Tetrahedron Letters No.11, pp. 1205-1210, 1966. Pergamon Press Ltd.
Printed in Great Britain.

A NOVEL REARRANGEMENT OF METHYL 6-CHLOROPENICILLANATE

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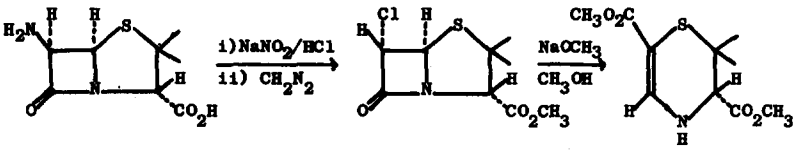
(Received 19 January 1966)

Deamination of 6-aminopenicillanic acid (I) with sodium nitrite in dilute hydrochloric acid leads to 6-chloropenicillanic acid (1). Although the product has been characterised as its N,N'-dibenzylethylenediamine salt (1) and its methyl ester (2), its configuration at C-6 has not been assigned.

In our hands deamination of I, followed by diazomethane esterification, gave methyl 6-chloropenicillanate (II) in about 20% yield; m.p. 77-78°, and $[\alpha]_D^{20}$ + 200° (0.25% in acetone), in good agreement with the reported constants. We conclude, on the basis of n.m.r. spectroscopy, that the stereochemistry of methyl 6-chloropenicillanate is correctly represented by II. The n.m.r. spectrum (60 Mc. in deuteriochloroform; tetramethylsilane as an internal standard) showed singlets at τ 8.55, 8.40 and 6.25 p.p.m. for the three methyl groups, a singlet at τ 5.48 p.p.m. for the tertiary proton and doublets at τ 5.25 and 4.70 p.p.m. (J = 2 c.p.s.) for the coupled protons at C-6 and C-5 respectively.

An examination of the n.m.r. spectra of a large number of derivatives of I in this and other laboratories (3) has shown that <u>cis</u> β-lactam ring protons have coupling constants of 4.0 - 4.5 c.p.s. Moreover, investigations of several simple β-lactams have always indicated that $J_{\underline{cis}} > J_{\underline{trans}}$ (4,5). For example, Barrow and Spotswood (5) have studied fourteen β-lactams and have shown that $J_{\underline{cis}}$ = 4.9 - 5.9 c.p.s. and $J_{\underline{trans}}$ = 2.2 - 2.8 c.p.s.. There is little doubt, therefore, that the β-lactam ring protons are <u>trans</u> in II and consequently deamination has proceeded with inversion of configuration.

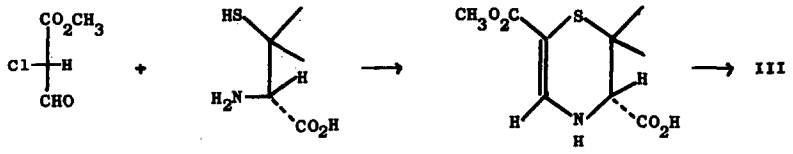


I II III

When II was treated with a molar equivalent of sodium methoxide in methanol it was smoothly transformed to 3D-carbomethoxy-6-carbomethoxy-2, 2-dimethyl-2,3-dihydro-1,4-thiazine (III); m.p. 164°; $[\alpha]_D^{20}$ - 36° (1.0% in chloroform); λ_{max}^{KBr} 3.0 (NH), 5.75 (saturated ester C=O), 6.02, 6.15, 6.23, 6.67 μ; λ_{max}^{EtOH} 280 (shoulder, ε, 3,200) and 312 mμ (ε, 10,000). The n.m.r. spectrum showed singlets at τ 8.75, 8.47, 6.26 and 6.16 p.p.m. for the four methyl groups, a doublet at τ 5.98 p.p.m. (J = 3 c.p.s.) for the tertiary proton, a broadened signal at τ 4.5 p.p.m. for the NH and a doublet at τ 2.34 p.p.m. (J = 6 c.p.s.) for the enamine proton. The NH proton exchanged upon addition of deuterium oxide to the deuteriochloroform solution and the doublets at τ 5.98 and 2.34 p.p.m. collapsed to singlets. Anal. Calcd. for $C_{10}H_{15}O_4NS$: C, 49.00; H, 6.17; N, 5.74; S, 13.10. Found: C, 48.91; H, 6.18; N, 5.65; S, 13.26.

In order to substantiate the proposed structure and stereochemistry of III we condensed D-penicillamine (V) as its hydrochloride with methyl formylchloroacetate (IV)[a]. 6-Carbomethoxy-3D-carboxy-2,2-dimethyl-2,3-dihydro-1,4-thiazine (VI) crystallised from the aqueous solution in about 30% yield; m.p. 160-163° (decomp.), $[\alpha]_D^{20}$ - 24° (1.2% in chloroform).

[a] A similar condensation involving penicillamine hydrochloride and ethyl formylchloroacetate is mentioned in reference (7), p.140. However, the product does not appear to have been characterised.



