Synthesis of 7-Oxo-3-sulphinyl-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates: Olivanic Acid Analogues

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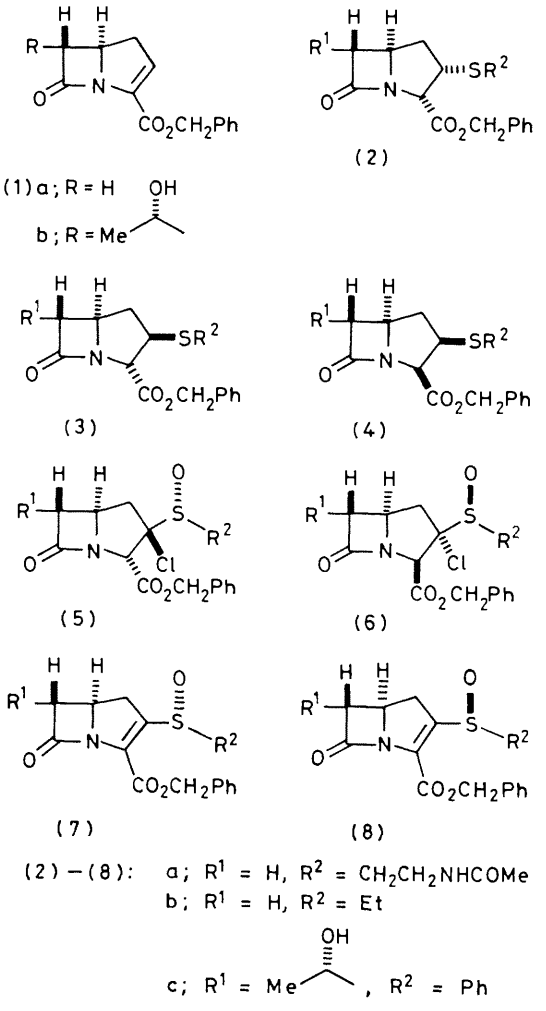
Summary Base-catalysed addition of thiols to 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates produces adducts of the saturated nucleus, which can be stereospecifically oxidised to α-chlorosulphoxides and then dehydrochlorinated to form antibacterially active sulphoxides of the corresponding unsaturated system.

INTRODUCTION of the C(3) sulphur substituent in syntheses of thienamycin and olivanic acid analogues has hitherto been accomplished either before construction of the pyrroline ring[1,2] or by displacement of a C(3)-toluene-*p*-sulphonate group in a bicyclic system.[3] We now report a versatile method for preparation of C(3)-sulphinyl compounds, which relies on a Michael-type addition of a thiol to readily available 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates.[4]

This procedure can be illustrated by the reaction of bicyclic compound (**1a**)† with 2-acetamidoethanethiol and potassium carbonate in dimethylformamide (20 °C, 1 h). Three separate isomers of the thiol addition product were isolated by column chromatography: (**2a**) (23%), ν_{max} ($CHCl_3$) 1765 (β-lactam carbonyl) and 1745 sh (ester carbonyl) cm^{-1}, δ ($CDCl_3$) 4·70 (d, *J* 7 Hz, C2-H); (**3a**) (43%), ν_{max} 1765 and 1745 sh cm^{-1}, δ 4·34 (d, *J* 5 Hz) and (**4a**) (17%), m.p. 117—118 °C, ν_{max} 1765 and 1740 cm^{-1}, δ 4·11 (d, *J* 7 Hz). Ethanethiol and benzenethiol added to the bicyclic systems with similar alacrity, but the three isomers were produced in different proportions. Thus, (**1a**) reacted with ethanethiol to form compounds (**2b**) and (**3b**) as an inseparable mixture (56%) (4:1 ratio), and (**4b**) (22%), m.p. 62—64 °C.

The *trans*-6-hydroxyethyl side chain did not interfere with this reaction, so that (**1b**) with benzenethiol produced a 3:1 mixture (49%) of (**2c**) and (**3c**), together with (**4c**) (13%), m.p. 111—112 °C. Information used for assigning stereochemistry of the isomers included the observation that compounds (**4**) can be converted into (**3**) by base catalysis (1,5-diazabicyclo[5.4.0]undec-5-ene, DBU), the knowledge that ^1H n.m.r. signals for the C(2) proton occur at lower field in those isomers of 'natural' C(2) stereochemistry (**2**) and (**3**), compared to the 'unnatural' series (**4**),[5] and an *X*-ray analysis of (**4b**).



Reintroduction of the double bond was achieved in two stages. Oxidation[6] of (**2a**) with iodobenzene dichloride (2 equiv.), pyridine (3 equiv.), and water (*ca.* 5 equiv.) in

† This and all other compounds are (±)-mixtures, but only one enantiomer is depicted for convenience.

chloroform at 0—20 °C was highly stereo- and regio-specific, producing a single α-chlorosulphoxide (**5a**) (69%), m.p. 89—93 °C, ν_{max} ($CHCl_3$) 1780 and 1745 cm^{-1}, δ ($CDCl_3$) 5·03 (s, C2-H). Brief treatment of (**5a**) with an equivalent amount of DBU in ethyl acetate gave a 60% yield of the unsaturated compound (**7a**),‡ m.p. 119—122 °C, ν_{max} ($CHCl_3$) 1795 and 1720 cm^{-1}, λ_{max} (ethanol) 306 nm (ε 5900). The acetamido isomer (**4a**) was likewise converted into a single chlorosulphoxide (**6a**) (50%), δ 4·41 (s, C2-H), which on treatment with DBU yielded the unsaturated sulphoxide (**8a**). This reaction sequence was less satisfactory for the other sulphide isomer (**3a**) because oxidation gave a mixture of diastereoisomers, which resulted in both sulphoxide relative chiralities in the final product.

In the ethyl series the mixture of (**2b**) and (**3b**) was oxidised to form predominantly (**5b**) (54%), m.p. 123—125 °C, which on elimination gave (**7b**) (95%). The other isomer (**4b**) gave an unstable gummy chlorosulphoxide (**6b**), which could be converted with base into (**8a**) [38% from (**4b**)], m.p. 121—126 °C. An analogous sequence of reactions could be carried out when the 6-hydroxyethyl unit was present in the molecule. Thus, the mixture of (**2c**) and (**3c**) was transformed to (**5c**) (48%), m.p. 154—159 °C, and then to (**7c**) (54%), m.p. 104—109 °C; whilst (**4c**) led to (**6c**) (67%), m.p. 141—143 °C, and (**8c**) (98%). Relative stereochemistries of representative α-chlorosulphoxides (**5c**) and (**6c**) were established by single-crystal *X*-ray crystallography. All compounds gave satisfactory analytical and spectral data. Compound (**7b**) has shown good activity when tested against a systemic *Escherichia coli* infection in mice.

We thank Professor T. J. King, University of Nottingham, for *X*-ray studies.

(*Received, 23rd November* 1979; *Com.* 1220.)

‡ Final products decomposed when chromatographed on silica gel or 'Florisil,' but were obtained in high purity after an aqueous wash. Crystalline compounds were stable, but non-crystalline ones were best stored in ethyl acetate solution.

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