SEMISYNTHETIC β-LACTAM ANTIBIOTICS.V. SYNTHESIS OF α-SULFOBENZYLPENICILLIN BY USING MIXED ANHYDRIDE AND ACTIVE ESTER OF α-SULFOPHENYLACETIC ACID

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The synthesis of α-sulfobenzylpenicillin (V) was first accomplished in our Research Laboratory. The compound exhibits the peculiar activity against G(+) and G(-) bacteria. For the preparation of this penicillin several activated derivatives of α-sulfophenylacetic acid (I) have been obtained in the purified form.

In the previous paper[1,2] of this series we reported the synthesis and biological activity of α-sulfobenzylpenicillin (V). The most convenient method to prepare this penicillin is the Schotten-Baumann reaction, in which 6-aminopenicillanic acid (6-APA) was acylated with the appropriate acid chloride in the alkaline solution.

In the course of our synthetic study of this compound (V), mixed anhydride and active ester method have been attempted. As the result several new derivatives of α-sulfophenylacetic acid (I) have been obtained, which successively leads to the coupling reaction with 6-APA to yield α-sulfobenzylpenicillin (V). Synthetic procedures were summarized in Figures 1 and 2.

The preparation of mixed anhydride of α-sulfophenylacetic acid has been successfully achieved by treating α-sulfophenylacetic acid (I) with ClCOOR (III) in the methylenchloride solution in the presence of trialkylamine. After the mixture was reacted at 40°C for 2 hrs., the precipitate was filtered off and the mother liquor was evaporated to dryness. The residue was recrystallized from benzene to give the white crystalline products (VI). In this experiment we observed that the reaction of α-sulfophenylacetic acid (I) which contains two acidic groups on the same carbon atom has been selectively progressed at the carboxylic acid group and there were no evidence in the formation of mixed sulfonic-carboxylic anhydride.[3] These derivatives are listed in Table 1. Ag salt (I") was also converted into its mixed anhydride (VII) by treating with the acid chloride (II). The preparation of the active ester of I, e.g. pentachlorophenyl ester has been also attempted in the DMF solution at room temperature in the presence of triethylamine. After the addition of ethanol to the reaction mixture, the crystalline product of VIII has been obtained. These esters were also the active acylating agent of 6-APA as shown in Figure 2.