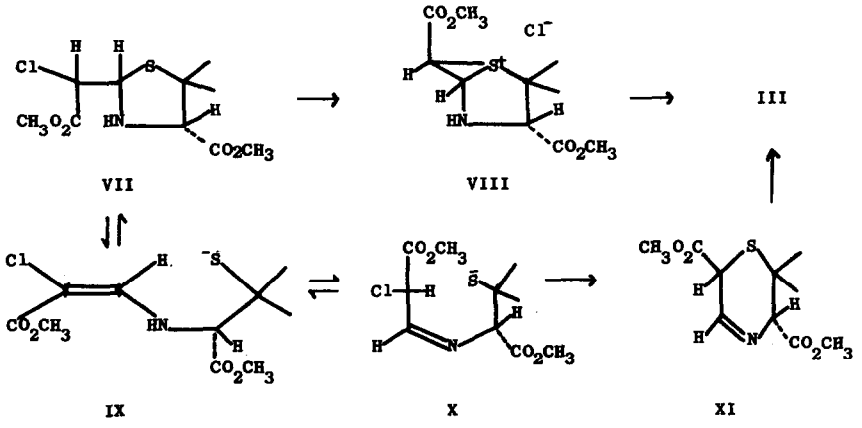
IV V VI III

The acid (VI) gave a crystalline methyl ester with diazomethane which was indistinguishable from III by i.r. and u.v. spectroscopy; m.p. 164° (undepressed when mixed with III); $[\alpha]_D^{20}$ - 37° (1.0% in chloroform).

Methyl 6-chloropenicillanate (II) was treated with one third of a molar equivalent of sodium methoxide in methanol and the product was fractionated by silica gel chromatography to give III (30%) and crude methyl 4D-carbomethoxy-5,5-dimethyl-α-chloro-2-thiazolidineacetate (VII) (27%). The structure of VII followed from analytical and spectral considerations; it gave a crystalline p-toluenesulphonate, m.p. 148-150°, $[\alpha]_D^{20}$ + 92° (0.31% in chloroform). Anal. Calcd. for $C_{17}H_{24}O_7NS_2Cl$: C, 45.00; H, 5.31; N, 3.09; Cl, 7.83. Found: C, 45.05; H, 5.49; N, 3.22; Cl, 7.76. Sodium bicarbonate decomposition of the tosylate gave pure VII as a colourless syrup; λ_{max}^{KBr} 5.75μ (saturated ester C=O); the n.m.r. spectrum showed singlets at τ8.67 and 8.40 p.p.m. for the gem dimethyl group, a singlet at τ6.63 p.p.m. for the tertiary proton, a singlet at τ6.24 p.p.m. for the two ester methyl groups and doublets centred at τ5.87 and 4.92 p.p.m. (J = 10 c.p.s.) for the protons at the α-position and C-2 respectively. The resonance for the NH proton of the thiazolidine ring was not detected and there was no splitting of the C-2 and C-4 proton signals.

When VII was treated with sodium methoxide in methanol it was readily converted to III. The mechanism of formation of III from II clearly involves nucleophilic opening of the β-lactam in the first step to give VII.

In principle VII could rearrange to III by one of two mechanisms. It could solvolyse to the episulphonium cation VIII and give III after proton loss. In such a process the ionisation is presumably the rate limiting step and consequently the rate of formation of III should be independent of the sodium methoxide concentration. Stork and Cheung (6) have recently reported the ring expansion of a thiazolidine to a dihydro-1,3-thiazine and favour such a mechanism, although they give no evidence for their choice. Alternatively, III could arise from VII by a sequence involving β-elimination to IX, tautomerisation to X, internal displacement to XI and finally tautomerisation to III. In this latter route the rate of formation of III from VII is dependent upon the sodium methoxide concentration.



VII as its crystalline p-toluenesulphonate was dissolved in methanol and sodium methoxide was added. The rate of formation of III was followed at room temperature by measuring the u.v. absorbance at 312 mμ. The results, which are shown in Table 1, indicate that the reaction does not proceed in the absence of sodium methoxide, and that the rate of formation of III can be speeded up by increasing the sodium methoxide concentration.

TABLE 1

Initial conc. of VII p-toluenesulphonate	Initial conc. of sodium methoxide	Time to complete 25% reaction
4.4×10^{-4}M	4.4×10^{-4}M	No reaction within 24 hours.
"	8.8×10^{-4}M	177 min.
"	1.32×10^{-3}M	87 "
"	1.76×10^{-3}M	39 "

The appearance of the peak at 312 mμ was preceded by an absorption at 280 mμ which reached a maximum and then decreased. The decline in the absorbance at 280 mμ coincided with an increase in the 312 mμ absorption, suggesting that the peak at 280 mμ represented an intermediate in the conversion of VII to III. It is perhaps noteworthy that penamaldic acids, which possess a chromophore similar to that depicted in IX, also absorb at 280 mμ (7). The available evidence precludes the intermediacy of the episulphonium cation (VIII) in the rearrangement of VII to III and supports the β-elimination mechanism.

ACKNOWLEDGEMENT

The authors are indebted to Beechams Research Laboratories for a generous supply of 6-aminopenicillanic acid and for the award of a research grant (to I.M.). They also thank Dr. J.H.C. Nayler for his interest and encouragement.

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