Registry No.—**6,** 54531-78-1; **6′,** 54531-79-2; **7,** 54531-80-5; **7′,** 54531-81-6; **8,** 54531-82-7; **9,** 54531-83-8; **10,** 54531-84-9; **11,** 54531-85-0; **12,** 54531-86-1; **13,** 54531-87-2; **14,** 54531-88-3; **15,** 54531-89-4; **16,** 54531-90-7; **17,** 54531-91-8; **18,** 54531-92-9; **22,** 54531-93-0; **23,** 54531-94-1; **26,** 17622-50-3; **27,** 54531-95-2; benzyl chloride, 100-44-7; benzophenone, 119-61-9; benzaldehyde, 100-52-7; anisaldehyde, 123-11-5; methyl benzoate, 93-58-3; benzonitrile, 100-47-0; chalcone, 94-41-7.

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Notes

One-Step, High Yield Conversion of Penicillin Sulfoxides to Deacetoxycephalosporins

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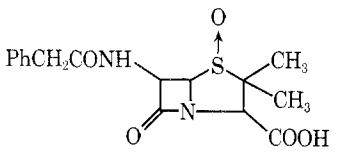
Morin and coworkers demonstrated the chemical relationship between the penicillin and cephalosporin skeleton by an unprecedented acid-catalyzed rearrangement.[1] Because of the therapeutic utility of cephalexin[2] (**2a**), a deacetoxycephalosporin, a high yield conversion of a penicillin sulfoxide to a deacetoxycephalosporanic acid would be very attractive. The known methods, of which some give yields of >80%,[3] have the disadvantage of being limited to the conversion of esters of a penicillin sulfoxide to the corresponding esters of the deacetoxycephalosporin, which requires two more reaction steps, viz., the esterification of the starting penicillin compound as well as the de-esterification of the deacetoxycephalosporin. Rearrangement of the acids gives either decarboxylated products[1] or 3-hydroxy-3-methylcepham compounds.[4] In some cases deacetoxycephalosporanic acids are also formed but the yields are low.[5]

The present paper describes a convenient and efficient method to convert penicillin sulfoxides to deacetoxycephalosporanic acids by using silyl protection.

The use of the silyl group for protection of a carboxyl group has advantages such as easy introduction and removability over the use of other protecting groups. The conversion of a penicillin sulfoxide to a deacetoxycephalosporin implies the liberation of a molecule of water. Accordingly, the known rearrangement procedures[3] fail when applied to silylated penicillin sulfoxides,[6] since silyl esters[7] are very susceptible to cleavage by water. The use of an excess of silyl compound, e.g., trimethylchlorosilane, seemed to offer the best chance of success for three reasons: the carboxyl group is protected against decarboxylation, the HCl that is



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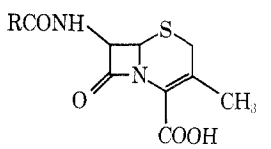
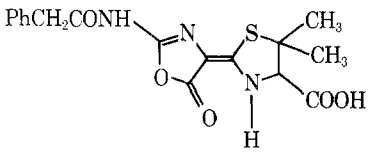


2a, R = PhCH(NH$_2$)

b, R = PhCH$_2$



3

formed catalyzes the ring enlargement reaction, and attack on the silylated carboxyl group is prevented because the excess silyl compound traps the water[8] formed during the reaction. However, when an attempt was made to rearrange benzylpenicillin sulfoxide (**1**) with a sufficiently large excess of trimethylchlorosilane to fulfil the conditions mentioned above, formation of deacetoxycephalosporanic acid could not be detected. Better results were obtained when a large excess of a rather weak base was added to the reaction mixture. In this way benzylpenicillin sulfoxide was converted in a yield of 75% to a mixture of ring-enlarged products, consisting of Δ^2- and Δ^3-benzyldeacetoxycephalosporanic acid and the decarboxylated cephalosporin (method A), from which the Δ^3 compound could be isolated in yields of up to 50%. Interesting is a side reaction, viz., the formation of the oxazolonethiazolidine compound (**3**), better known as "dehydrobenzylpenicillin".[9] The control of this product ratio was insufficient which is obviously related to the triple role played by the silyl compound and especially to the fact that the amount of HCl present during the reaction is

