

6- β -[BISTRIFLUOROMETHANESULFONYL]AMIDOPENICILLANIC ACID. A NOVEL β -LACTAMASE
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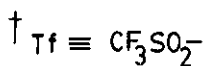
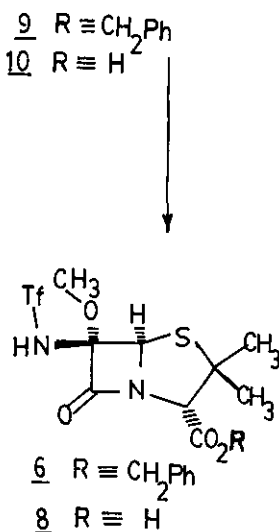
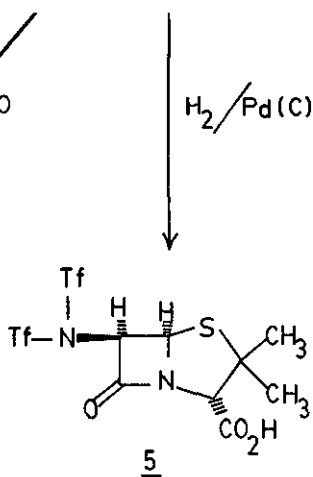
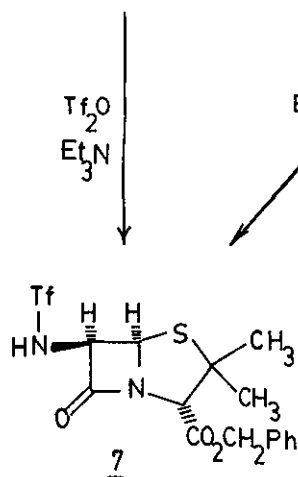
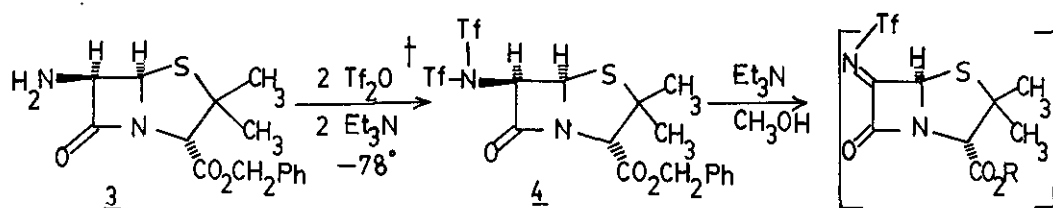
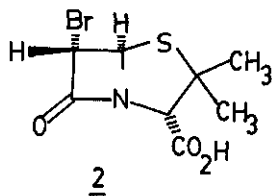
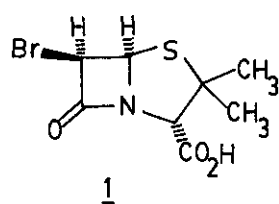
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Abstract - Benzyl 6- β -[bistrifluoromethanesulfonyl]amidopenicillanate, **4**,
was prepared by reaction of benzyl 6- β -aminopenicillanate, **3**, with two
equivalents of trifluoromethane sulfonic anhydride. In the presence of
aqueous base **4** undergoes detriflation to yield **7** and in the presence of
basic methanol **4** yields the α -methoxymonotriflamide **6**. The free acid **5**
obtained by hydrogenolysis of **4** has β -lactamase inhibitory properties.

The limitations imposed on the chemotherapeutic applications of penicillins by the ability of
bacteria to produce enzymes, β -lactamases, which inactivate β -lactam antibiotics, were recognized
some time ago.¹ In recent years there has been significant progress made towards overcoming this
problem through the development of effective β -lactamase inhibitors derived directly from natural
sources² and also derived from natural penicillins through chemical modification.³

Pratt and Loosemore⁴ and also Waley and coworkers⁵ have reported that 6- β -bromopenicillanic acid
4 is a potent inhibitor of β -lactamases. The early reports indicated that **4** could be synthesized
only as a minor component (< 28%) of a mixture containing the C₆ α epimer, **3**, and that the epimers
could not be separated.⁶ Because of our continuing interest in the inhibition of β -lactamases⁷,
we undertook a study aimed at the design and synthesis of analogs of **4** which would possess a
potential leaving group at C₆ and which could be prepared as pure C₆ β -isomers. We report herein
the preparation and reactions of one such analog **5**. The known tendency of bistriflamido groups
to function as leaving groups in S_N2 type displacement reactions⁸ suggested that **5** might behave
chemically (and hopefully biochemically) as an analog of **4**.

