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SYNTHESIS OF OLIVANIC ACID ANALOGUES: A FACILE ROUTE TO 3-(2-PYRIMIDINYLTHIO-) SUBSTITUTED DERIVATIVES

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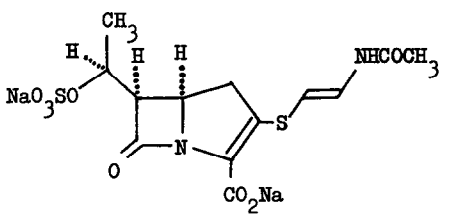
Summary: 3-(2-Pyrimidinylthio-) substituted olivanic acid analogues, with and without a C-6 hydroxyethyl substituent, have been synthesised in high yield using an intramolecular Wittig reaction followed by deprotection to afford zwitterions with high antibacterial activity.

Several methods have recently been developed for the synthesis of the olivanic acids, e.g. MM 13902 (1)[1] thienamycin (2)[2] and related analogues. Of the approaches described, the more common ring closure process involves formation of the C2 - C3 bond.[3,4,5] More recently a further route has been developed utilising a carbene insertion reaction to generate the bicyclic ring system by N-C2 ring closure[6]. One of the methods of C2 - C3 bond formation incorporates concomitant introduction of the C2 - C3 double bond and involves the use of the intramolecular Wittig reaction. This reaction we have used extensively, initially to give rise to simple analogues (3a and 3b)[5,7] of the olivanic acids, and subsequently to include thioesters (3c and 3d)[8,10] leading directly to analogues containing a C-3 sulphur substituent. To date these thioester reactions have led to moderate yields of bicyclic material (20 - 40%). We now report a cyclisation reaction involving the intramolecular Wittig reaction which provides sulphur-containing analogues of the olivanic acid/thienamycin family in high yield.



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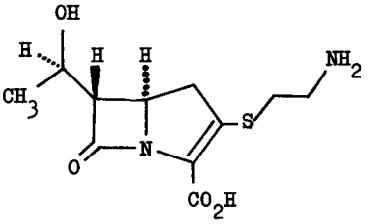

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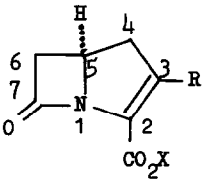
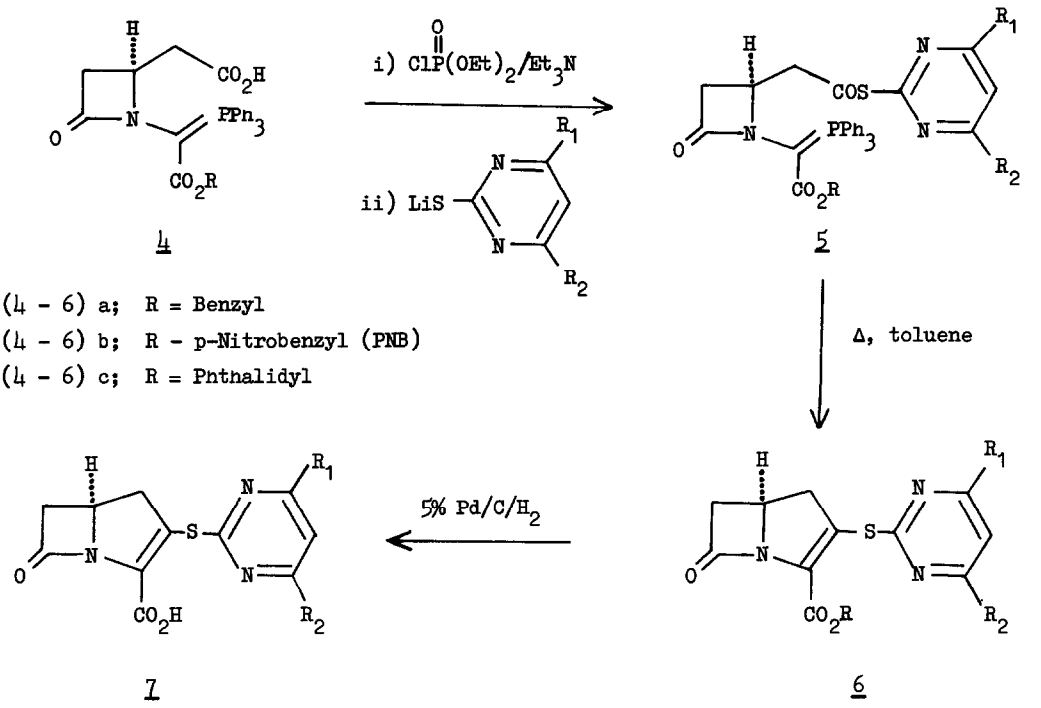


