

Reactions of Sulphur Nucleophiles with Activated Derivatives of Clavulanic Acid

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Summary Allylic halides (*e.g.* **2**), prepared from 4-nitrobenzyl clavulanate, react with salts of thiocarboxylic, thiocarbamic, and sulphinic acids to give thioesters, thio-carbamates, and sulphones; dehydrohalogenation of the halides affords the diene (**4**), from which sulphur derivatives may also be prepared *via* a stereospecific 1,4-addition reaction.

CLAVULANIC ACID (**1a**), a naturally occurring β -lactamase inhibitor, exhibits moderate broad-spectrum antibacterial activity.¹ We now report reactive derivatives of clavulanic acid which allow the preparation of new compounds, with generally improved β -lactamase inhibitory activity.

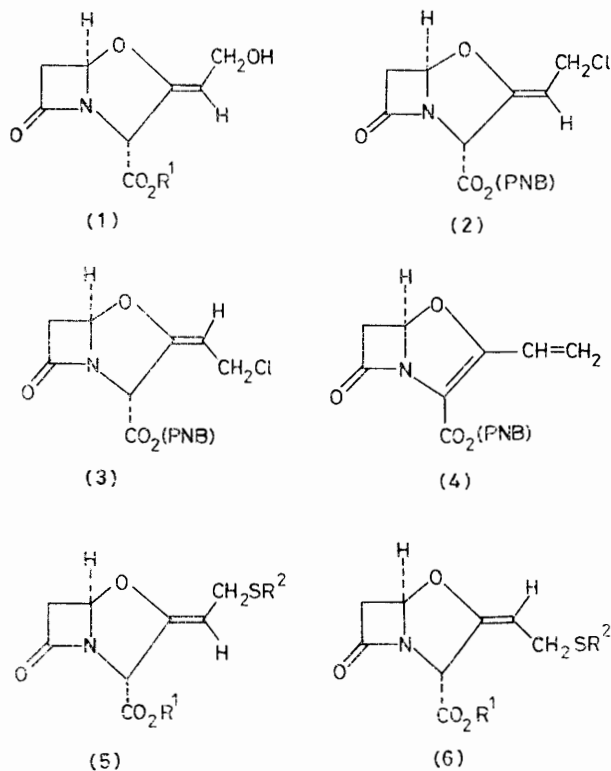
Treatment of 4-nitrobenzyl clavulanate (**1b**)² with thionyl chloride in tetrahydrofuran-ether-pyridine at -20°C provided a mixture of allylic chlorides, which on

crystallisation gave the sparingly soluble *Z*-isomer (**2**; 44%); $[\alpha]_D + 30^\circ$ (Me₂SO); ν_{max} (CHBr₃) 1800 (β -lactam) and 1753 cm⁻¹ (ester); τ [(CD₃)₂CO] values include 4.98 (t, *J* 8 Hz, =CH-). Concentration of the mother-liquors afforded the *E*-isomer (**3**) as a minor product (8%); ν_{max} (Nujol) 1800 and 1740 cm⁻¹; τ [(CD₃)₂CO] values include 4.72 (t, *J* 8 Hz, =CH-).[†] A similar halogenation with thionyl bromide gave the *Z*-isomer of the corresponding allylic bromide; ν_{max} (Nujol) 1790 and 1752 cm⁻¹.

Reaction of these halides with thiocarboxylic, thiocarbamic, and sulphinic acid salts proceeded with retention of the geometry of the double bond to give the sulphur-substituted derivatives (**5b**; R² = COMe, CPh, CONH₂, CSM₂, CSNH₂, CSNHMe, or CSNMe₂) and (**6b**; R² = CSNH₂); these were de-esterified (by catalytic hydrogenolysis or by dissolving metal reduction) to the corresponding

[†] Assignments of *E,Z*-stereochemistry were based on a comparison of the positions of the olefinic triplets with those in the 4-nitrobenzyl ester of clavulanic acid (τ 5.10) and the corresponding *E*-isomer (τ 4.77) in (CD₃)₂CO; unpublished results from these laboratories

carboxylic acids, which were isolated as their sodium salts.† Reaction of (2) with sodium trithiocarbonate, followed by decomposition of the hemithiocarbonate *in situ* with dilute aqueous acid,³ gave the thiol (5b; R² = H, 49%); m.p. 136°; [α]_D + 23° (Me₂SO); ν_{max} (CHBr₃) 1798 and 1755 cm⁻¹. Alkylation of this thiol afforded a convenient route to alkylthio derivatives (5b; R² = alkyl).⁴



