Tetrahedron Letters,Vol.23,No.48,pp 5089-5092,1982 0040-4039/82/485089-04$03.00/0
Printed in Great Britain

CLAVULANIC ACID. THE REARRANGEMENT OF 4-SUBSTITUTED AZETIDINONES DERIVED FROM CLAVULANIC ACID TO β-HYDROXY PYRROLES

J. Sydney Davies
Beecham Pharmaceuticals Research Division, Brockham Park,
Betchworth, Surrey RH3 7AJ

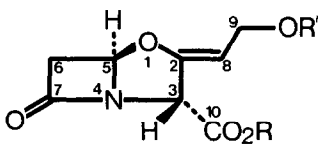
Summary 4-substituted azetidinones derived from clavulanic acid have been transformed, in the presence of acetic acid, into β-hydroxy pyrroles; rationalisation of the co-production of the pyrroles from a common intermediate is discussed.

Penicillins and related compounds undergo a plethora of rearrangements to provide heterocyclic compounds of interest[1]. Clavulanic acid[2] (1), a naturally occurring β-lactamase inhibitor, posessing a fused oxazolidine-azetidinone ring system also undergoes a number of rearrangements to heterocyclic compounds[3]; some further investigations are reported in this note.

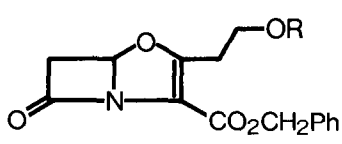
In the search for compounds with similar or enhanced biological activity the hydroxyl group has been acylated or etherified, or replaced by a sulphur, carbon or nitrogen group[4]. Furthermore, clavulanic acid (1) has been manipulated to give the clavem system[5] and has also been transformed into penems[6]. A common feature of the last two transformations involves the migration of the exocyclic double bond of clavulanic acid and its derivatives into conjugation with the carboxylate group, and the formation of a betaine or β-oxoester unit.

Treatment of benzyl clavulanate (2) in dichloromethane with triethylamine (1 equiv.) gave, after 20 min., a pale yellow solution which showed (t.l.c. analysis) that all of the benzyl clavulanate had been consumed. [Presumably the solution was a mixture of the clavem (4) and the betaine (5)][5]. Addition of acetic acid (5 equiv.) to the solution and stirring at room temperature for 2 hours gave, after rapid chromatography on Merck Kieselgel 60, the 4-acetoxy-azetidinone (8) (75%), $[\alpha]_D^{20}$ 0° ± 1° (c1.0, $CHCl_3$), M^+ 349.1164 ($C_{17}H_{19}NO_7$), $\nu_{max.}$ (EtOH) 262 nm (ε 8900), δ($CDCl_3$) 1.97 (s, $OCOCH_3$). 2.60(t, J 7Hz, $-CH_2CH_2OH$), 2.88(dd, J 15 and 2Hz, 3-H), 3.23 (dd, J 15 and 4Hz, 3-H), 3.82(t, J 7Hz, CH_2CH_2OH), 5.18(s, Ar-CH_2), 6.06(dd, J 4 and 2Hz, 4-H), 7.28(s, Ar-H). Similarly the methyl ether (3) afforded (11) (30%). The 4-substituted azetidinones (9) (72%) and (10) (25%) were isolated after treatment of (4 or 5) with methanol and acrylic acid respectively.

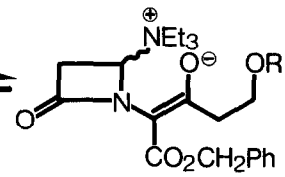
More prolonged treatment of the clavem (4) and betaine (5) with acetic acid (2 days) afforded the azetidinone (8) (10%), the β-hydroxypyrrole [7] (12) (10%) m.p. 80-81° (ethyl acetate-petrol) and a compound, isomeric with benzyl clavulanate (2), which has been shown to be the pyrrole (13) (10%), m.p. 97-98° (ethyl acetate-petrol), M^+ 289.0950 ($C_{15}H_{15}NO_5$), $\nu_{max.}$ (EtOH) nm



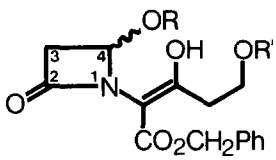
1 R=R'=H
2 R=CH_2Ph, R'=H
3 R=CH_2Ph, R'=CH_3



