A Novel Rearrangement of a Penicillanic Acid Derivative

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Summary Triethylamine in chloroform triggers the rearrangement of methoxymethyl 6β-*p*-nitrobenzylideniminopenicillanate to methoxymethyl 2,3,4,7-tetrahydro-2,2-dimethyl-6-*p*-nitrobenzylidenimino-7-oxo-1,4-thiazepine 3(*S*)-carboxylate, which rearranges further to the triethylamine salt of 3-(1-carboxy-2-methylprop-1-enyl)-2,3-dihydro-5-*p*-nitrobenzylidenimino-6-oxo-1,3-thiazine.

THERE has been considerable recent interest in the epimerisation of penicillanic acid derivatives at position 6.[1] In attempting to prepare 6α-aminopenicillanic acid, we investigated the reaction of some benzylidene derivatives of 6β-aminopenicillanic acid with base. We now report an intriguing, deep-seated molecular rearrangement which we encountered during this study.

The triethylamine salt of (I) was converted with chloromethyl methyl ether into the methoxymethyl ester (II) which was isolated as its crystalline toluene-*p*-sulphonate (62%), $[\alpha]_D$ + 142° (EtOH). The ester (II) afforded the Schiff base (III) (66%) as pale yellow crystals, m.p. 95—96°, $[\alpha]_D$ + 182° ($CHCl_3$), with *p*-nitrobenzaldehyde in methylene chloride.

When treated with a molar equivalent of triethylamine in chloroform, (III) was transformed into a salt which, after reaction with diazomethane and alumina chromatography, yielded an optically inactive methyl ester (37%) as pale orange crystals, m.p. 196—197°. The latter material is formulated as 2,3-dihydro-3-(1-methoxycarbonyl-2-methylprop-1-enyl)-5-*p*-nitrobenzylidenimino-6-oxo-1,3-thiazine (VI). Microanalysis and mass spectroscopy indicated the molecular formula, $C_{17}H_{17}N_3O_5S$. I.r. analysis (KBr) revealed absorptions at 1715 (unsaturated CO_2Me), 1620, 1615, 1595, 1555, 1515 (asym. NO_2), and 1340 (sym. NO_2) cm^{-1}, while u.v. spectroscopy (EtOH) showed maxima at 260 (ε 12,400) and 384 nm (ε 21,800). The n.m.r. spectrum ($CDCl_3$) showed signals at τ 7·84 and 7·69, which indicated that the methyl groups were attached to a double bond, at 6·16 for the ester methyl group, at 5·20 for the methylene protons, and at 2·65 for the vinylic hydrogen; the aromatic protons appeared as an AB quartet (*J* 9 Hz) centred at 1·95 and the C*H*=N as a singlet at 0·60.

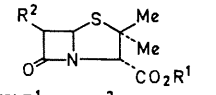
A vital clue to the mechanism of formation of the thiazine (VII) from (III) was provided when the reaction was performed in deuteriochloroform solution and monitored by n.m.r. spectroscopy. The signals attributable to (III) disappeared within 30 min. of adding the triethylamine and were replaced by those of an intermediate. The intermediate rearranged to the salt (VII) in a slower step, the reaction being complete in *ca.* 22 hr. If a half of a molar equivalent of base was employed only 50% conversion into the salt (VII) was observed.

The intermediate, which could be isolated (50%) as yellow plates, m.p. 119—120°, $[\alpha]_D$ + 7° ($CHCl_3$), by quenching the reaction after 30 min., is considered to be methoxymethyl 2,3,4,7-tetrahydro-2,2-dimethyl-6-*p*-nitrobenzylidenimino-7-oxo-1,4-thiazepine 3(*S*)-carboxylate (VIII). Micro-analysis and mass spectroscopy indicated that the substance was isomeric with (III). It exhibited

