Synthesis of Olivanic Acid Analogues. Preparation of 7-Oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylates containing the 3-(2-Acetamido-ethenylthio) Side Chain

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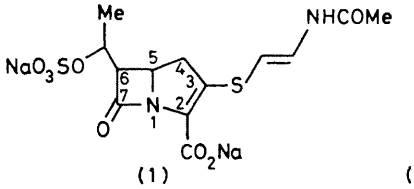
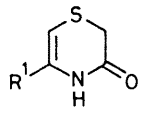
Summary 2-Acetamidoethenylthioesters have been prepared from 4-carboxymethylazetidin-2-one and cyclised *via* an intramolecular Wittig reaction to provide 3-(2-acetamidoethenylthio)-7-oxo-1-azabicyclo[3 2 0]hept-2-ene-2-carboxylates, closely related analogues of the naturally occurring antibiotic MM 13902 (**1**)

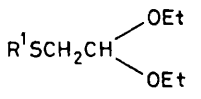
MM 13902 (**1**)[1] and thienamycin[2] are representatives of a family of novel β-lactam antibiotics with remarkable antibacterial properties. Both the olivanic acid and thienamycin series possess members[3,4] which have the unusual 3-(2-acetamidoethenylthio) side chain coupled to the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system. We have previously described[5] the synthesis of 7-oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates using an activated thioester in an intramolecular Wittig reaction. We now report an extension of this method to include suitably activated ethenylthioesters as precursors to 3-ethenylthio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates and the synthesis of the 6-unsubstituted analogue of MM 13902.

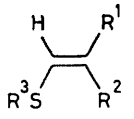


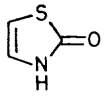
(**1**)



(**2**)a; R^1=Me
b; R^1=H







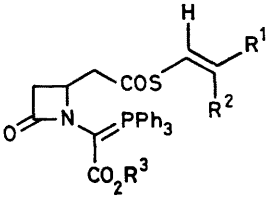
(**3**)a; R^1=CH_2CONH_2
b; R^1=Ph_3C

(**4**)

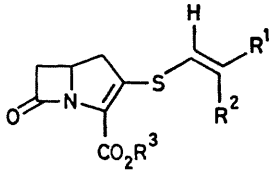
(**5**)

For (**4**) **a**; R^1 = Me, R^2 = NHCOMe, R^3 = Na
b; R^1 = H, R^2 = NHCOMe, R^3 = Na
c; R^1 = H, R^2 = NHCOMe, R^3 = Li
d; R^1 = H, R^2 = NHCOMe, R^3 = MeCO
e; R^1 = NHCOMe, R^2 = H, R^3 = MeCO
f; R^1 = NHCOMe, R^2 = H, R^3 = Ag
g; R^1 = H, R^2 = NHCOMe, R^3 = Ph_3C
h; R^1 = NHCOMe, R^2 = H, R^3 = Ph_3C
i; R^1 = H, R^2 = NHCOMe, R^3 = Ag
j; R^1 = H, R^2 = $NHCO_2Me$, R^3 = Ag

The initial target in the synthesis of these compounds was the preparation of the appropriate metal thiolates. A close analogue, (**4a**), of the required thiolates, has been derived[6] by cleavage of the 5-substituted 1,4-thiazin-3-one (**2a**) using sodium in liquid ammonia. We have now prepared the corresponding unsubstituted 1,4-thiazin-3-one (**2b**) by treatment of thioglycolamide with bromoacetaldehyde diethyl acetal and sodium ethoxide in ethanol solution (reflux, 75% yield), followed by acid catalysed (toluene-*p*-sulphonic acid, benzene) cyclisation of the resulting amide acetal (**3a**)† to the 1,4-thiazin-3-one (**2b**)† (92%), m.p. 74·5—75 °C. Cleavage of (**2b**) using sodium or lithium in liquid ammonia gave the *Z*-sodium (**4b**) or *Z*-lithium (**4c**) thiolates in quantitative yield as buff-coloured solids, ν_{max} (Nujol) 3350, 1650 (sh), and 1610 cm^{-1}. The *E*-isomer (**4f**) was prepared by acetylation of the *Z*-sodium thiolate (**4b**) and base catalysed (1,5-diazabicyclo[5.4.0]undec-5-ene) isomerisation (benzene, 70 °C, 2 h) of the resulting thioester (**4d**),† leading to a 1:1 mixture of *Z* and *E* isomers§ which were separable by chromatography on silica. Cleavage of the *E*-thioester (**4e**)† using silver nitrate–pyridine in methanol led to the *E*-silver thiolate (**4f**) in quantitative yield ν_{max} (Nujol) 3250, 1665, and 1635 cm^{-1}. An alternative and more direct synthesis of the ethenethiolates (**4i**) and (**4f**) was carried out by reaction of trityl thiol using sodium ethoxide in ethanol solution under reflux with bromoacetaldehyde diethyl acetal which provided (**3b**)† (80%). Treatment of (**3b**) with a five molar excess of acetamide containing 1 equiv. of toluene-*p*-sulphonic acid in refluxing benzene (3 h) gave (**4g**)† and (**4h**)† in a ratio *Z*:*E* of 4:1 (40%), whereas in dimethylformamide (3 h) at 90 °C (**4g**) and (**4h**) were produced in a ratio *Z*:*E* of 2:3 (60%). Cleavage of either (**4g**) or (**4h**) with silver nitrate-pyridine in methanol provided the silver salts (**4f**) and (**4i**) in high yield (>90%). Urethanes of type (**4j**)† were similarly prepared from the thiazolone (**5**)[7] by silver nitrate–pyridine cleavage in methanol.