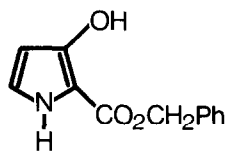
4 R=H
6 R=CH_3



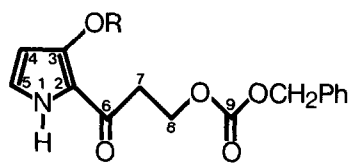
5 R=H
7 R=CH_3



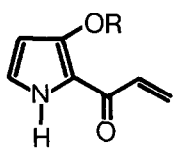
8 R'=H; R=$COCH_3$
9 R'=H, R=CH_3
10 R'=H, R=CO-CH=CH_2
11 R'=CH_3, R=$COCH_3$



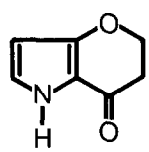
12



13 R=H
14 R=CH_3



15

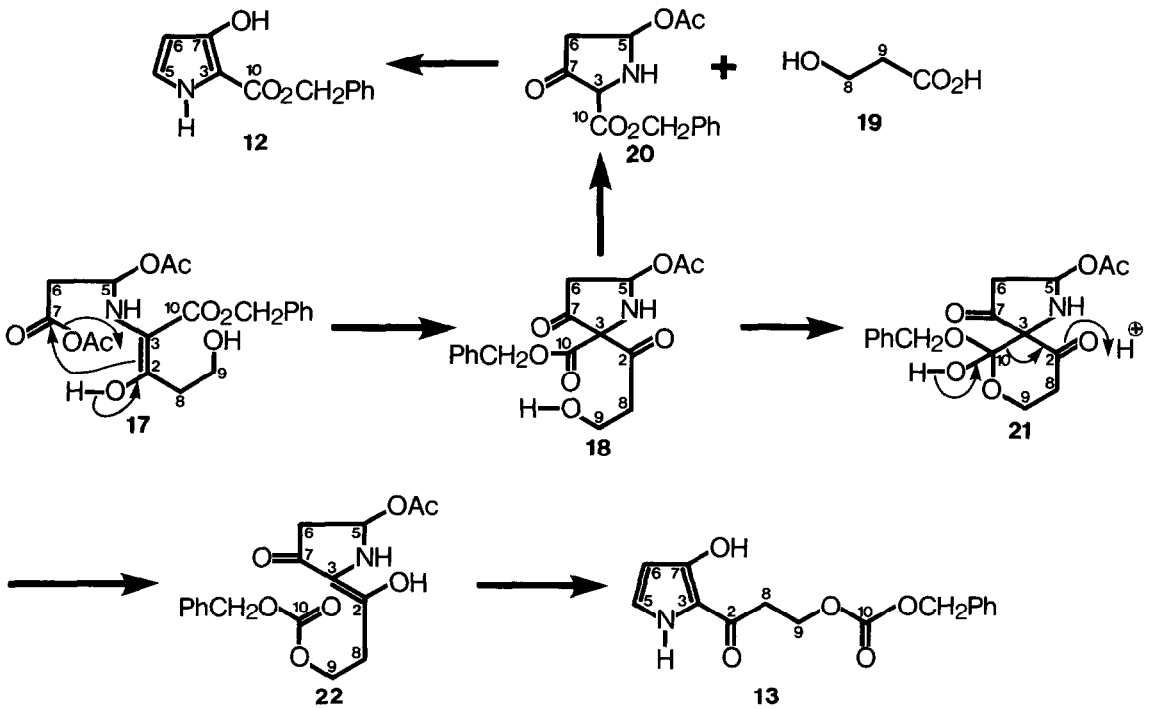


16

(ε 14,300); $\nu_{max.}$ ($CHCl_3$) 3450, 3250 1740 and 1620 $cm.^{-1}$; ^1H n.m.r. δ $(CD_3)_2$ SO 3.04(t, J 7Hz, $-COCH_2CH_2$), 4.38(t, J 7Hz, CH_2CH_2O), 5.08(s,Ar-CH_2), 5.63(dd, J 2.72 and 2.71Hz, 4-H), 6.76(dd, J 2.72 and 3.55 Hz, 5-H), 7.30(s, Ar-H), 9.80(br, s, N-H), 10.78(br. s,-OH), ^{13}C n.m.r. δ ($CDCl_3$) 37.12(t, 7-C), 63.64(t, 8-C), 69.9(t, Ar-CH_2), 98.63(d,4-C), 117.2(s, 2-C), 125.74(d, 5-C), 128.24, 128.65 and 135.0 (Ar-C), 155.13(s,9-C), 157.35(s, 3-C), 186.69(s, 6-C). Treatment of (8) with acetic acid (4 equiv.) and triethylamine (1 equiv.) at room temperature for 1 week gave complete conversion to the pyrroles (12) and (13). When treated under the conditions described above compound (13) was recovered intact. Thus the azetidinone (8) is implicated in the formation of (12) and (13).

The 4-acetoxyazetidinone (8) in dimethylformamide was treated at 60° for 1 hr with acetic acid (4 equiv.) and gave as the only isolable products (12) (51%) and the bicyclic pyrrole (16) (11%), m.p. 106-108° (ethyl acetate-petrol), M^+ 137.0464 ($C_7H_7NO_2$), $\nu_{max.}$ ($CHCl_3$) 3450 and 1640 cm^{-1}. In the absence of acetic acid the azetidinone (8) was recovered intact. Treatment of a solution of the methyl ether (3) with triethylamine (1 equiv.) gave a solution of (6 and 7) which on the addition of acetic acid (4 equiv.) afforded, after 2 days at room temperature, the

SCHEME



azetidinone (11) (23%) and the β-hydroxypyrrole (12) (18%). No compound (13) was detected. These observations imply that the formation of (13) is acid catalysed and that the terminal hydroxyl is involved in the formation of (13), but not the formation of (12).