Treatment of the benzyl ester of 6- β -aminopenicillanic acid **3** with two equivalents of freshly
distilled triflic anhydride at -78° in methylene chloride containing two equivalents of triethyl-
amine yielded after aqueous workup the bistriflamide **4** as a crystalline solid (i.r. 1810
(β -lactam), 1750 (ester); ¹H n.m.r. δ (CDCl₃) 1.45 (s, 3; C₂ α or β -CH₃), 1.72 (s, 3; C₂ β or α -CH₃)
4.52 (s, 1; C₃-H), 5.20 (s, 2; OCH₂-Ph), 5.48 (d, J = 4.1; C₅-H), 5.73 (d, J = 4.1; C₆-H) 7.37
(s, 5; ArH). Anal. Calcd. for C₁₇H₁₇N₂O₇S₃F₆: C, 35.78; H, 2.83; N, 4.91; S, 16.86; F, 19.98;



Found: C, 36.06; H, 2.96; N, 4.88; S, 16.98; F, 19.67.) ¹⁹F n.m.r. 7.80 relative to external CF₃CO₂H (s, CF₃SO₂N).

It was clear from the proton and ¹³C n.m.r. that 4 was obtained as a single epimer with the β-configuration (J_{5,6} = 4 Hz) at C-6. C-6-α-epimers show a smaller (J_{5,6} = 1-2 Hz) coupling⁴. Hydrogenolysis of 4 in methanol yielded the free acid 5. Preliminary experiments have indicated that 5 is capable of rapid complete inhibition of β-lactamase-I from *B. cereus* 569/H at inhibitor concentrations on the order of 10⁻⁵ molar⁹.

Since we expected that the β -lactamase inhibitory action of $\mathfrak{5}$ involved reaction with an enzyme-bound nucleophilic group we examined the base catalyzed reaction of $\mathfrak{4}$ with water and methanol. Two reaction modes have come to light. With triethylamine in aqueous DMF, $\mathfrak{4}$ acts as a triflating agent towards water yielding the monotriflamide $\mathfrak{7}$ which was also obtained by monotriflation of $\mathfrak{3}$. The free acid $\mathfrak{8}$ had no β -lactamase inhibitory properties but interestingly is apparently β -lactamase resistant.

In methanol containing excess triethylamine, $\mathfrak{7}$ was obtained as a minor product ($\sim 5\%$). The major product was the 6- α -methoxymonotriflamide $\mathfrak{6}$ (^1H n.m.r. 1.40 (s, 3, $\text{C}_{2\alpha}$ or $\beta\text{-CH}_3$), 1.58 (s, 3, $\text{C}_{2\beta}$ or $\alpha\text{-CH}_3$), 3.60 (s, 3, OCH_3), 4.54 (s, 1, $\text{C}_3\text{-H}$), 5.21 (s, 2, $\text{Ar-CH}_2\text{O-C-}$), 5.53 (s, 1, $\text{C}_5\text{-H}$), 7.38 (s, 5, Ar-H) ^{19}F n.m.r. 0.42 (s, $(\text{CF}_3\text{SO}_2)_2\text{N}$) which presumably arises via an elimination-addition sequence via $\mathfrak{9}$ as shown. The stereochemistry of $\mathfrak{6}$ is assumed to be α at C-6 by analogy with the known stereoselectivity of additions of alcohols to 6-acyliminopenicillanic acid derivatives.¹⁰ Analogous elimination-addition reactions have been observed with *N,N*-bisaryl-sulfenylaminopenicillanic acid derivatives which also show some β -lactamase inhibitory activity.¹

These observations suggest the possibility that triflation of a key functional group of the β -lactamase by $\mathfrak{5}$ or alkylation by $\mathfrak{10}$ derived from $\mathfrak{5}$ may account for the β -lactamase-inhibitory properties of the distrifamide $\mathfrak{5}$. Detailed chemical and spectroscopic studies of the inhibition process are in progress. In addition the possible utility of the elimination process, $\mathfrak{4} \rightarrow \mathfrak{9}$ in the preparation of 6 α -alkoxy penicillins or 7 α -alkoxycephalosporins is under investigation.

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