ag_2O in CH_3OH at room temperature over 10 min, followed by stirring for an additional 15 min gave benzyl 6α-methoxy-6-benzaliminopenicillanate (3) (50% yield after prep. t.l.c.): ir (film) 5.61μ, 5.72μ, 6.09μ: nmr ($CDCl_3$) τ: 1.50 (C=N H), 4.43 (C-5 H), 4.88 (C_6H_5-CH_2-O), 5.53 (C-3 H), 6.47 (OCH_3), 8.43 and 8.61 (gem dimethyl): m/e 424. 3 was contaminated with about 10% of 3-phenylcarbonyl-6α-methoxy-6-benzalimino-2,2-dimethylpenam (4) which arises from attack of phenyl lithium on the benzyl ester of 1.

The stereospecific formation of 3 from 2 can be accounted for if one assumes the formation of ion 5 as an intermediate to which the solvent (CH_3OH) adds exclusively from the less hindered α-side. The presence of silver oxide is desirable to neutralize the strong acid (HBr) formed in the reaction since lower yields are obtained when the silver oxide is omitted.

When the imine 3 was hydrolyzed under the usual acidic conditions, some 6α-methoxy-6-amino derivative 6 was produced as evidenced by the formation of 7 upon

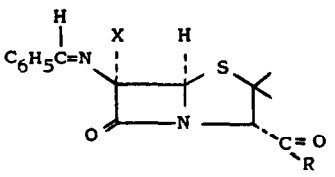
simultaneous phenylacetylation. The palladium chloride catalyzed hydrolysis of imines [3] suggested the necessary neutral conditions required to improve the yield of the transformation 3 to 6. Treatment of 3 with 1.2 eq. of $PdCl_2$ in aq. THF for 3 hrs, at r.t., followed by removal of solvent and washing the residue with hexane gave 6 probably as its $PdCl_2$ complex by analogy to the work cited above. [3] Without further purification the product was dissolved in methylene chloride and acylated with 1 eq. of phenylacetyl chloride and excess pyridine, to give benzyl 6α-methoxy-6-phenylacetamidopenicillanate (7) (41% yield from 3 after prep. t.l.c.): ir (film), 3.06μ, 5.64μ, 5.72μ, 5.95μ: nmr ($CDCl_3$) τ: 2.63 and 2.66 ($C_6\underline{H}_5$), 3.43 (NH), 4.40 (C-5 H) 4.8 ($C_6H_5-\underline{CH}_2-O$), 5.59 (C-3 H), 6.34 ($C_6H_5-\underline{CH}_2-\underset{\underset{O}{\|}}{C}$), 6.59 ($OCH_3$), 8.7 (gem dimethyl): m/e 454: identical by spectroscopic data and tlc with the product reported by us previously. [1] Along with (7) was isolated 3-phenylcarbonyl-6α-methoxy-6-phenylacetamido-2,2-dimethylpenam (8); m/e 424; ir (film) 3.02μ, 5.62μ, 5.91μ, nmr ($CDCl_3$) τ; 3.46 (NH); 4.25 (C-5 H), 4.60 (C-3 H); 6.33 ($C_6H_5-\underline{CH}_2-C=O$), 6.50 ($OCH_3$), 8.56 and 8.76 (gem dimethyl); in 10% yield, which is derived from 4.

Apparently the use of 6 complexed with $PdCl_2$ in the acylation step affords no difficulties, the complexed amine being sufficiently basic to undergo acylation while the acylated product is not basic enough to complex with $PdCl_2$. The same results would be obtained if an equilibrium between free and complexed amine exists.

Under essentially identical conditions benzhydryl 7-benzalimino-desacetoxycephalosporanate (9): ir (film) 5.62μ, 5.79μ, 6.1μ: nmr ($CDCl_3$) τ: 1.36 ($\underset{\underset{H}{\backslash}}{C}=N$), 4.64 (C-7 H, d of d), 4.86 (C-6 H, d), 6.7 (C-2 H), 7.94 (C-3 $C\underline{H}_3$); was converted to benzhydryl 7α-methoxy-7-benzalimino desacetoxycephalosporanate (10): ir (film), 5.65μ, 5.79μ, 6.1μ; nmr ($CDCl_3$) τ: 1.32 ($\underset{\underset{H}{\backslash}}{C}=N$), 4.90 (C-6 H), 6.39 ($OCH_3$), 6.79 (C-2 H), 7.9 (C-3 $C\underline{H}_3$), m/e 498, in 50% yield, and 10 to benzhydryl 7α-methoxy-7-phenylacetamidodesacetoxycephalosporanate (11): ir (film), 3.02μ, 5.65μ, 5.79μ, 5.95μ. nmr ($CDCl_3$) τ: 3.36 (NH), 5.0 (C-6 H), 6.36 ($C_6H_5-\underline{CH}_2-\underset{\underset{O}{\|}}{C}$), 6.53 ($OCH_3$), 6.91 (C-2 H), 7.83 (C-3 CH_3): m/e 528, in 60% yield from 10. The methoxy group of 10 and 11 is assigned the 7α-sterochemistry by analogy to the penicillin compounds 3 and 7.

The C-6 and C-7 bromo Schiff's bases are useful intermediates and have been converted to other derivatives, e.g., the fluoro, azido and isonitrilo derivatives,

which will be reported elsewhere.



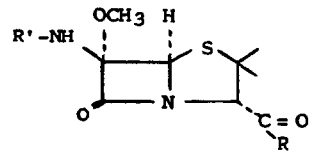
1, X=H; R=$C_6H_5CH_2O$

2, X=Br; R=$C_6H_5CH_2O$

(C-6 sterochemistry unknown)

3, X=OCH_3; R=$C_6H_5CH_2O$

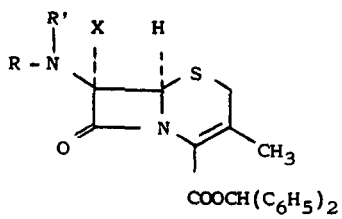
4, X=OCH_3; R=C_6H_5



6, R'=H; R=$C_6H_5CH_2O$

7, R'=$C_6H_5CH_2\overset{O}{\overset{\|}{C}}$; R=$C_6H_5CH_2O$

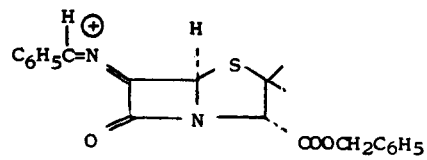
8, R'=$C_6H_5CH_2\overset{O}{\overset{\|}{C}}$; R=$C_6H_5$



9, X=H; R,R'=C_6H_5C=

10, X=OCH_3; R,R'=C_6H_5C=

11, X=OCH_3; R=$C_6H_5CH_2\overset{O}{\overset{\|}{C}}$-, R'=H



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