SYNTHETIC STUDIES ON β -LACTAM ANTIBIOTICS 9^{\dagger} TRANSFORMATIONS OF PENICILLIN TO 3'-SUBSTITUTED CEPHALOSPORINS

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An important antibiotic cephalothin $\underline{4b}$ was prepared from $2\beta\text{-acetoxymethyl}$ penicillin $\alpha\text{-}$ sulfoxide la which was derived from penicillin.

Chemical conversion of penicillins into 3'-functionalized cephalosporins has been a subject of intensive studies. We now wish to report our own work in this field.

In a previous paper of this series, 2 we reported a useful method for preparing 2 β -functionalized-methyl penicillin α -sulfoxides. The present paper deals with conversion of one of these α -sulfoxides la into cephalosporanate 4a.

Although every attempt to convert $\underline{1a}$ directly into $\underline{4a}$ by the Morin rearrangement under various experimental conditions failed, 3 we could accomplish preparation of the cephem $4\underline{a}$ by

a sequence of reactions using benzothiazole disulfide $\underline{2a}$ as a key intermediate. Thus, the disulfide $\underline{2a}$ prepared according to the method developed by Kamiya et al. 4 was treated with molecular bromine to afford penam $\underline{3a}$, which upon heating in DMSO at 100°C was rearranged to the desired cephem $\underline{4a}$ in 20% overall yield from the sulfoxide $\underline{1a}$. A better overall yield of 43% was obtained when the disulfide $\underline{2a}$ was treated with AgF in acetonitrile. 5

The cephem <u>4a</u> thus obtained was identified by comparison with an authentic specimen prepared from 7-ACA by the usual procedure. Since <u>4a</u> is known to be transformed to cephalothin <u>4b</u>, an important parenteral cephalosporin antibiotic, by a two-step synthesis involving side-chain exchange and deblocking, the above conversion represents an achievement of

cephalothin synthesis from penicillin-V. Similarly, 2β -chloromethyl penicillin α -sulfoxide $\underline{5}$ prepared from penicillin-V in a straightforward manner, was transformed to penam $\underline{7}$ via disulfide $\underline{6}$ in 70% yield. Compound $\underline{7}$ could also be prepared directly from $\underline{5}$, though in a low yield (20%), on heating with 48% HBr in dimethylacetamide at 50°C. Further conversion of $\underline{7}$ to 3-chloromethyl cephem $\underline{8}$ was, however, unsuccessful even under various experimental conditions. The fact contrasts with the successful conversion of the acetoxy analog 3a described above.

RICON S CI RICON S S Br CO₂R²

$$\frac{5}{2}$$
 $\frac{5}{2}$
 $\frac{6}{2}$
 $\frac{7}{2}$
 $\frac{7}{2}$

Thermal rearrangement of the penam sulfoxide 5 directly to the cephem 8 was also attempted, but no desired product was formed as in the case of the acetoxy analog 1, and instead a compound tentatively assigned to the thiolsulfinate 10 was obtained in low yield. The chloromethyl penam derivatives 5 and 7 were thus found to be reluctant to the ring expansion reactions, but the compound 5 could be finally converted to the exomethylene-cepham sulfoxide 9 in 50% yield on heating 5 in dioxane at 50°C with AgClO4. Compound 9 has been reported to be prepared from penicillin sulfoxide by a different method and to be transformed to various kinds of cephalosporins.

Several other routes to the cephem derivatives were also explored. Thus, reaction of $\underline{13}$ with triethyl phosphite provided a high yield of a thiazoline derivative $\underline{14}$ as expected. When treated with AgClO_4 in dioxane, the thiazoline ring of this compound $\underline{14}$ could be opened giving either its $\operatorname{Ag-salt}\ \underline{15}$ or a re-cyclized exomethylene-cepham $\underline{11}^9$ depending upon the experimental conditions. Treatment of $\underline{15}$ with $\operatorname{H}_2\mathrm{S}$ gave the free mercapto derivative $\underline{12}$.

Ozonolysis of the thiazoline 14 afforded the enol 16, which was cyclized to the 3'-norcephalosporin derivative 17 in a low overall yield. This low yield contrasts with a result obtained in the case of our alternative 3'-norcephalosporin synthesis described previously. The thiazolines 14 and 16 and the mercapto derivatives 12 and 15 could thus be suitable intermediates for synthesizing

Chart 3

$$R^{1}CON$$

$$CO_{2}R^{2}$$

$$11$$

$$CO_{2}R^{2}$$

$$13$$

$$R^{1}CON$$

$$R^{1}C$$

 β -lactam antibiotics of a novel skeleton.

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† Dedicated to Professor Doctor Adolf Butenandt on the occasion of his 75th birthday.

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