Reaction of Olivanic Acids with Hypobromous Acid: The Preparation and Use of a Versatile Intermediate, the C-3 Thiol

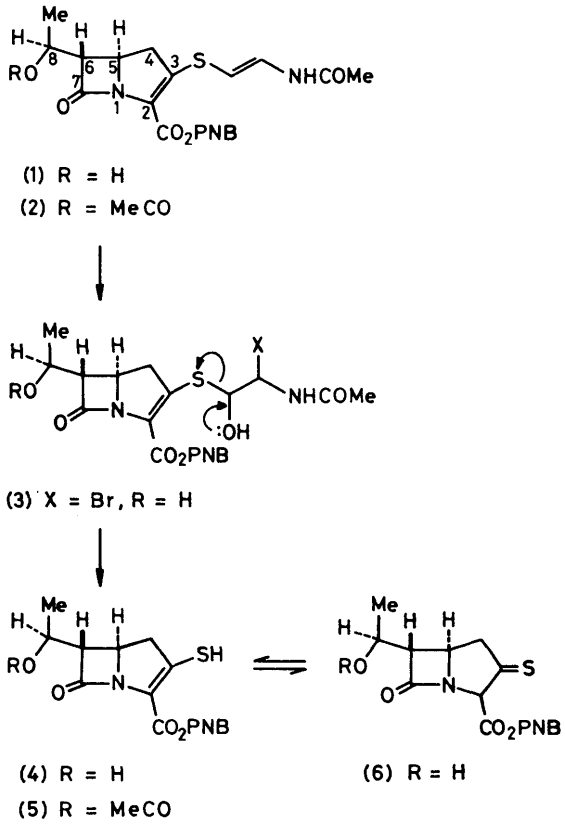
By DAVID F. CORBETT

(*Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey* RH3 7AJ)

Summary The 3-(*E*)-2-acetamidoethenylthio-substituent of olivanic acid derivatives reacts with hypobromous acid to afford a C-3 thiol which undergoes alkylation reactions and addition to propiolates.

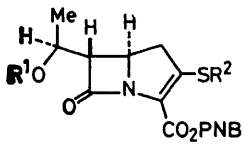
THE olivanic acids are a family of naturally occurring β-lactam antibiotics containing the 7-oxo-1-azabicyclo-[3.2.0]hept-2-ene ring system and possessing either a 2-acetamidoethylthio- or (*E*)-2-acetamidoethenylthio-substituent at C-3.[1–3] It has now been discovered that the double bond in derivatives of the latter group is susceptible to electrophilic addition of hypobromous acid (HOBr) to afford an unstable bromohydrin which breaks down to a C-3 thiol. Subsequent alkylation with a variety of reagents or addition to propiolates then provides a series of novel olivanic acid derivatives with different C-3 substituents. In certain cases, addition of HOBr occurs in the opposite regio-sense to afford an oxazoline.

In principle, the introduction of a hydroxy-group α to sulphur in the C-3 substituent of olivanic acid derivatives would provide an intermediate which is capable of breaking down to a C-3 thiol (Scheme). The presence of a double bond in the C-3 side chain of MM 13902,[1] MM 22382,[3] and MM 22383[3] allowed this possibility to be explored. Consequently, the ester (**1**) was treated with HOBr, conveniently generated by the use of *N*-bromoacetamide (NBA) in aqueous acetone, and the product obtained indeed contained the thiol (**4**), presumably in equilibrium with the thione (**6**) [$\nu_{max.}$($CHCl_3$) 1780, 1750sh, and 1700 cm^{-1}]. The intermediate bromohydrin (**3**), derived from electrophilic addition of HOBr to the double bond, therefore fragments in the expected manner. Isolation and full characterisation of the thiol (**4**) was not possible owing to decomposition of the



SCHEME. PNB = *p*-nitrobenzyl.

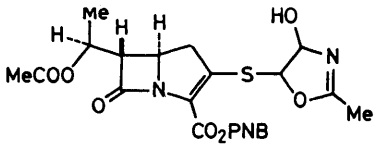
material on chromatographic systems, but its presence in the reaction product was confirmed by alkylation with ethyl iodide [K_2CO_3, *NN*-dimethylformamide (DMF), room temp.] to afford the C-3 ethylthio-derivative (**7**), m.p. 180—183 °C [27% from (**1**)]. The thiol also underwent addition to ethyl propiolate to give the 2-ethoxycarbonylethenylthio-derivative (**8**) [ratio of (*Z*):(*E*)-isomers = *ca.* 9:1] (26%).