3 a, R = H; b, R = CH_3;
c, R = SPh
d, R = S–(CH=CH)–$NHCOCH_3$

The 4-carboxymethyl azetidin-2-ones[7,8] 4(a-c) were used as the source of thioester-phosphoranes 5(a-c; $R_1 = R_2 = CH_3$). The acid (4a) was treated as the mixed phosphonic anhydride ($ClPO(OEt)_2$, Et_3N, tetrahydrofuran) with lithium 4,6-dimethyl-2-pyrimidinyl thiolate to provide the thioester-phosphorane (5a; $R_1 = R_2 = CH_3$)[9] (72%), ν_{max} ($CHCl_3$) 1740 cm^{-1}.



4 5 6 7

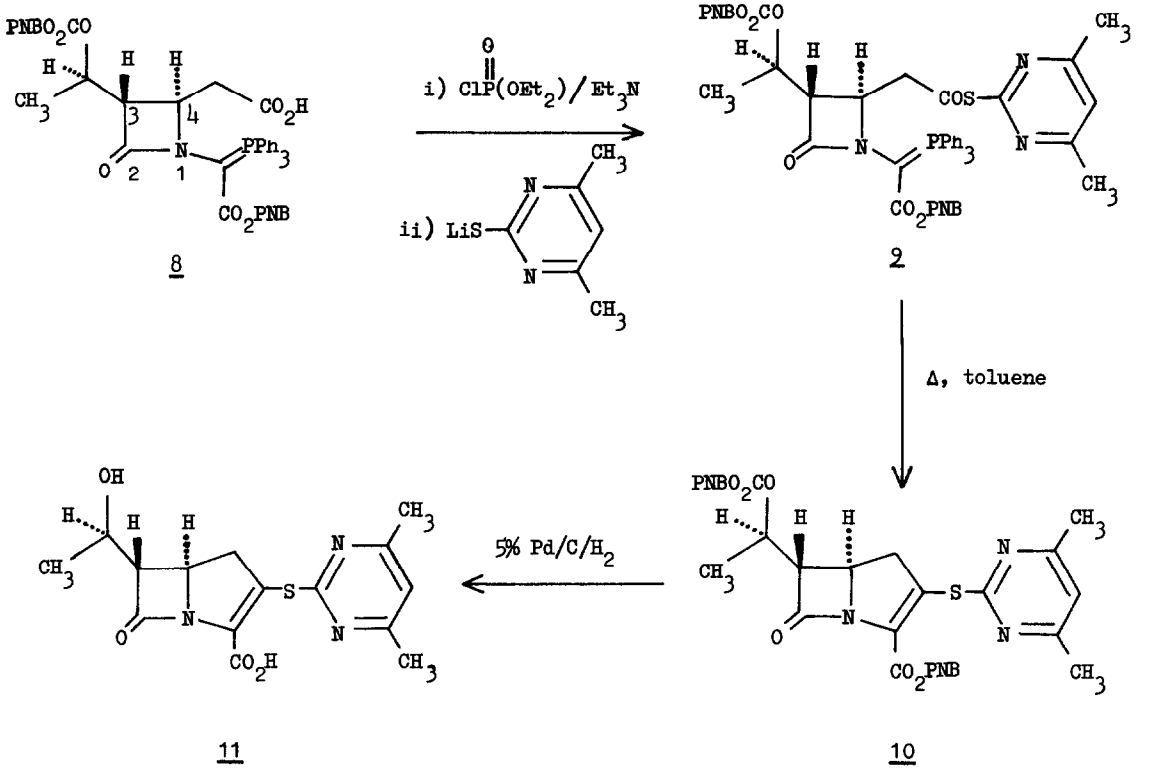
(4 - 6) a; R = Benzyl
(4 - 6) b; R - p-Nitrobenzyl (PNB)
(4 - 6) c; R = Phthalidyl

