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FUNCTIONALIZATION OF $C_{6(7)}$ OF PENICILLINS AND CEPHALOSPORINS via 1,3-DIPOLAR INTERMEDIATE

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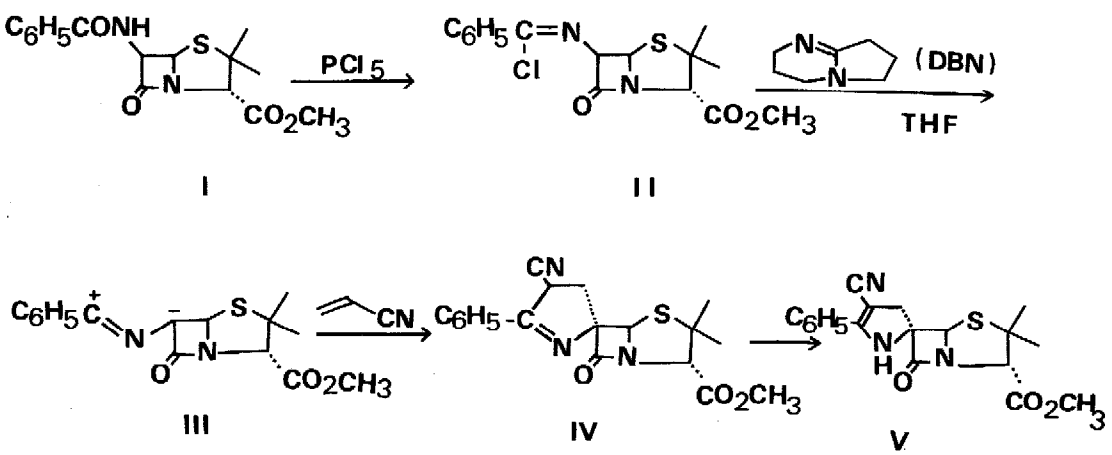
The isolation and structure proof of the 7-methoxy cephalosporin derivative have arisen considerable interest[1], and many efforts have been directed toward the introduction of substituents at the position. The first general method for the functionalization at the C-7 position of cephalosporins was to use the carbanion generated from the nitrobenzaldehyde Schiff base and various electrophiles[2]. In 1973 Baldwin and Eli Lilly chemists developed a new one-step introduction of a methoxy group at the C-6 position of penicillins and the C-7 position of cephalosproins by treating the acylamino derivatives of these antibiotics with $^{t}BuOCl$ and $LiOCH_3$ at -78° C in THF[3].

We report here another method for the introduction of a substituent at the C-6 or C-7 position of these antibiotics by means of a 1,3-dipolar cyclic



addition reaction[4]. A 1,3-dipolar intermediate (III) is generated by base treatment (strong organic base such as DBN or DBU, and triethylamine was not effective) of the iminochloride (II), which is easily prepared from the corresponding amide (I) and phosphorus pentachloride. The representative dipolarophiles are acrylonitrile, methyl acrylate, dimethyl acetylenedicarboxylate, diethyl azodicarboxylate, chloral, phenylisothiocyanate and so on.

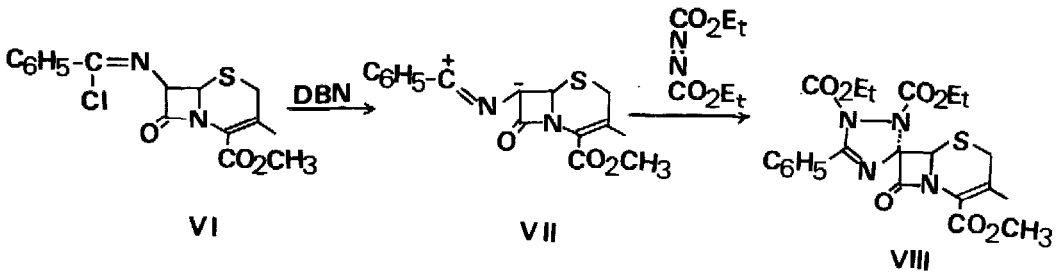
The general procedure is as follows.

