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PENICILLIN TRANSFORMATIONS

I. CONVERSION OF A PENICILLIN INTO A 7-OXO-2,3,4,7-TETRAHYDRO-1,4-THIAZEPINE STRUCTURE

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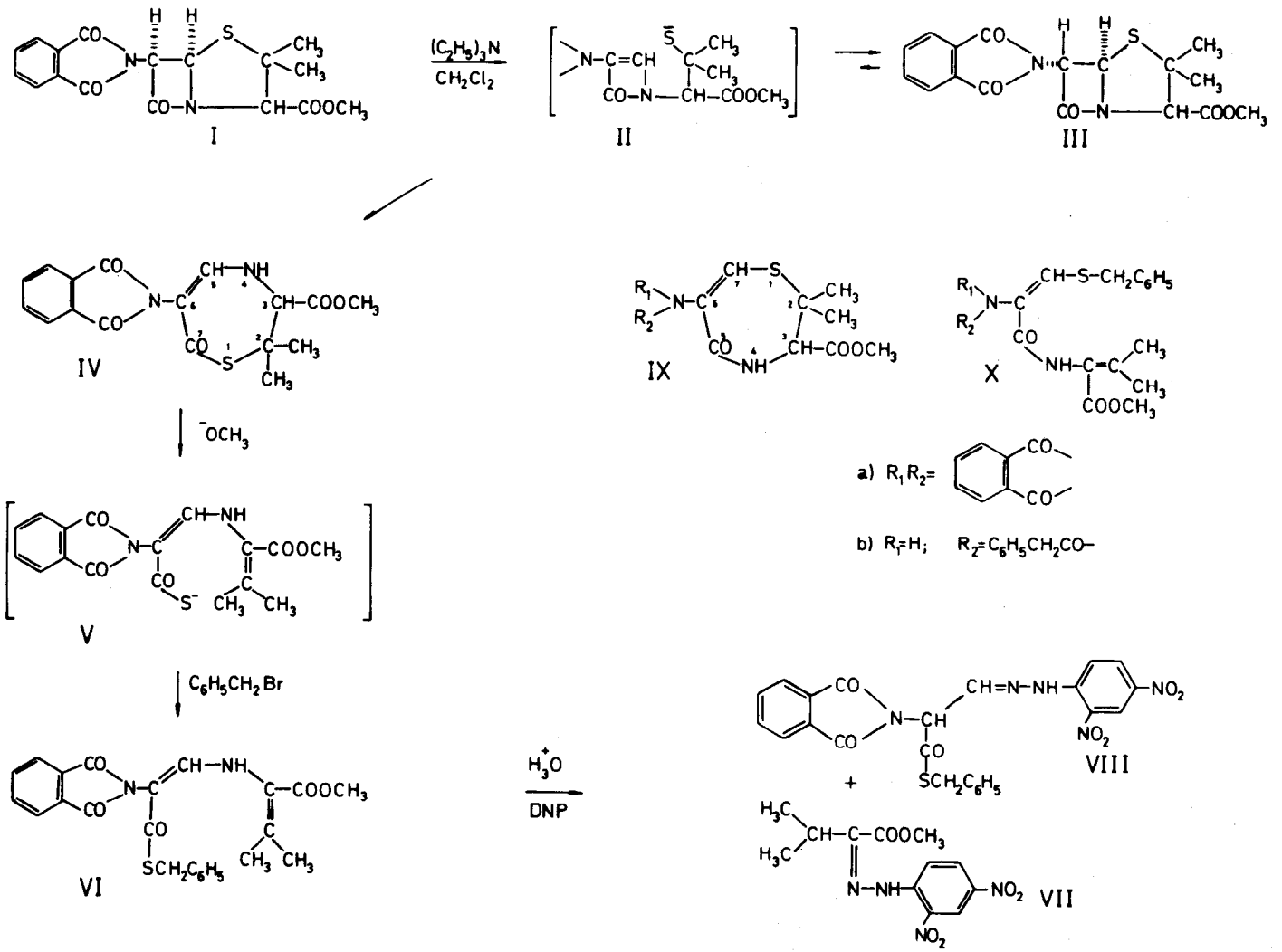
In a recent paper Wolfe and Lee (1) reported the epimerization at C-6 of methyl 6-phthalimidopenicillanate (I) on treatment with basic reagents such as sodium hydride, potassium t-butoxide, or triethylamine. They suggested a reaction mechanism (I → II → III) involving a β-elimination with rupture of the bond between C-5 and S, but could not substantiate it by isolating or trapping the intermediate thiol structure.

On preparing the C-6 epimer (III) of methyl 6-phthalimidopenicillanate according to Wolfe and Lee by treatment of I with triethylamine (3 equiv.) in methylene chloride at room temperature, an additional product (IV) was detected by thin layer chromatography. The compound, m.p. 217-218°, $[\alpha]_D^{20}$: -201.8 (c = 2.0, pyridine), was isolated in a 25 % yield by preparative thin layer chromatography or later on by conventional work up on a larger scale. Elemental analysis and molecular weight determination showed it to be isomeric with I and III.