Cyclisation of the thioester-phosphorane (Δ, toluene, 3 h.) gave after chromatography on silica an 80% yield of bicyclic product (6a; $R_1 = R_2 = CH_3$), λ_{max} (EtOH) 317 nm. ν_{max} ($CHCl_3$) 1785, 1710 cm^{-1}. δ ($CDCl_3$) inter alia 2.90 (1H, dd, J 17, 3 Hz, C6-Ha), 3.05 (1H, dd, J 17, 9 Hz, C4-Ha), 3.44 (1H, dd, J 17, 5.5 Hz, C6-Hb), 3.72 (1H, dd, J 17, 9 Hz, C4-Hb), 4.20 (1H, m, C5-H). The cyclisation reaction was equally effective when the ester group was the deactivating p-nitrobenzyl (PNB) ester as in (5b; $R_1 = R_2 = CH_3$), the bicyclic product (6b; $R_1 = R_2 = CH_3$) being obtained in 70% yield after 3 h. reflux in toluene. Even when the ester function contained the very bulky phthalidyl ester group as in (5c; $R_1 = R_2 = CH_3$), 3½ h. reflux afforded a 27% yield of (6c; $R_1 = R_2 = CH_3$). Other examples where ($R_1 = CH_3$, $R_2 = H$) and ($R_1 = R_2 = H$) readily formed thioesters and cyclised with similar ease.

Removal of the protecting group in (6b; $R_1 = R_2 = CH_3$) was carried out by hydrogenolysis using 5% Pd/C in aqueous dioxan and M/20 phosphate buffer to provide the zwitterion (7; $R_1 = R_2 = CH_3$) in aqueous solution[11], λ_{max} (H_2O) 296 nm.

Application of these reactions to the series bearing a protected C-3 (1-hydroxyethyl) substituent indicated the generality of the method.

Reaction of the appropriate phosphorane-acid[7,12] as a pure diastereoisomer e.g. (8) (having the 1R side-chain stereochemistry) in the form of the mixed phosphonic anhydride with lithium 2-pyrimidinyl thiolate gave (9) (73%).



Cyclisation of the thioester-phosphorane (9) in refluxing toluene under argon over 3 h. gave the protected bicyclic azetidin-2-one (10) in 76% yield, λ_{max} (EtOH) 320, 264 nm. ν_{max} ($CHCl_3$) 1785, 1735 cm^{-1}. δ ($CDCl_3$) inter alia 3.25 (1H, dd, J 10, 18 Hz, C4 - Ha), 3.44 (1H, dd, J 3, 8.0 Hz, C6-H), 3.82 (1H, dd, J 10, 18 Hz, C4-Hb), 4.28 (1H, ddd, J 3, 10, 10 Hz, C5-H), 5.20 (1H, dq, J 6.0, 8.0 Hz, C8-H). When the thioester-phosphorane was prepared and cyclised as a mixture of side-chain diastereoisomers the bicyclic products were fortunately still separable by chromatography.

Removal of the protecting groups in (10) was carried out as before by hydrogenolysis in aqueous dioxan using 5% Pd/C and $^{M}/20$ phosphate buffer to provide the zwitterion (11) which could be isolated as a freeze-dried solid λ_{max} (H_2O) 301 nm. ν_{max} (KBr) 1765 cm^{-1}. Analogues prepared in this way demonstrated a spectrum of antibacterial activity equivalent to that shown by naturally occurring materials. Details of these tests will be reported later.

References and Notes

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8. R. J. Ponsford, P. M. Roberts and R. Southgate, J.C.S. Chem. Commun., 847, (1979).
9. All new compounds were satisfactorily characterised.
10. A. J. G. Baxter, R. J. Ponsford and R. Southgate, J.C.S. Chem. Commun., 429, (1980).
11. Isolation of the zwitterions often led to marked decomposition. Compounds without a C6-substituent were usually better handled in aqueous solution.
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