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2-Thioxopenams, Useful Intermediates for Penem Synthesis

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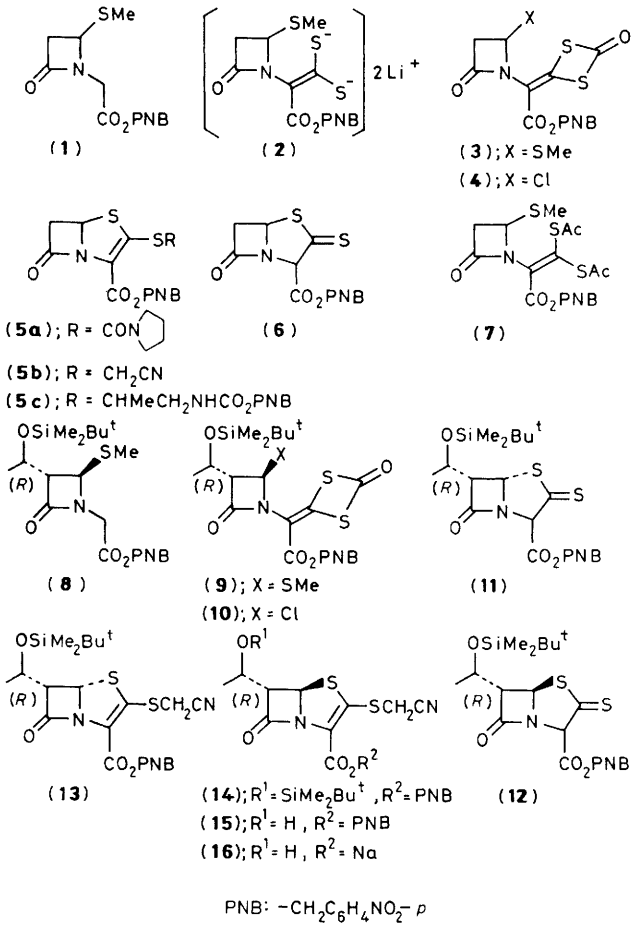
The new penam derivatives, 2-thioxopenams, are prepared by a novel synthetic method and treated with alkylating agents to give penem derivatives.

In a previous paper[1] we described a novel synthesis of penem compounds involving the cleavage of a 1,3-dithiolan ring and subsequent cyclization to the penem nucleus. As an extension of this study, we have synthesized 1,3-dithietan derivatives and found them to be good precursors to the hitherto unknown 2-thioxopenam compounds. We report herein the synthesis of thioxopenams which can undergo alkylation reactions with alkyl halides or Mitsunobu reactions[2] with alcohols leading to a wide variety of antibacterial penem compounds.

The dithiolate anion (**2**) was prepared from *p*-nitrobenzyl (±)-4-methylthio-2-oxoazetidin-1-ylacetate (**1**) and carbon disulphide as described previously,[1] and allowed to react with phosgene in tetrahydrofuran (THF) at −78 °C to afford the 2-oxo-1,3-dithietan derivative (**3**) in 85% yield. The methylthio group of (**3**) was replaced by chlorine by treatment with an equimolar amount of chlorine or sulphuryl chloride in methylene dichloride at 0 °C. Treatment of the crude chloro-derivative (**4**) with pyrrolidine in methylene dichloride at room temperature led to the expected penem derivative (**5a**), whereas treatment of (**4**) with methylamine in methanol at 0 °C gave rise to the 2-thioxopenam derivative (**6**) as a foam in 63% yield; ^{1}H n.m.r. ([$^2H_7$]-dimethylformamide) δ 3.62 (dd, J_1 17.5, J_2 2.0 Hz, 6-H), 4.08 (dd, J_1 17.5, J_2 4.0 Hz, 6-H), 5.45 (s, CO_2CH_2), 5.55 (s, 3-H), 6.11 (dd, J_1 4.0, J_2 2.0 Hz, 5-H), 7.77, and 8.31 (A_2B_2, J 9.5 Hz, C_6H_4). This thioxopenam formation appears to involve the penem derivative (**5**, R=CONHMe) as a transient intermediate which may undergo further reaction with methylamine with cleavage of the S–CO bond. Therefore different precursors to the thioxopenams could be prepared using various acyl halides. For example, the reaction of the dithiolate anion (**2**) with 2 mol. equiv. of acetyl chloride in THF at −78 °C gave the diacetyl derivative (**7**), which was chlorinated with chlorine then treated with ammonia in ether to give the thioxopenam (**6**). Although (**6**) may exist as a mixture of thioxo and enethiol tautomers, it takes the thioxo form exclusively in $CDCl_3$ solution, as is evident from the ^{1}H n.m.r. spectrum. The thioxopenam (**6**) forms a 1:1 complex with triethylamine.

(8*R*,6*S*,5*S*)-6-(1-t-Butyldimethylsilyloxyethyl)-2-thioxopenam (**11**) was similarly prepared from compound (**8**).[1] The dithietan derivative (**9**) formed first was treated with chlorine or sulphuryl chloride in methylene dichloride at 0 °C and the resulting chloro derivative (**10**) gave (**11**) on treatment with methylamine in methanol–methylene dichloride. Ring closure to form the penam nucleus proceeded with inversion at the



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4-position affording the *cis*-2-thioxopenam (**11**) as a foam; ^{1}H n.m.r. ($CDCl_3$) δ 0.12 (s, $SiMe_2$), 0.87 (s, $SiBu^t$), 1.38 (d, *J* 6.0 Hz, $CHCH_3$), 3.92 (dd, J_1 10.0, J_2 4.0 Hz, 6-H), 4.03—4.57 (m, 8-H), 5.34 (s, 3-H, CO_2CH_2), 6.02 (d, *J* 4.0 Hz, 5-H), 7.54, and 8.23 (A_2B_2, *J* 9.5 Hz, C_6H_4). The *cis*-thioxopenam isomerized slowly to the *trans*-isomer (**12**)† on heating in xylene containing a small amount of hydroquinone at 140 °C and eventually reached equilibrium (*cis*: *trans ca.* 1:2). The thioxopenams (**6**) and (**11**) reacted with a number of alkylating agents to yield antibacterial penem derivatives and the following are selected examples. Iodoacetonitrile reacted with (**6**) in the presence of triethylamine in methylene dichloride for 1 h at room temperature to give the penem derivative (**5b**) in 67% yield. Alternatively the thioxopenams were alkylated using the Mitsunobu reaction; (**6**) was treated with an alcohol in the presence of triphenylphosphine and ethyl azodicarboxylate in THF between 0 °C and room temperature. Thus, when (**6**) was treated with $HOCHMeCH_2NHCO_2PNB$ alkylation resulted to give two diastereoisomers (A: B, 1.8: 1) of (**5c**) in 44% yield. The thioxopenam derivative (**11**) was also subjected to the alkylation reaction with iodoacetonitrile under the same conditions. The penem derivative (**13**) thus obtained was heated under reflux for 5 h in xylene containing a small amount of hydroquinone to give a mixture of the *cis*- (**13**) and *trans*-isomers (**14**) in equilibrium.[3] The *trans*-isomer was isolated by column chromatography and the t-butyldimethylsilyl group was deprotected with tetrabutylammonium fluoride to give (**15**) which was converted into (**16**) by hydrogenolysis over 10% Pd–C as described previously.[1]

† Preparation of the pure *trans*-thioxopenam (**12**) will be described elsewhere.

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