The IR-spectrum of the compound contained no β-lactam absorption band and appeared very similar to although not identical with the spectrum of a compound, m.p. 237-237.5°, (2) tentatively assigned the structure IXa, 2,2-dimethyl-3-carbomethoxy-5-oxo-6-phthalimido--2,3,4,5-tetrahydro-1,4-thiazepine, with racemic C-3. The UV-spectrum of IV was found to be almost identical with that reported for IXa. The NMR-spectrum of IV (in $(CD_3)_2SO$) showed peaks attributable to a gem-dimethyl group, τ = 8.32 and 8.36 p.p.m., an ester methoxyl, τ = 6.20 p.p.m. and a phthalyl group, τ = 2.08 p.p.m. and three multiplets: τ = 5.42 p.p.m. (d. J = 6 c.p.s.), τ = 2.68 p.p.m. (d. J = 9 c.p.s.) and τ = 1.32 p.p.m. (2 d. J = 6 and 9 c.p.s.), each corresponding to one proton and forming an AMX-system. Such a coupling pattern can be accommodated to the structure IX only by assuming a long range coupling between the protons at N-4 and C-7. However, in the NMR-spectrum of compound IXb, no such coupling has been observed, the proton at C-7 appearing as a sharp singlet at τ = 2.38 p.p.m. (3). The obtained spectrum instead suggested that our compound should be assigned the 2,2-dimethyl-3-



-carbomethoxy-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine structure (IV), the AMX-system being formed by the protons at C-3, C-5 and N-4 respectively. The other spectral data observed for the compound were in accordance with this structure. In infra-red a broad absorption band with minor peaks at 1752 and 1720 cm^{-1} and a strong one at 1690 cm^{-1} could be attributed to the phthalyl, the methyl ester and the thiol ester groups and the UV-spectrum would appear consistent with the chromophoric system of IV as well as with that of IX. Further evidence for the thiol ester group in IV was obtained from the mass spectrum which contained two peaks at m/e = 300 (relative intensity 10 %) and 60 (relative intensity 35 %) indicating the loss of COS from the molecular ion. The mass of the first one could be estimated by high resolution mass spectrometry and was found to correspond well to that of the expected ion (found m/e = 300.1121; calc. for $[C_{16}H_{16}N_2O_4]^{\cdot+}$ m/e = 300.1110). Both ions were absent or of very low intensity in the spectra of I and III.

Chemical evidence for the adopted structure was obtained by desulphurization of IV with Raney-Ni and subsequent hydrolysis, yielding a.o. phthalic acid and valine but no alanine as expected for IX and found with IXb (3). Treatment of IV with sodium methoxide (1 equiv.) in methanol at room temperature caused rapid loss of the optical activity in an elimination reaction leading to the carbothiolate V which without isolation was converted into the S-benzyl ester VI (m.p. 151-152.5°) by treatment of the reaction solution with benzyl bromide. Elimination reactions of the penicillamine structure under basic conditions leading to the dehydrovaline system are previously known, e.g. in the rearrangement of penicillins to anhydropenicillins (4). Under reaction conditions identical to ours IXb has been found to give the vinyl sulphide derivative Xb (5) *via* an enethiolate.

The NMR-spectrum of VI in $CDCl_3$ was in agreement with the adopted structure VI. In addition to peaks corresponding to the isopropylidene, the ester methoxyl, the benzyl and the phthalyl groups, the spectrum contained only one coupling pattern, an AX-system formed by two protons with chemical shifts (τ = 3.26 and -0.09 p.p.m., J = 13 c.p.s.), attributable to the enamine moiety of VI. In contrast the NMR-spectrum of Xb shows no such pattern, the vinylic proton appearing as a singlet (5).

Finally hydrolysis of VI with ethanolic hydrochloric acid for two days at room temperature, in the presence of 2,4-dinitrophenylhydrazine, gave in nearly quantitative yield a mixture of two 2,4-dinitrophenylhydrazones (VII, VIII) which could be separated by column chromatography. VII (m.p. 180-181°) was identified as the 2,4-dinitrophenylhydrazone of methyl

α-oxo-isovalerate (6) by comparison with an authentic sample. VIII (m.p. 110-114°) gave correct elemental analysis as a 2,4-dinitrophenylhydrazone of benzyl α-phthalimidothiomalonaldehydate and showed properties (IR, NMR) in agreement with this structure.

Our results show that IV should be assigned the structure 2,2-dimethyl-3-carbomethoxy--6-phthalimido-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine. This compound can arise from I only by nucleophilic attack of the sulphur on the carbonyl group of the β-lactam ring, i.e. via the intermediate thiol structure II. We have thus found that when methyl 6-phthalimidopenicillanate is epimerized at C-6 by treatment with triethylamine in methylene chloride a β-elimination with fission of the bond between C-5 and S does occur as required by the mechanism of the epimerization put forward by Wolfe and Lee (1). According to chromatographic evidence we have found that IV can also be obtained from the epi-ester (III) after a prolonged reaction time. This provides additional support for but does not prove their hypothesis. Other mechanisms may well be operating and recently simple de- and reprotonization at C-6 has been proposed as a mechanism for the epimerization of various penicillanic acids in aqueous systems (7).

The NMR-spectra were run at 60 Mc. with tetramethylsilane as internal standard.

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