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# NOVEL PENICILLIN TRANSFORMATION PRODUCTS

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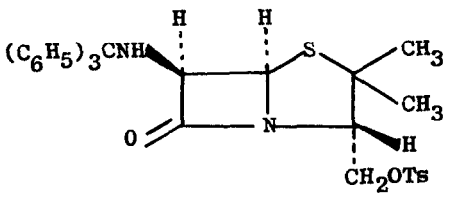
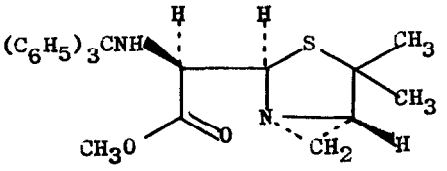
As part of a program to synthesize novel penicillin derivatives we examined the products of the base-catalyzed methanolysis of the tosylates I (mp 102-105°) and III (mp 118-119.5°) prepared from the corresponding alcohols (1).

In the presence of excess sodium bicarbonate in boiling methanol the tosylate I was rapidly converted in high yield to the aziridine II (mp 130-131.5°). The spectra were in accord with the assigned structure. The nmr spectrum exhibited peaks at 104 cps (2H, apparent triplet) and 127 cps (1H, apparent quartet) corresponding to the three protons of the aziridine ring (2, 3). Identical treatment of the tosylate III led to a mixture of approximately equal parts of the aziridine IV (mp 104-106.5°) and the episulfide-enamine VI (mp 112.5-114°). The aziridine IV may be obtained in essentially quantitative yield by use of excess diethylamine in hot methanol; it was transformed in high yield to the episulfide VI by sodium bicarbonate in hot methanol.

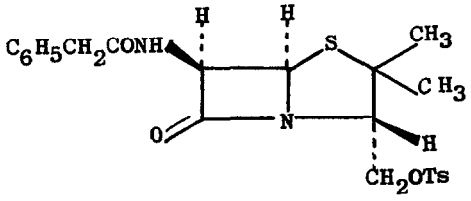
The nmr spectrum of IV exhibited peaks at 102 cps (2H, apparent quartet) and 137 cps (1H, apparent quartet) assigned to the three protons of the aziridine ring (2, 3). The disappearance of these signals after treatment of IV with dilute aqueous mineral acid provides additional evidence for an aziridine ring (4). The structure of VI follows from its strong ultraviolet absorption at 280 mμ, characteristic of the β-aminoacrylic ester chromophore (5), and its desulfurization by triphenylphosphine (6) in boiling acetonitrile



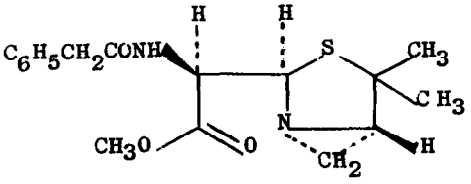
I



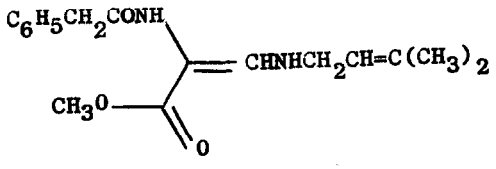
II



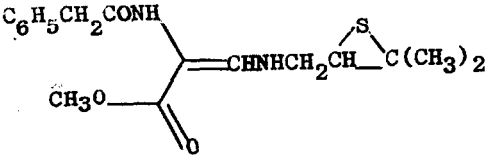
III



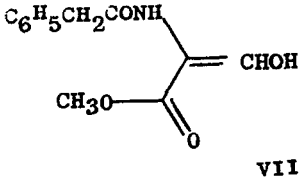
IV



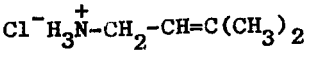
V



VI



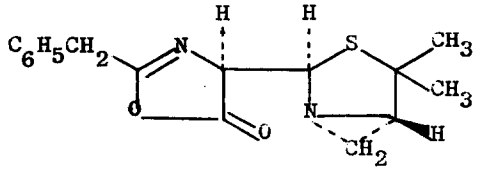
VII



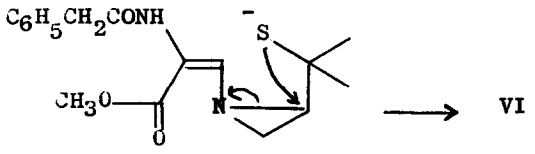
VIII

to the optically inactive enamine V (mp 80-84°) without change in the ultraviolet absorption. Mild acid hydrolysis of V led to penaldic acid methyl ester (7) (VII, isolated as the 2,4-DNP derivative) and 3-methyl-2-butenylamine (8) (VIII, isolated as the hydrochloride), both obtained in good yield and identical with authentic specimens.

The formation of the aziridines is base-catalyzed since neither tosylate was affected by boiling methanol alone. This observation suggests the reaction is not initiated by ionization of the tosylate with participation by the electron pair on the lactam nitrogen atom to give an acyl aziridine. If it is assumed that an appreciable amount of methoxide is generated in a hot solution of sodium bicarbonate in methanol, a reasonable picture of the reaction course would be attack by methoxide at the lactam carbonyl followed



IX



X

by formation of the aziridine ring. The lack of formation of diethylamide in the transformation of III to IV in the presence of a two-fold excess of diethylamine suggests the reaction is initiated by removal of the proton from the side chain nitrogen atom and formation of the oxazolone-aziridine intermediate IX. The expected high reactivity of the oxazolone as an acylating agent would account for its reaction with solvent rather than the more nucleophilic diethylamine (9). The intermediate X, derived from IV or IX by a base-catalyzed elimination process, may be envisioned as the precursor to the episulfide-enamine.

Satisfactory analyses and spectra were obtained for all new compounds.

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2. The spectrum was measured in 20% $DCCl_3$ on a Varian A-60 spectrometer. Chemical shifts are in cycles per second from tetramethylsilane.

3. The four protons on carbon of ethyleneimine appear as a singlet at 97 cps in Spectrum No. 372 of the Varian NMR Spectra Catalog.

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