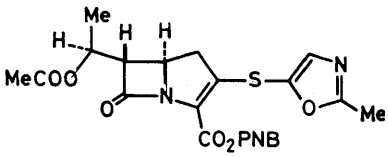
(**7**) R^1 = H, R^2 = Et

(**8**) R^1 = H, R^2 = CH=CHCO$_2$Et

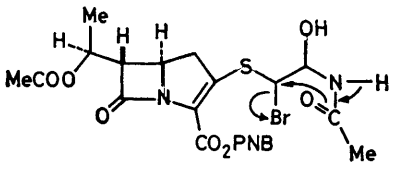
(**9**) R^1 = MeCO, R^2 = CH=CHCO$_2$Et



(**10**)



(**11**)

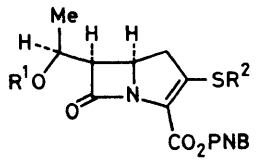


(**12**)

PNB = *p*-nitrobenzyl

The use of the acetoxy-derivative (**2**) in the reaction with HOBr afforded less polar, more easily isolable products and it became apparent that the thiol (**5**) was not the sole product. Thus treatment of (**2**) with NBA (Me_2CO, H_2O, −10 °C) followed by ethyl propiolate (K_2CO_3, DMF, room temp.) furnished the expected derivative (**9**) [ratio of (*Z*):(*E*)-isomers = *ca.* 7·5:1] (15%) and a new product which was deduced to consist of isomers of the hydroxyoxazoline (**10**) (25%). The structure of (**10**) was based on spectroscopic evidence and its conversion into the oxazole (**11**) with methanesulphonyl chloride (Et_3N, CH_2Cl_2, 0 °C). The formation of the oxazoline (**10**) can be rationalised by addition of HOBr to the double bond in the opposite regiomanner to afford the bromohydrin (**12**). Cyclisation with loss of hydrogen bromide would then give rise to the observed product (**10**).

If the reaction of olivanic acid derivatives with NBA was performed in 15% aqueous 1,4-dioxan (room temp., 4·5 min) then oxazoline formation was minimised and a more efficient conversion into the desired thiol occurred. For instance, the ester (**13**) when treated with NBA (dioxan, H_2O, room temp.) followed by ethyl iodide afforded the ethylthio-derivative (**14**), m.p. 140—142 °C, in 42% overall yield. The reaction sequence was also successfully applied to the sulphated olivanic acids by use of the quaternary ammonium salt of the MM 13902 ester (**15**); sequential reaction of (**15**) with NBA (dioxan, H_2O, room temp.) and ethyl propiolate (K_2CO_3, DMF, room temp.) gave the new derivative (**16**) [ratio of (*Z*):(*E*)-isomers = *ca.* 9:1] in 49% yield.



(**13**) R^1 = H, R^2 = CH=CH.NHCOMe (*E*)

(**14**) R^1 = H, R^2 = Et

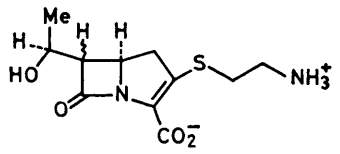
(**15**) R^1 = Q$^+$ $^-$O$_3$S, R^2 = CH=CH.NHCOMe (*E*)

(**16**) R^1 = Q$^+$ $^-$O$_3$S, R^2 = CH=CHCO$_2$Et

(**17**) R^1 = H, R^2 = CH$_2$CH$_2$NHCO$_2$PNB

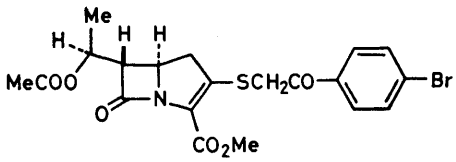
Q = $(C_{16}H_{33})BzlMe_2N$

PNB = *p*-nitrobenzyl



(**18**) (5*R*, 6*R*, 8*S*)

(**19**) (5*R*, 6*S*, 8*S*)



(**20**)

The C-3 thiol derived from each of the olivanic acids MM 13902, MM 22382, and MM 22383 has been utilised to prepare a wide range of new C-3 side chain analogues. The versatility of the process can be demonstrated by the facile preparation of isomers of thienamycin.[4] The thiol produced from the MM 22382 ester (**13**) was alkylated with 2-*p*-nitrobenzyloxycarbonylaminoethyl bromide to afford derivative (**17**) (27%). Hydrogenolysis (H_2, 5% Pd–C, dioxan, pH 7 phosphate buffer) then furnished the zwitterionic product (**18**), a diastereoisomer of thienamycin. A similar sequence from the MM 22383 ester (**1**) correspondingly gave the thienamycin isomer (**19**). The methodology has also been employed to prepare the *p*-bromophenacylthio-derivative (**20**), m.p. 160—162 °C. An *X*-ray structure

determination of this compound unambiguously confirmed the absolute configuration of the molecule to be (5*R*, 6*S*, 8*S*).

The *p*-nitrobenzyl esters of all new derivatives were converted into their respective sodium salts by hydrogenolysis (H_2, 5% Pd–C, 30% aqueous dioxan) and several of these salts possessed antibacterial activity.

We thank Professor T. King of the University of Nottingham for the *X*-ray structure determination of compound (**20**).

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[2] D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, **954**.
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