Methylation of (13) [MeI/K_2CO_3/acetone] afforded two products; the least polar product was shown to be the pyrrole (15, R= CH_3), m.p. 123-125° (ethyl acetate-petrol); $\underline{M}^+$ 151.0622($C_8H_9NO_2$); $\nu_{max.}$ 3450 and 1640 cm^{-1}. The more polar product was shown to be the monomethylated product (14), m.p. 88-90° (ethyl acetate-petrol); $\underline{M}^+$ 303.1111 ($C_{16}H_{17}NO_5$). Reaction of (13) with diazomethane gave (14) (80%). Presumably (15; R = CH_3) arises by β-elimination from (14), whereas a similar elimination in (13) affords (16) by way of (15; R = H).

A rationalisation of the formation of (13) from the acetoxyazetidinone (8) can now be made and also provides an explanation for the pyrrole (12). Internal acylation of the mixed anhydride (17) [from the reaction of (8) with acetic acid] as shown in the SCHEME produces the key intermediate (18). On the one hand (18) can be cleaved by a reverse Claisen-type condensation to give hydracrylic acid (19) and (20), which can eliminate acetic acid and enolise to give the β-hydroxypyrrole (12). Intermediate (18) can also undergo intramolecular attack on the hydroxyl group to give a transient ortho-acid type intermediate (21). Acid catalysed cleavage of (21) leads to (22) which can readily be transformed into (13) by obvious procedures.

† The numbering of the atoms in the SCHEME refers to their positions in the starting benzyl clavulanate. Further, the reaction pathway shown in the SCHEME has been studied using ^{13}C labelled benzyl clavulanate as the starting material and will be reported in a forthcoming publication.

The author wishes to thank Professor R. A. Raphael for helpful discussions.

References:

1. R. J. Stoodley, Tetrahedron, 31, 2321 (1975).
2. T. T. Howarth, A. G. Brown and T. J. King, J. C. S. Chem. Comm., 1976, 266.
3. J. Sydney Davies and T. Trefor Howarth, Tetrahedron Letters, 3109 (1982)
4. See 'β-lactam Antibiotics: Mode of Action, new developments and future prospects', ed. M. R. J. Salton and G. D, Shockman, Academic Press, 1981,p. 287.
5. P. C. Cherry, C. E. Newall and N. S. Watson, J.S.C. Chem. Comm., 1978, 469.
6 P. C. Cherry, C. E. Newall and N. S. Watson, J.S.C. Chem. Comm., 1979, 663.
7. T. Momose, T. Tanaka, T. Yokota, N. Nagmoto and K. Yamada, Chem. Pharm. Bull. 26, 2224 (1978).

(Received in UK 13 September 1982)