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CLAVULANIC ACID. REARRANGEMENT TO 3, 4-DISUBSTITUTED PYRROLES

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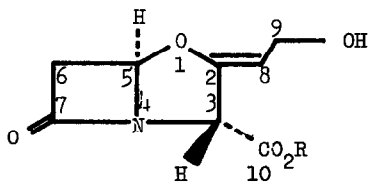
Abstract: The methanolysis of clavulanic acid (2) and subsequent base catalysed rearrangement to 3, 4-disubstituted pyrroles is described.

Reports from these laboratories[1] have described the isolation and structural elucidation of clavulanic acid (2), a potent β-lactamase inhibitor produced by Streptomyces clavuligerus. Subsequently, a programme was initiated to investigate the primary and secondary processes involved in the degradation of clavulanic acid (2). We now report the facile rearrangement of clavulanic acid to 3, 4-disubstituted pyrroles which share structural similarities with Verrucarin E (7), an antimitotic agent isolated from Myrothecium verrucaria[3].

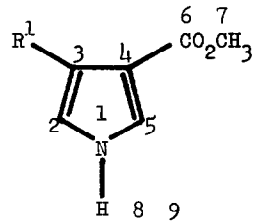
Treatment of sodium clavulanate (1) with methanol (reflux, 15 min.) afforded, after chromatography, three products. The most polar product gave a positive(purple)coloration with Ehrlich's reagent and was identified as methyl 3-(2-hydroxyethyl)-pyrrole-4-carboxylate (3; 62%), m.p. 66-67° (ethyl acetate-cyclohexane); $\underline{M}^+$ 169.0740 ($C_8H_{11}NO_3$); $\nu_{max.}$ ($CHCl_3$) 3460 and 1690 cm^{-1}; $\lambda_{max.}$ (EtOH) 230 (8400) nm ; ^1H n.m.r. δ ($CDCl_3$) 2.93 (2H, t, J6Hz, 8-CH_2), 3.73(3H, s, 7-CH_3), 3.77(2H, t, J6Hz, 9-CH_2), 6.4(1H, m, 5-C$\underline{H}$), 7.28(1H, dd, J4 and 2Hz, 2-$\underline{H}$), 9.1-9.6(1H, m, 1-N$\underline{H}$ [disappears after addition of D_2O]; ^{13}C n.m.r. δ ($CDCl_3$) 29.32 (t, C-8), 50.79 (q, 7-C) 63.31 (t, 9-C), 113.29 (s, 3-C), 118.44 (d, 5-C), 121.61 (s, 4-C), 125.39 (d, 2-C), 166.81 (s, 6-C). The second least polar product (pink coloration with Ehrlich's) was assigned structure (4; 3%), m.p. 38.5-40° (ethyl acetate); structure (5; 1%) was attributed to the least polar product.

A solution of the 3, 4-disubstituted pyrrole (3) in benzene, containing a catalytic amount of p-toluene sulphonic acid, under Dean and Stark conditions afforded the δ-lactone (6; 90%), $\underline{M}^+$ 137.0481 ($C_7H_7NO_2$); ν_{max} ($CHCl_3$) 3450 and 1710 cm^{-1}; δ ($CDCl_3$) 2.82 (2H, t, J5Hz, 8-CH_2), 4.42(2H, t, J6Hz, 9-CH_2), 6.54(1H, m, 5-H), 7.38(1H, m, 2-$\underline{H}$), 8.8-9.4(1H, br, s, 1-N$\underline{H}$).



