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THE FORMATION AND X-RAY CRYSTAL STRUCTURE ANALYSIS OF ISOCLAVULANIC ACID

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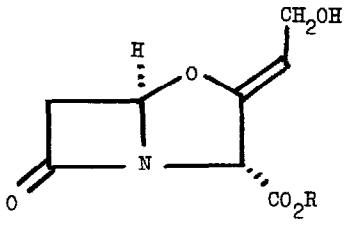
Following the isolation[1] and structure elucidation[2] of clavulanic acid (1a), a potent β-lactamase inhibitor produced by Streptomyces clavuligerus, a programme was initiated to investigate structural modification of (1a). To facilitate chemical manipulation of clavulanic acid it was decided to convert the carboxylic acid group into an ester function which would undergo subsequent de-esterification under mild conditions. Preliminary experiments[3] had indicated that reduction of the double bond in methyl clavulanate (1e) occurred slowly and it was anticipated that debenzylation of (1c) might be accomplished selectively.



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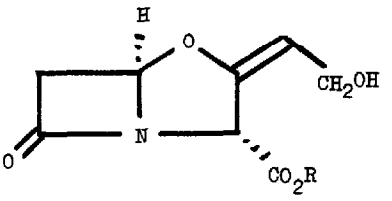

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(a) R = H
(b) R = Na
(c) R = $C_6H_5CH_2$
(d) R = p-$BrC_6H_4CH_2$
(e) R = CH_3

Alkylation of sodium clavulanate with benzyl bromide in dimethylformamide gave (1c)[4] as an oil (72%). Hydrogenolysis of (1c) over 10% Pd/C in aqueous ethanol containing sodium hydrogen carbonate gave substantially pure (1b) which crystallised from acetone-water; the material thus obtained was identical with authentic sodium clavulanate tetrahydrate.

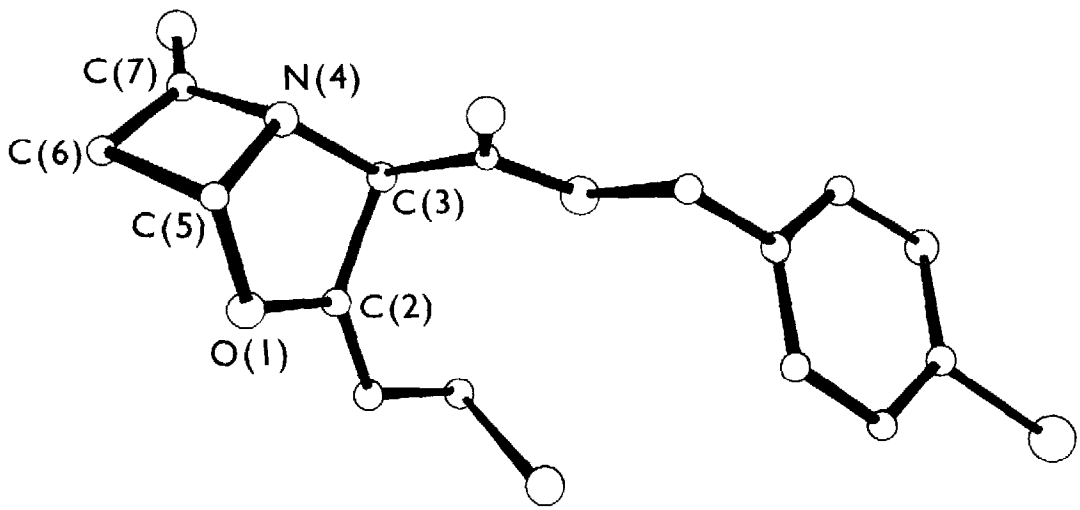
Thorough investigation of (1b) prior to crystallisation indicated the presence of a minor contaminant; the yield of this by-product varied with different batches of catalyst but was usually less than 10%. To expedite identification of this product, the crude reaction mixture obtained from the debenzylation process was alkylated with p-bromobenzyl bromide in dimethylformamide. Chromatographic separation gave p-bromobenzyl clavulanate (1d) and a minor, less polar ester which, on the basis of its spectral properties, was shown to be p-bromobenzyl isoclavulanate (2d).[4]

The structure of p-bromobenzyl isoclavulanate (2d), m.p. 134-134.5°, was confirmed by

X-ray analysis using the heavy atom method (R value 0.079) and the absolute configuration (see Figure) determined as described[2] for p-bromobenzyl clavulanate. Crystal data: $C_{15}H_{14}BrNO_5$ M 368.2, monoclinic, space group P2, a = 11.996 (2), b = 5.113 (1), c = 12.346 (2) Å, β = 92.92 (2).°

The low and variable yields of isoclavulanic acid (2a) obtained in the above process led us to investigate alternative isomerisation procedures, and we subsequently found that irradiation of benzyl clavulanate (1c) in benzene under nitrogen, using two Hanovia 40W low pressure lamps in a Reading Photochemical Reactor, gave a mixture from which benzyl clavulanate (1c) and benzyl isoclavulanate (2c) were isolated in 50% and 40% yield after chromatography.

Hydrogenolysis of (2c) over 10% Pd/C in ethanol containing sodium hydrogen carbonate gave sodium isoclavulanate (2b)[4] as an amorphous solid (65%).



REFERENCES AND FOOTNOTES

1. C. Reading and M. Cole, unpublished results.
2. T. T. Howarth, A. G. Brown and T. J. King, J. C. S. Chem. Comm., 1976, 266.
3. A. G. Brown, T. T. Howarth and R. J. Ponsford, unpublished results.
4. This compound had spectral properties in accord with the proposed structure.