SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS 9†
TRANSFORMATIONS OF PENICILLIN TO 3'-SUBSTITUTED CEPHALOSPORINS

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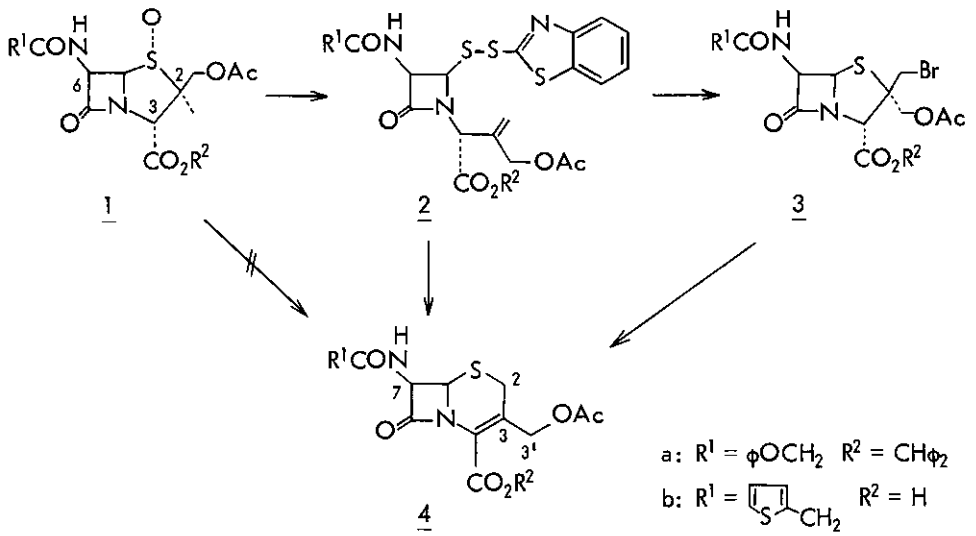
An important antibiotic cephalothin 4b was prepared from 2β-acetoxymethyl penicillin α-sulfoxide 1a which was derived from penicillin.

Chemical conversion of penicillins into 3'-functionalized cephalosporins has been a subject of intensive studies.[1] 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 2β-functionalized-methyl penicillin α-sulfoxides. The present paper deals with conversion of one of these α-sulfoxides 1a into cephalosporanate 4a.

Although every attempt to convert 1a directly into 4a by the Morin rearrangement under various experimental conditions failed,[3] we could accomplish preparation of the cephem 4a by

Chart 1

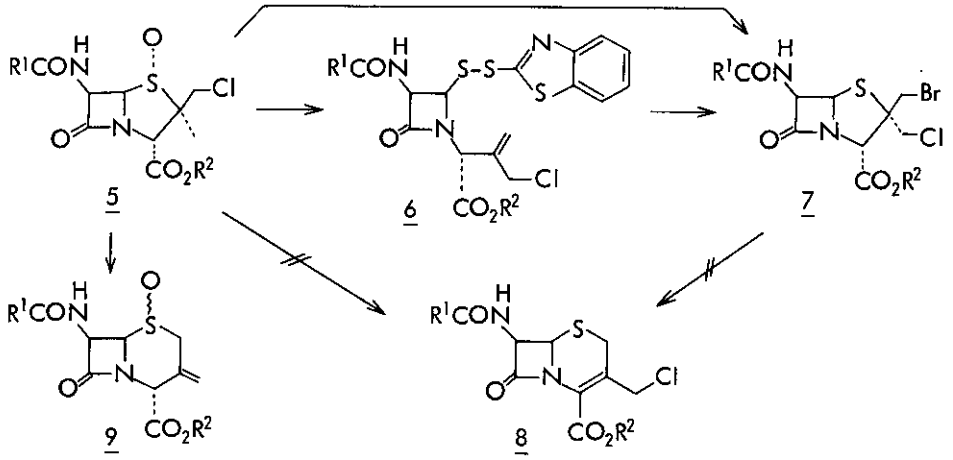


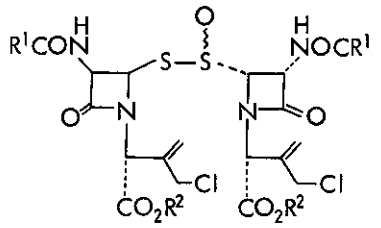
a sequence of reactions using benzothiazole disulfide 2a as a key intermediate. Thus, the disulfide 2a prepared according to the method developed by Kamiya et al.[4] was treated with molecular bromine to afford penam 3a, which upon heating in DMSO at 100°C was rearranged to the desired cephem 4a in 20%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

The cephem 4a thus obtained was identified by comparison with an authentic specimen prepared from 7-ACA by the usual procedure. Since 4a is known to be transformed to cephalothin 4b, 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 5 prepared from penicillin-V in a straightforward manner,[2] was transformed to penam 7 via disulfide 6 in 70% yield. Compound 7 could also be prepared directly from 5, though in a low yield (20%), on heating with 48% HBr in dimethylacetamide at 50°C. Further conversion of 7 to 3-chloromethyl cephem 8 was, however, unsuccessful even under various experimental conditions. The fact contrasts with the successful conversion of the acetoxy analog 3a described above.