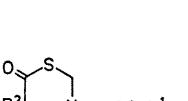
peaks at 1735 (CO_2·CH_2OMe), 1625, 1605, 1570, 1550, 1530 (asym. NO_2), and 1340 (sym. NO_2) cm^{-1} in the i.r. region and maxima at 258 (ϵ 10,800) and 380 nm (ϵ 15,200) in its u.v spectrum. The n.m.r. spectrum [$(CD_3)_2SO$] displayed signals at τ 8·39 and 8·35 for the *gem*-dimethyl group and at 6·55 and 4·63 for the methoxymethylene protons; doublets were observed at 5·36 (J 6 Hz) and 2·22 (J 9 Hz) for the tertiary and vinylic protons respectively, an AB quartet centred at 1·95 (J 9 Hz) represented the aromatic hydrogens while the NH appeared as a broad signal at *ca.* 0·9 and the C*H*=N as a singlet at 0·56. The signal for the NH disappeared upon addition of D_2O to the sample and the doublets collapsed to single lines.

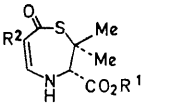
The formation of the thiazepine presumably involves cleavage of the S-1–C-5 bond of (III) by a β-elimination, followed by an intramolecular attack of the thiol group at the β-lactam. Precedent for this rearrangement has been provided recently by Kovacs *et al.*,[2] who have shown that the formation of (IX) can compete with the epimerisation of methyl 6-β-phthalimidopenicillanate (IV). In the present example thiazepine formation appeared to be quantitative.

The rearrangement of (VIII) to (VII) may be accommodated by an intermediate such as (X), derivable from the thiazepine by a β-elimination† and a migration of the methoxymethyl group. Although we have no direct evidence for the timing of these steps it is worth pointing out that methyl 2,3,4,7-tetrahydro-6-*p*-nitrobenzylideneimino-7-oxo-1,4-thiazepine 3(*S*)-carboxylate,‡ m.p. 171—172° (decomp.), $[\alpha]_D$ + 78° ($CHCl_3$), showed no loss of optical activity under conditions in which (III) was transformed into (VII). Consequently we suspect that (XI) may be implicated in the rearrangement, the lactone ring providing the activation for the β-elimination step.§



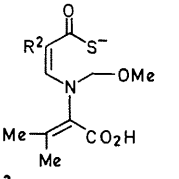
(I) R^1 = H, R^2 = NH_2
(II) R^1 = CH_2OMe, R^2 = NH_2
(III) R^1 = CH_2OMe, R^2 = *p*-NO_2·C_6H_4·CH=N
(IV) R^1 = Me, R^2 = phthalimido
(V) R^1 = Me, R^2 = *p*-NO_2·C_6H_4·CH=N



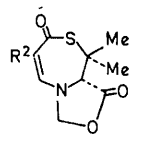


(VIII) R^1 = CH_2OMe, R^2 = *p*-NO_2·C_6H_4·CH=N
(IX) R^1 = Me, R^2 = phthalimido

(VI) R^1 = Me R^2 = *p*-NO_2·C_6H_4·CH=N
(VII) R^1 = Et_3NH, R^2 = *p*-NO_2·C_6H_4·CH=N



(X) R^2 = *p*-NO_2·C_6H_4·CH=N



(XI) R^2 = *p*-NO_2·C_6H_4·CH=N

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† Workers from Astra Pharmaceuticals have shown that a strong base (sodium methoxide) will induce (IX) to undergo this reaction (see ref. 2).

‡ This compound was prepared (30%) by stirring (I) with an excess of triethylamine and *p*-nitrobenzaldehyde in methylene chloride (2 hr.), followed by diazomethane esterification.

§ A referee has suggested that (VIII) may rearrange by transfer of the methoxymethyl group to sulphur and that the resultant sulphonium group may then provide the assistance for β-elimination.

[1] S. Wolfe and W. S. Lee, *Chem. Comm.*, 1968, 242; D. A. Johnson, D. Maria, C. A. Panetta, H. H. Silvestri, *Tetrahedron Letters*, 1968, 1903; J. P. Clayton, J. H. C. Nayler, R. Southgate, and E. R. Stove, *Chem. Comm.*, 1969, 129; D. A. Johnson and D. Maria, *Tetrahedron Letters*, 1969, 267.

[2] O. K. J. Kovacs, B. Ekstrom, and B. Sjöberg, *Tetrahedron Letters*, 1969, 1863.