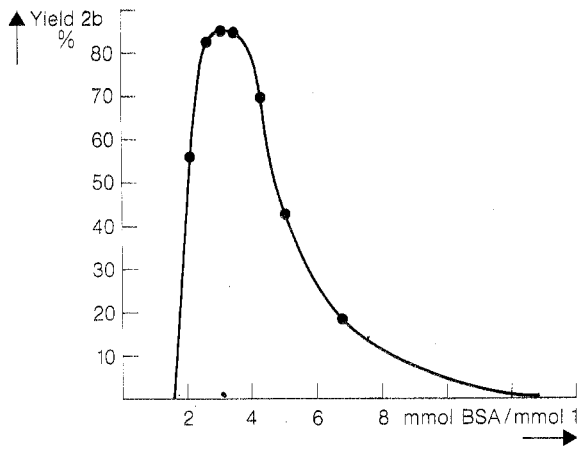


Figure 1. Correlation between the yield of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid (**2b**) and the amount of BSA.

not constant. The problem was solved by the use of silylating agents which could not give rise to the formation of acids during the reaction and which are more reactive than the silylated β-lactams toward reactive intermediates. Such a compound is *N,O*-bis(trimethylsilyl)acetamide (BSA), which has a strong silylating capacity.

An acid sufficiently strong to prevent its own silylation by BSA was now required as catalyst. After extensive experimentation it became apparent that HBr gave higher yields than other strong acids. Also, the amount of base could be reduced drastically which had the advantage of preventing the formation of the Δ^2 isomer. When the amount of BSA was varied, the yield of deacetoxycephalosporanic acid showed a peak at a ratio of BSA: 1 of ~3:1 (Figure 1), which suggests that only one of the two silyl groups of the BSA molecule is reactive enough to ensure both sufficient protection of the carboxyl group and the trapping of the water formed during the ring enlargement. The use of still larger amounts of BSA causes considerable silylation of HBr and consequently a strong decrease in the yield. Under the right conditions yields of >80% of Δ^3-deacetoxycephalosporanic acid were obtained[10] (method B).

Experimental Section[11]

Preparation of Benzylpenicillin Sulfoxide (1). A mixture of 75 g (0.19 mol) of the potassium salt of benzylpenicillin, 1 l. of water, and 45.5 g (0.20 mol) of sodium metaperiodate was stirred for 2 hr at 25°. After cooling to 0°, the reaction mixture was extracted with chloroform at pH 1. The chloroform layer was concentrated to a volume of ~150 ml and 400 ml of diethyl ether was added. The precipitated benzylpenicillin sulfoxide was filtered off, washed with diethyl ether, and dried under reduced pressure to yield 64 g (90% 1): mp 142.5–143.5° dec; NMR ($CDCl_3$) δ 1.23 (s, 3), 1.66 (s, 3), 3.55 (s, 2) 4.52 (s, 1), 4.98 (d, 1, J = 4.5 Hz), 5.81 and 5.98 (dd, 1, J = 4.5 and 10 Hz), 7.23 (s, 5), 7.37 (d, 1, J = 10 Hz).