Chart 2





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$R^1 = \phi OCH_2$

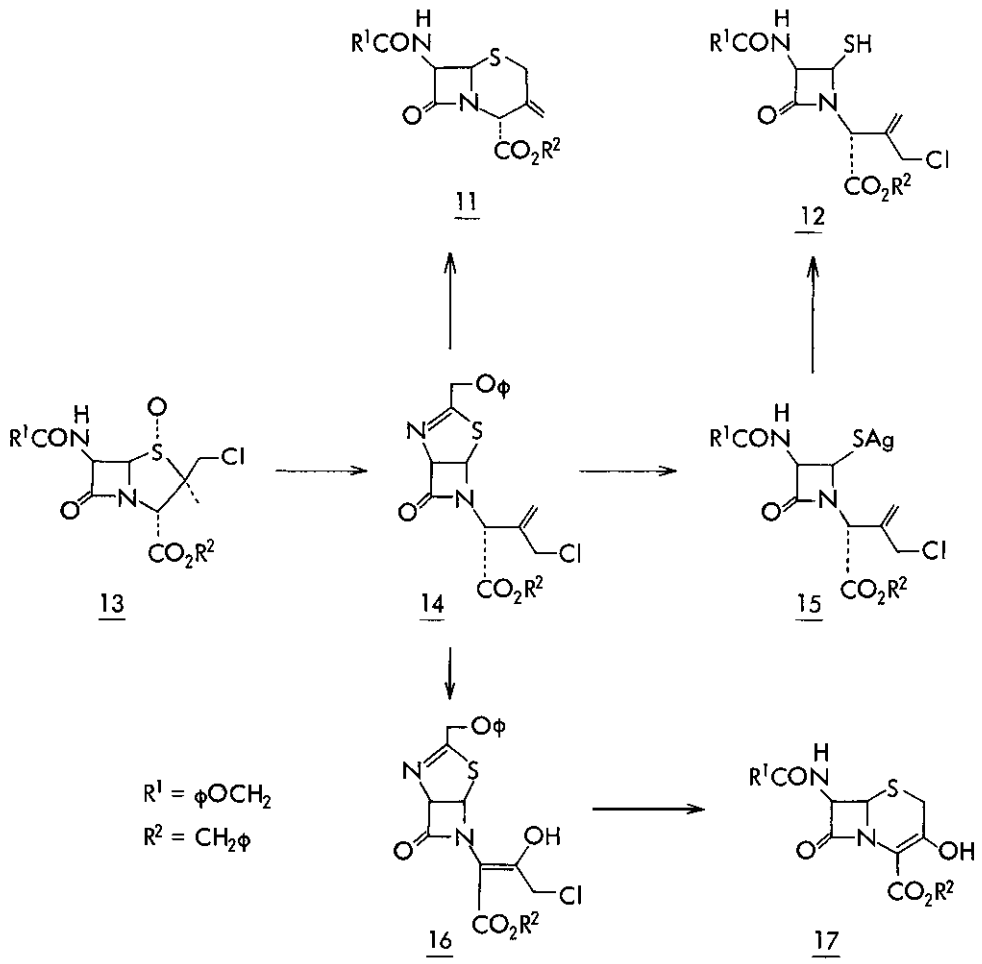
$R^2 = CH\phi_2$

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[6] 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 $AgClO_4$.[7] Compound 9 has been reported to be prepared from penicillin sulfoxide by a different method[8] and to be transformed to various kinds of cephalosporins.[1]

Several other routes to the cephem derivatives were also explored. Thus, reaction of 13 with triethyl phosphite provided a high yield of a thiazoline derivative 14 as expected. When treated with $AgClO_4$ in dioxane, the thiazoline ring of this compound 14 could be opened giving either its Ag-salt 15 or a re-cyclized exomethylene-cepham 11[9] depending upon the experimental conditions. Treatment of 15 with H_2S gave the free mercapto derivative 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.[10] The thiazolines 14 and 16 and the mercapto derivatives 12 and 15 could thus be suitable intermediates for synthesizing

Chart 3



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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