(**6**)



(**7**)

a; R^1 = H, R^2 = NHCOMe, R^3 = CH_2Ph
b; R^1 = NHCOMe, R^2 = H, R^3 = CH_2Ph
c; R^1 = H, R^2 = NHCOMe, R^3 = $CH_2C_6H_4NO_2$-*p*
d; R^1 = NHCOMe, R^2 = H, R^3 = $CH_2C_6H_4NO_2$-*p*
e; R^1 = H, R^2 = $NHCO_2Me$, R^3 = CH_2Ph
f; R^1 = H, R^2 = NHCOMe, R^3 = Na
g; R^1 = NHCOMe, R^2 = H, R^3 = Na.

The thioester phosphoranes (**6a—e**)† were synthesised by reaction of the corresponding acid[5] as the mixed phosphonic anhydride [$EtO_2(O)PCl$, Et_3N, tetrahydrofuran] or as the acid chloride ($SOCl_2$, C_5H_5N, acetonitrile) with the appropriate metal thiolate. The *Z*-isomers (**6a**) and (**6c**) were best prepared using a mixed phosphonic anhydride and the *Z*-sodium or *Z*-lithium thiolates (**4b**) or (**4c**) (45—60%), whereas good yields of *E*-thioesters (**6b**) and (**6d**) were obtainable using the acid chloride and *E*-silver thiolate (**4f**) (40—70%).

Cyclisation of the thioester phosphoranes‡ (**6a—e**) was carried out by heating the compound in refluxing toluene under argon. Thus the *Z*-isomer (**6a**) gave (**7a**)† in 32% yield after 9 h. The *E*-isomer (**6b**) afforded (**7b**) in similar yield but purification of the product was difficult as the starting phosphorane was almost identical in polarity to the product. When the ester group was *p*-nitrobenzyl, the

† The ^1H n.m.r., i.r., and microanalytical and/or mass spectral data of all new compounds were consistent with the proposed structures.

‡ Cyclisations were carried out at a concentration of 1 mg ml^{-1}. Yields quoted are true yields. Yields based on recovered phosphorane were invariably higher. Reactions allowed to proceed longer than times stated often led to decomposition of product.

§ The stereochemistry of the *Z* (*cis*) and *E* (*trans*) isomers was assigned on the basis of the coupling constants of the olefinic protons in the n.m.r. spectrum, J_{cis} 8, J_{trans} 14 Hz.

rates of reaction were predictably slower but separation of the product was easier. The *Z*-isomer (**6c**) gave (**7c**)† (21%), m.p. 158—161 °C, after 8 h. The *E*-isomer (**6d**) gave (**7d**)† (25%) m.p. 196—200 °C, after 48 h. Cyclisation of the urethane (**6e**) gave (**7e**)† (20%) as an oil, after 9 h.

Hydrogenolysis of the *p*-nitrobenzyl esters (**7c**) and (**7d**) (H_2–Pd/C–aqueous dioxan) followed by addition of 1 equiv. of sodium hydrogen carbonate gave the sodium salts (**7f**), $\lambda_{max}(H_2O)$ 303 and 236 nm, ν_{max}(KBr) 1755 cm^{-1} and (**7g**) $\lambda_{max}(H_2O)$ 307 and 229 nm, ν_{max}(KBr) 1750 cm^{-1}. Antibacterial tests *in vitro* showed both (**7f**) and (**7g**) to be active against a wide range of Gram positive and Gram negative organisms with (**7g**) including activity against *Pseudomonas* species.

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