REACTION OF 6-AMINOPENICILLANIC ACID WITH THE MIXED ANHYDRIDES

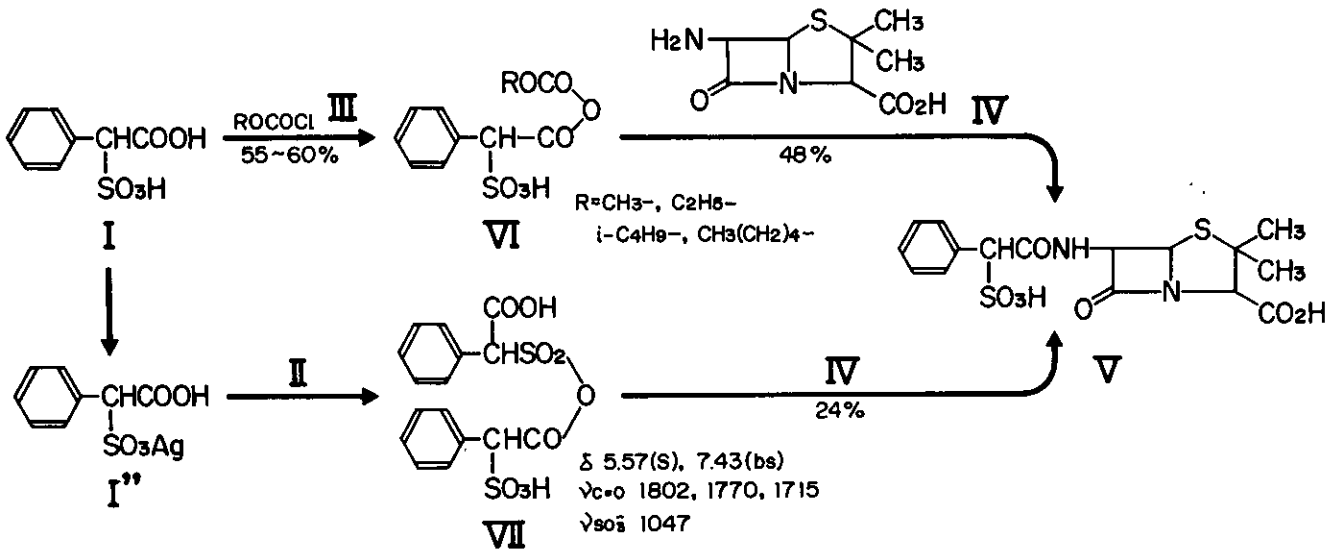


Figure 1

REACTION OF 6-AMINOPENICILLANIC ACID WITH THE ACTIVATED ESTERS

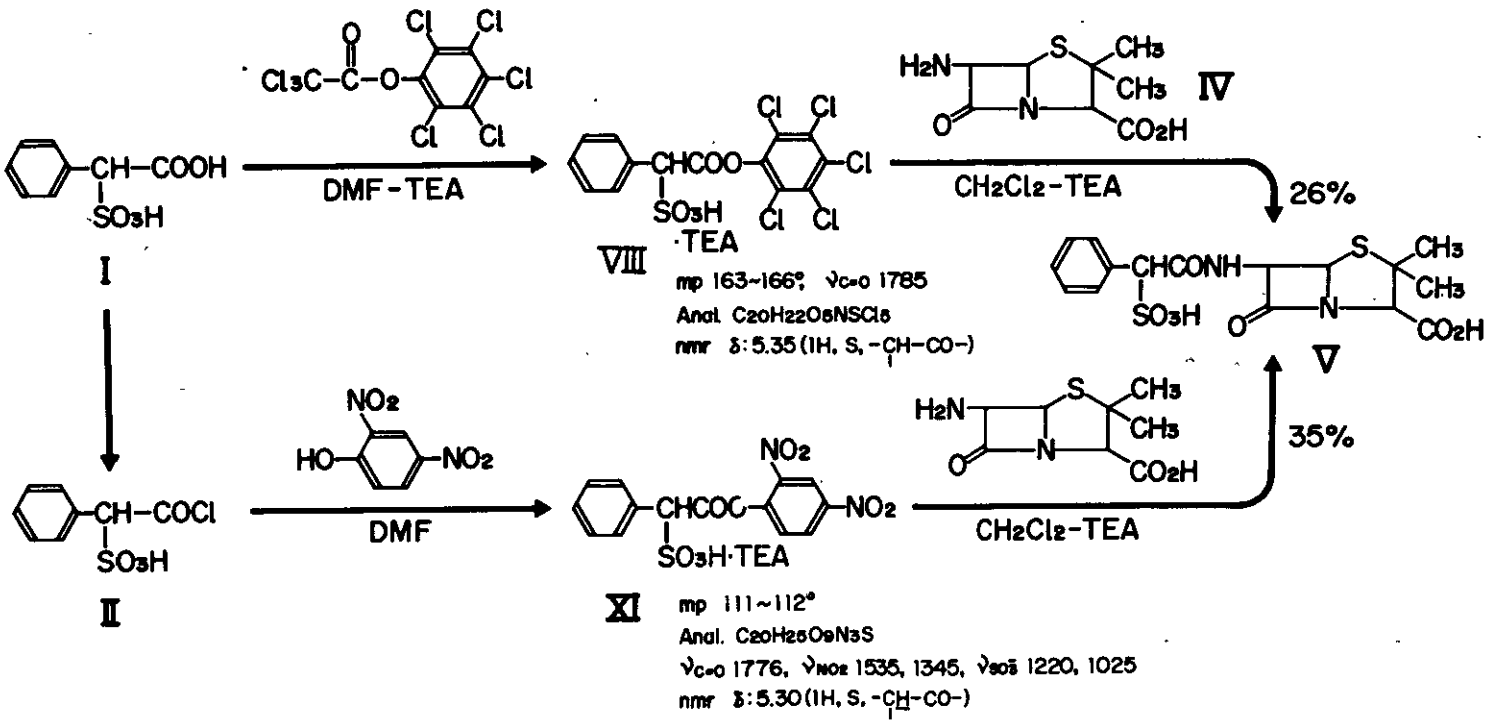
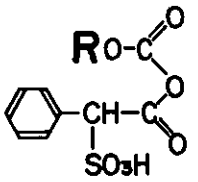


Figure 2

TABLE I. THE MIXED ANHYDRIDES OF α-SULFOPHENYLACETIC ACID



VI

ROC– [a]	mp °C	nmr (60 Mc, ppm) [b] α-Methine	nmr (60 Mc, ppm) [b] Phenyl	ir (cm⁻¹) $\nu_{C=O}$	ir (cm⁻¹) ν_{-SO_2-}, $-SO_3^-$
CH_3O-C-	oil	4.93, s	7.2~7.8, m	1820, 1772	1240, 1090, 1028
CH_3CH_2O-C-	86~90	5.00, s	7.2~7.8, m	1818, 1755	1240, 1190, 1090, 1048, 1011
$(CH_3)_2CHCH_2O-C-$	82~84	5.01, s	7.2~7.8, m	1817, 1758	1233, 1190, 1085, 1035, 1015
$CH_3(CH_2)_4O-C-$	oil	5.00, s	7.2~7.8, m	1817, 1759	1240, 1190, 1090, 1025

a) Triethylamine salt
b) $CDCl_3$

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