1 R = Na

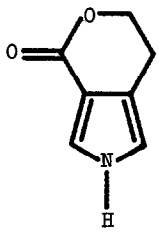
2 R = H



3 $R^1 = CH_2CH_2OH$

4 $R^1 = CH_2CH_2OCH_3$

5 $R^1 = CH=CH_2$



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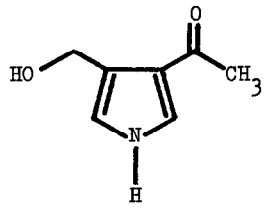

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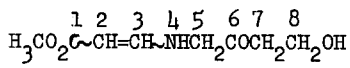
Whilst monitoring (t.l.c.) the methanolysis described above a more polar product than the pyrrole (3) was observed; none was apparent after completion of the reaction. Consequently, a solution of sodium clavulanate (1) in methanol was heated at reflux for 2 mins. and the rapidly cooled solution diluted with water. The sole product isolated was shown to be methyl-4-aza-8-hydroxy-6-oxo-oct-2-enoate [2] (8; 70%), m.p. 72-74° (ethyl acetate); $\lambda_{max.}$ (EtOH) 268 n.m.; $\nu_{max.}$ ($CHCl_3$) 3600, 3410, 1720, 1685 and 1610 $cm.^{-1}$; δ ($CDCl_3$) 2.74 (2H, t, J6Hz, 7-CH_2), 3.62(3H, s, -CO_2CH_3), 3.8-4.1(4H, m, 8-CH_2 and 5-CH_2), 4.57(d, J8Hz, H_A- cis), 4.62 (d, J14Hz, H_A-trans), 5.3-5.7 (br, s, N-H-trans), 6.47(dd, J8 and 14Hz, H_B-cis), 7.49(dd, J14 and 8Hz, H_B-trans), 7.4-8.1 (br. s, NH-cis).

It was apparent from the foregoing data that compound (8) existed as a mixture of cis (10) and trans (9) isomers in chloroform solution in the ratio 40:60. After exchange with D_2O the isomer ratio approximated to 50:50. H-N-C-H coupling constants in compounds of this type in which the amino and ester groups are cis to one another are generally higher and less variable (12-15Hz) than in compounds in which the groups are trans (7.5-14Hz)[4]. In the cis compound (10) intramolecular hydrogen bonding will force these protons into an anti configuration[5], whereas in the trans compound (9) one might expect an equilibrium mixture of syn and anti forms (9). The p.m.r. of the enamine (8) in DMSO had resonances at δ $(CD_3)_2SO$ 2.54(2H, t, J6Hz, 7-CH_2), 3.46(3H, s, -CO_2CH_3), 3.68(2H, t, J6Hz, 8-CH_2), 3.92 (2H, d, J5Hz, 4-CH_2), 4.44(1H, d, J14Hz, H_A trans), 4.52-4.7(1H, m, -OH), 6.8-7.2(1H, m, N-H),

7.36(1H, dd, J14 and 8Hz, H_B trans). Such data implies that the enamine (8) takes up a predominantly trans configuration (9) in DMSO solution.

Treatment of a solution of clavulanic acid (1) in methanol with diethylamine (3 equivalents) at room temperature for 10 mins. gave the enamine (8; 78%). The enamine (8) was recovered unchanged after treatment with methanol at reflux for 1 hour; similarly clavulanic acid (2) was recovered intact after heating in methanol at reflux for 0.5 hours. However, a methanolic solution of (8) containing either 1 equivalent or a catalytic amount of sodium carbonate or sodium bicarbonate at reflux for 0.75 hours gave the pyrroles (3; 61%),(4; 14%) and (5; 1%). Thus the enamine (8) is implicated in the formation of the pyrrole (3) and the intramolecular condensation of (8) is base catalysed.

Prolonged reaction (2 days at R.T.) of a methanolic solution of clavulanic acid (1) containing diethylamine (3 equivalents) at room temperature gave three products. The most polar product was shown to be the enamine (8; 18%) and the pyrrole (3; 14%) was also isolated. The third and most mobile component (t.l.c.) was the acrylic ester (11; 20%) isolated as a colourless oil, $\nu_{max.}$ ($CHCl_3$) 2980, 1690 and 1610 cm^{-1}; δ ($CDCl_3$) 1.12 (6H, t, J7Hz, $-CH_2\underline{CH_3}$), 3.13 (4H, q, J7Hz, $-\underline{CH_2}CH_3$), 3.58 (3H, s $-CO_2\underline{CH_3}$), 4.49(1H, d, J13Hz, $=C\underline{H}-CO_2CH_3$), 7.36(1H, d J13Hz, $=C\underline{H}N$).



