Reactions of Sulphur Nucleophiles with Activated Derivatives of Clavulanic Acid

By PETER C. CHERRY, GORDON I. GREGORY, CHRISTOPHER E. NEWALL,* PETER WARD, and NIGEL S. WATSON
(*Organic Chemistry Department, Glaxo Research Ltd., Greenford, Middlesex* UB6 0HE)

Summary Allylic halides (*e.g.* **2**), prepared from 4-nitrobenzyl clavulanate, react with salts of thiocarboxylic, thiocarbamic, and sulphinic acids to give thioesters, thiocarbamates, 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.

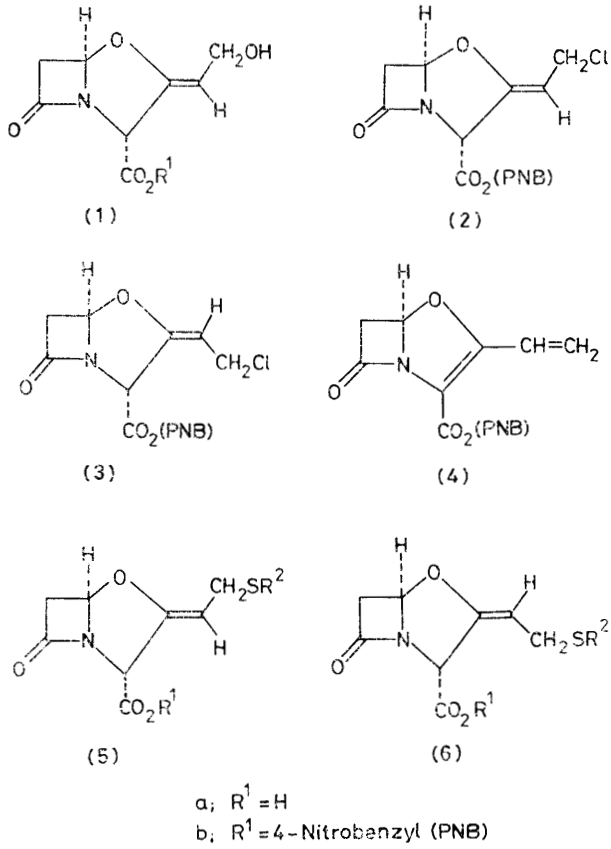
CLAVULANIC ACID (**1a**), a naturally occurring β-lactamase inhibitor, exhibits moderate broad-spectrum antibacterial activity.[1] We now report reactive derivatives of clavulanic acid which allow the preparation of new compounds, with generally improved β-lactamase inhibitory activity.

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° (Me_2SO); ν_{max} ($CHBr_3$) 1800 (β-lactam) and 1753 cm^{-1} (ester); τ [$(CD_3)_2CO$] 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 [$(CD_3)_2CO$] 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**; R^2 = COMe, COPh, $CONH_2$, CSMe, $CSNH_2$, CSNHMe, or $CSNMe_2$) and (**6b**; R^2 = $CSNH_2$); 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 $(CD_3)_2CO$; 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 hemitrithiocarbonate *in situ* with dilute aqueous acid,[3] gave the thiol (**5b**; R^2 = H, 49%); m.p. 136°; $[\alpha]_D$ + 23° (Me_2SO); ν_{max} ($CHBr_3$) 1798 and 1755 cm^{-1}. Alkylation of this thiol afforded a convenient route to alkylthio derivatives (**5b**; R^2 = alkyl).[4]



Treatment of (**2**) with triethylamine at 0 °C gave the crystalline diene (**4**); $[\alpha]_D$ + 11° ($CHCl_3$); ν_{max} ($CHBr_3$) 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 Et_3N 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 Et_3N in dichloromethane at 0 °C gave the acetylthio derivative (**5b**; R^2 = COMe), $[\alpha]_D$ + 9° (Me_2SO), which was deprotected and isolated as the sodium salt; $[\alpha]_D$ + 24° (H_2O); 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 Et_3N.

Similarly, reaction of the diene (**4**) with benzene sulphinic acid (dichloromethane–K_2CO_3–18-crown-6) gave the sulphone (**5b**; SR^2 = SO_2Ph), m.p. 164 °C; $[\alpha]_D$ + 34·5° (Me_2SO); which resembled a sample, m.p. 165 °C; $[\alpha]_D$ + 38° (Me_2SO), 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 stereospecific 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 Et_3N with a four-fold excess of deuteriated thioacetic acid (MeCOSD) in dichloromethane provided a deuteriated sample of (**5b**; R^2 = 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 deuteriated 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**; R^2 = $CSNH_2$); ν_{max} ($CHBr_3$) 1800, 1750, and 1688 cm^{-1}. None of the corresponding *Z*-isomer (**5b**; R^2 = $CSNH_2$) 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 PC1, TEM, and K1 β-lactamases.[6] Their antibacterial activity was similar to that of clavulanic acid; a notable exception was the sodium salt of the dithiocarbamate (**5a**; R^2 = $CSNH_2$), which was significantly more active against most of the bacterial strains examined.

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‡ 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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