Phosphorus pentachloride (350 mg.) was dissolved in 5 ml. of hot chloroform and after cooling 440 mg. of quinoline was added to form the PCl_5-quinoline complex. Addition of 500 mg. of methyl 7-benzoylaminopenicillanate (I) to this well-stirring suspension resulted in disappearance of the complex. Stirring was continued for one hour and then the solvent was removed under reduced pressure (2 mm. Hg). Tetrahydrofuran (6 ml.) was added to the residue and the precipitate was filtered off quickly by suction. To the filtrate were added 0.27 ml. of DBN and 0.53 ml. of acrylonitrile successively under ice-cooling by a syringe through a septum. After stirring for one hour at room temperature the solvent was removed under reduced pressure and the product was separated by the preparative TLC[5]; Rf=0.7 (benzene:acetone=6:1); yield, 290-390 mg. (52-71% from I); Mp. 196-7°C. The structure of the product was determined as methyl 3'-cyano-2'-phenyl-2'-pyrroline-5'-spiro-6-penicillanate (V) by the usual criteria. The IR (Nujol) shows an NH absorption band at 3300 cm^{-1}, a C≡N absorption band at 2175 cm^{-1} and a strong characteristic β-lactam absorption band at 1780 cm^{-1}. The UV shows λ_{max} at 227 and 320 nm (in EtOH). The elemental analysis shows the molecular formula of $C_{19}H_{19}N_3O_3S$, (C, 61.78; H, 5.19; N, 11.38; S, 8.66. Found: C, 61.88; H, 5.14; N, 11.41; S, 8.79.) and the MS shows M^+ at m/e 369. The NMR ($CDCl_3$)[6] shows singlets at 1.50 and 1.66 (6H, the dimethyl group), 3.75 ($COOCH_3$), 4.50 (1H, C-3) and 5.40 (1H, C-5). The signals of the methylene group in the newly introduced pyrroline part appeared as AB type signal at 3.30 (d.) and 3.55 (d.) (J=16.5 Hz). The NH appears at about 5.20 (br. m.) and the phenyl group appears at 7.2-8.0 (5H).

This product is considered to be formed by the cyclic addition of

acrylonitrile toward the 1,3-dipolar intermediate (III) from the α and less hindered face of the molecule[3a] and the successive isomerization of the adduct (IV) under those basic conditions. Two examples of this type of spiro structure have been reported[2),7)] and this is the first example of constructing such a spiro structure via 1,3-dipolar intermediate.[8)] Similarly the other dipolarophiles listed above were reacted to form the corresponding spiro adducts in 40-70% yield.

In the case of cephalosporin derivatives the cycloaddition reaction was performed similarly, however in this case the double bond isomerization ($\Delta^3 \rightarrow \Delta^2$) occurred in part. Performing the cycloaddition reaction at lower tem-



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perature (0° C) and careful separation of the product by preparative TLC gave the pure sample of spiro adduct of cephalosporin derivative. By this procedure diethyl azodicarboxylate adduct of cephalosporin derivative (VIII) was obtained in 38% yield and the structure was determined as methyl 3',4'-dicarboethoxy-2'-phenyl-1'-triazoline-5'-spiro-7-deacetyl cephalosporanate by the following physico-chemical data:

IR: ν_{max}^{film} 1780, 1750, 1725, 1620, 1260 cm^{-1}. UV: λ_{max} 244 nm (EtOH). Mass spectrum and the elemental analysis shows the molecular formula of $C_{22}H_{24}N_4O_7S$ (M^+ at m/e 488). The NMR spectrum shows the following characteristic signals: δ 1.10 (3H, t., J=7 Hz, CH_3), 1.40 (3H, t., J=7 Hz, CH_3), 2.30 (3H, s., CH_3), 3.30 and 3.50 (2H, AB type, -S-CH_2-, J=16 Hz), 3.86 (3H, s., OCH_3), 4.20 (2H, q., J=7 Hz, CH_2), 4.37 (2H, q., J=7 Hz, CH_2), 5.20 (1H, s.,

6-H), 7.3-7.6 (3H, m and p of C_6H_5) and 7.7-8.0 (2H, o of C_6H_5).

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5) Merck Preparative TLC-plates Silica Gel F_{254} pre-coated, layer thickness 2 mm were used.

6) NMR spectra were taken in $CDCl_3$ on Varian T-60 instrument. TMS was used as an internal standard (δ value was used), s., singlet; d., doublet; t., triplet; q., quartet; m., multiplet; p, para position; o, ortho position.

7) G.A. Koppel and R.E. Koehler, Tet. Lett. 1943 (1973).

8) Spitzer et al. reported a reaction of iminochloride with LDA at -78° C to form anion at $C_{6(7)}$ of penicillins or cephalosporins. However in our case such an electrophile as bromine did not react with the proposed intermediate (III). W.A. Spitzer, T. Goodson, Jr., M.O. Chaney, and N.D. Jones, Tet. Lett. 4311 (1974).