- a; R¹ = H
b; R¹ = 4-Nitrobenzyl (PNB)

Treatment of (2) with triethylamine at 0 °C gave the crystalline diene (4); [α]_D + 11° (CHCl₃); ν_{max} (CHBr₃) 1810 and 1710 cm⁻¹; λ_{max} (dioxan) 265 (ε 11,670) and 318 nm (ε 10,340).§ Mesylation of (1b) in dichloromethane at 0 °C in the presence of Et₃N also gave the diene. If either of these reactions was conducted at room temperature the diene formed was racemic; a possible explanation for the racemisation of the 7-oxo-4-oxa-1-azabicyclo[3.2.0]-hept-2-ene ring system has been discussed elsewhere.⁵

Treatment of the optically active diene (4) with thioacetic acid and Et₃N in dichloromethane at 0 °C gave the acetylthio derivative (5b; R² = COMe), [α]_D + 9° (Me₂SO), which was deprotected and isolated as the sodium salt; [α]_D + 24° (H₂O); ν_{max} (Nujol) 1784 cm⁻¹. This material was chemically and biologically indistinguishable from a sample prepared by reaction of the chloride (2) with thioacetic acid and Et₃N.

Similarly, reaction of the diene (4) with benzene sulphonic acid (dichloromethane-K₂CO₃-18-crown-6) gave the sulphone (5b; SR² = SO₂Ph), m.p. 164 °C; [α]_D + 34.5° (Me₂SO); which resembled a sample, m.p. 165 °C; [α]_D + 38° (Me₂SO), prepared by treating the chloride (2) with sodium benzenesulphinate in dimethylformamide (DMF). No isomeric products were detected in the reaction mixtures. Thus the attack of a sulphur nucleophile on the diene and the subsequent protonation are both regio- and stereo-specific and regenerate the (2*R*)-configuration in the 4-oxa-1-azabicyclo[3.2.0]heptane ring system and the *Z*-geometry in the exocyclic double bond.

Reaction of (4) at 0 °C in dry DMF containing Et₃N with a four-fold excess of deuterated thioacetic acid (MeCOSH₂) in dichloromethane provided a deuterated sample of (5b; R² = COMe) in which deuterium incorporation at C-2 was >50% (by n.m.r. spectroscopy). A sample of the acetylthio derivative prepared from (2) under similar conditions was not deuterated at C-2 (deuterium incorporation <5% by n.m.r.), indicating that such reactions proceed primarily by direct displacement of chloride ion rather than by an elimination and addition mechanism.

The *E*-isomer of the allylic chloride (3) also appears to undergo direct displacement with sulphur nucleophiles. Thus, reaction with ammonium dithiocarbamate gave the dithiocarbamate (6b; R² = CSNH₂); ν_{max} (CHBr₃) 1800, 1750, and 1688 cm⁻¹. None of the corresponding *Z*-isomer (5b; R² = CSNH₂) which would have been formed had the diene (4) been an intermediate, was detected in the reaction mixture.

The sodium salts of the acids (5a) were generally more active than clavulanic acid as inhibitors of the PCl, TEM, and KI β-lactamases.⁶ Their antibacterial activity was similar to that of clavulanic acid; a notable exception was the sodium salt of the dithiocarbamate (5a; R² = CSNH₂), which was significantly more active against most of the bacterial strains examined.

(Received, 3rd March 1978; Com. 223.)

† Satisfactory spectroscopic data were obtained for all new compounds reported.

§ A similar diene, but of unspecified chirality, has been prepared as the corresponding benzyl ester (D. F. Corbett, T. T. Howarth, and I. Sterling, *J.C.S. Chem. Comm.*, 1977, 808).

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² T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.

³ D. J. Martin and C. C. Greco, *J. Org. Chem.*, 1968, **33**, 1275.

⁴ Belg. P., 851,821.

⁵ P. C. Cherry, C. E. Newall, and N. S. Watson, following communication.

⁶ C. H. O'Callaghan, R. B. Sykes, A. Griffiths, and J. E. Thornton, *Antimicrobial Agents and Chemotherapy*, 1976, **9**, 511.