Conversion of Benzylpenicillin Sulfoxide to Δ^3-7-Phenylacetamidodeacetoxycephalosporanic Acid (2b). Method A. A mixture of 90 g (0.257 mol) of benzylpenicillin sulfoxide, 210 ml (1.66 mol) of trimethylchlorosilane, 900 ml (9 mol) of α-picoline, and 900 ml of chloroform was heated for 20 hr at 83°. The reaction mixture was cooled and stirred with water, after which the pH was adjusted to 7.5 with a 4 *N* potassium hydroxide solution. The aqueous layer contained 52 g (55% yield) of the potassium salt of **2b** as estimated by a direct microbiological assay using *Escherichia coli* as the test microorganism. The aqueous layer was separated, adjusted to pH 1.5 with 4 *N* hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate was then replaced by 1-propanol (925 ml) and the propanolic solution cooled to ~0°. Addition of 3.5 ml of water and 100 ml of a 1.25 *M* solution of the potassium salt of 2-ethylcaproic acid in butyl acetate gave a precipitate which was filtered off and dried. The solid material (57 g) contained 45 g of the potassium salt of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid (yield 47%) and 7 g of the Δ^2 isomer.

Method B. To 10.5 g (30 mmol) of benzylpenicillin sulfoxide were added successively 195 ml of dioxane, 25 ml (102 mmol) of *N,O*-bis(trimethylsilyl)acetamide, 6 ml (61 mmol) of α-picoline, and 5.2 ml of a 5.8 *M* solution of α-picoline hydrobromide in dichloromethane. After refluxing for 6 hr at 102°, the reaction mixture was cooled to 20° and poured into 1500 ml of ice–water. Then 650 ml of ethyl acetate and 50 ml of butyl acetate were added and with stirring the pH was adjusted to 7 with 4 *N* potassium hydroxide solution. The mixture was allowed to separate and the organic layer was set aside. The aqueous layer was washed with 300 ml of ethyl acetate and 50 ml of butyl acetate. The resulting organic layer was combined with the one obtained before and the combination re-extracted with 200 ml of a 0.75 *M* potassium phosphate aqueous solution buffered to pH 7. The extract was added to the main aqueous solution. This combined aqueous mixture contained 9.2 g of the potassium salt of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid as determined by a direct microbiological assay using *Escherichia coli* as the test microorganism. After addition of 500 ml of butyl acetate to the aqueous solution, the mixture was stirred and the pH was adjusted to 2 with 4 *N* sulfuric acid. The mixture was allowed to stand and the organic extract was separated. The aqueous layer was re-extracted with 250 ml of butyl acetate. The combined butyl acetate extracts were filtered through a water repellent filter. To the butyl acetate solution was then added with rapid strring 2.65 g of anhydrous, finely powdered potassium acetate. After the mixture stirred for 3 hr at room temperature, the precipitate was isolated by filtration, washed with a little butyl acetate, and dried in vacuo at 30°, giving 10.2 g of the potassium salt of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid, with a purity of 85% as estimated by microbiological assay (yield 78%). The NMR spectrum (D_2O) showed signals at δ 1.94 (s, 3), 2.99 (d, 1, J = 18 Hz), 3.44 (d, 1, J = 18 Hz), 3.62 (s, 2), 4.97 (d, 1, J = 4.5 Hz), 5.58 (d, 1, J = 4.5 Hz), and 7.27 (s, 5), which corresponded exactly, as did the ir and uv spectra, with those of an authentic sample prepared according to Stedman et al.[12]

Correlation between the Yield of Δ^3-7-Phenylacetamidodeacetoxycephalosporanic Acid and the Amount of BSA. A mixture of 1.05 g (3 mmol) of benzylpenicillin sulfoxide, 0.9 ml (9 mmol) of α-picoline, and a solution of 3.0 mmol of hydrogen bromide in dioxane was refluxed for 4.5 hr with different amounts of BSA (the total volume was always 2.4 ml). The yield of Δ^3-7-phenylacetamidodeacetoxycephalosporanic acid was estimated by microbiological assay and plotted against the amount of BSA (Figure 1).

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Registry No.—**1**, 4052-54-4; **2b**, 27255-72-7; **2b** potassium salt, 34708-38-8; benzylpenicillin potassium salt, 113-98-4; trimethylchlorosilane, 75-77-4; BSA, 10416-59-8.

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