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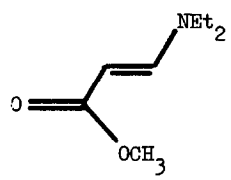

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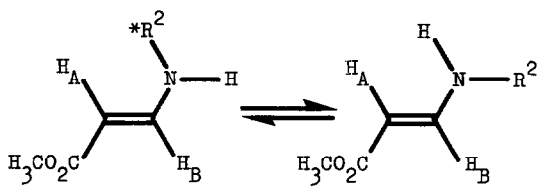

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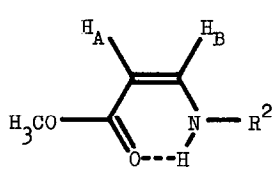

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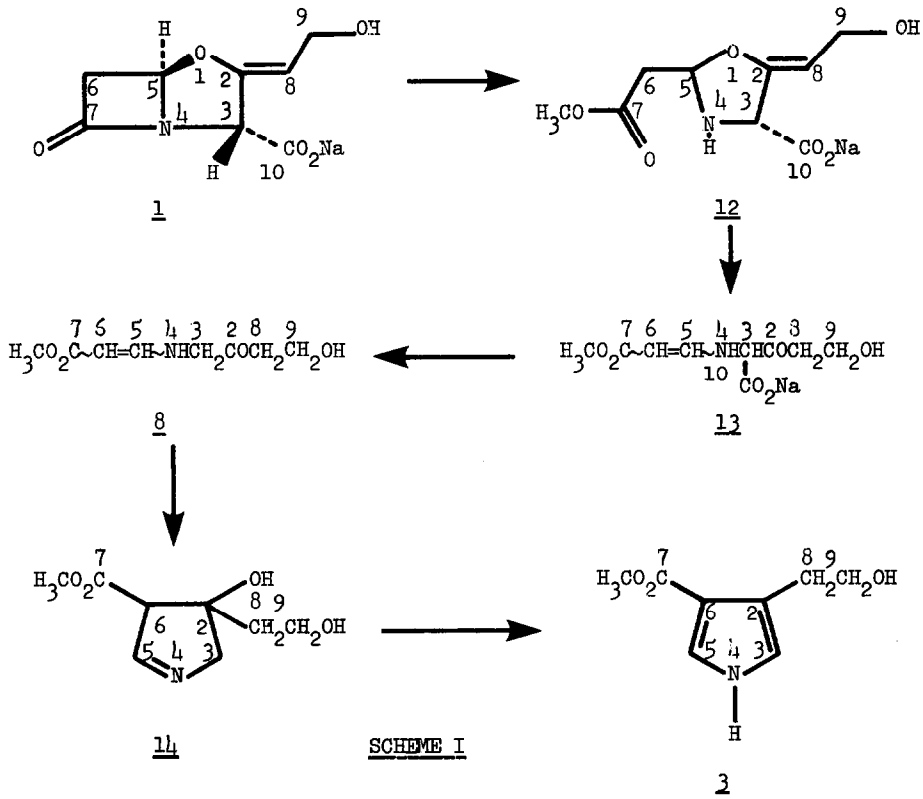
*R^2 = $CH_2COCH_2CH_2OH$



SCHEME I

The rationalisation of the formation of the enamine (8) and the pyrrole (3) is illustrated in Scheme I. Methanolysis of the β-lactam of (1) would provide (12) and eliminative fragmentation of the oxazolidine (12) would give the β-ketoacid (13); loss of C-10† by decarboxylation of (13) would provide the enamine (8) which on base catalysed intramolecular condensation affords the pyrrole (3).

† The numbering of the atoms in Scheme I refers to their position in the starting sodium clavulanate (1).

‡ Details concerning the formation of (11) will be presented in a future communication.

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