The Isomeric 9,10-Oxides of *trans*-7,8-Dihydroxy-7,8-dihydrobenzo[*a*]pyrene

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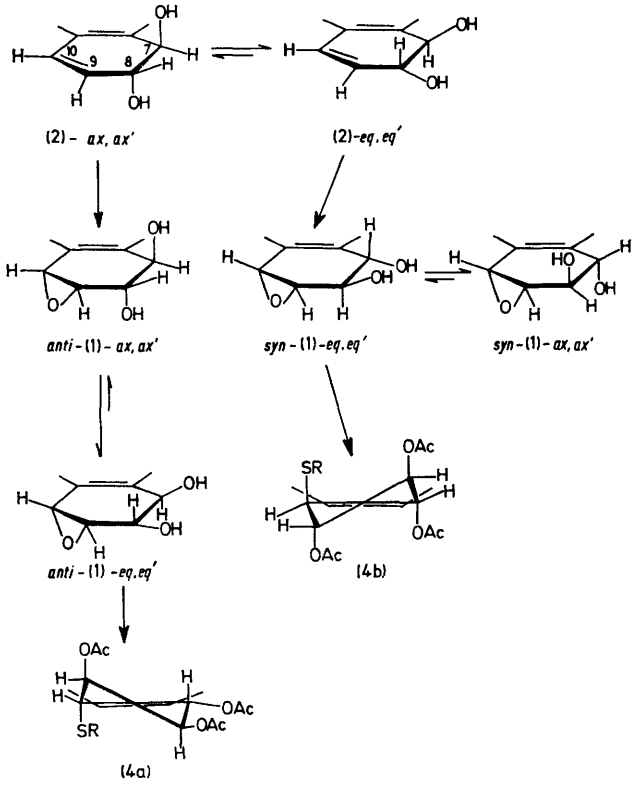
Summary Synthesis of the isomeric *syn*- and *anti*- forms of the title compound, proof of their structures, and their reactions with the nucleophile t-butyl-mercaptan is described.

RECENT evidence[1,2] indicates that the potent carcinogen benzo[*a*]pyrene (BaP) is metabolically activated through transformation to *trans*-7,8-dihydroxy-7,8-dihydro-BaP 9,10-oxide (**1**). It has also been postulated[3] that the isomer

here designated as *syn*† should have much greater chemical reactivity due to assistance of epoxide ring opening by the 7-hydroxy function, enabling it to react with DNA *in vivo*. Synthesis of one of these isomers was reported,[1,4] although the stereochemistry was not established.



We now report the synthesis of the second isomer, stereochemical assignment of both isomers, and their reactions with the model nucleophile t-butylmercaptan. Reaction of *trans*-7,8-dihydroxy-7,8-dihydro-BaP (**2**) with *m*-chloroperbenzoic acid according to the published method[4] gave a single isomer of (**1**) identified as *anti*-(**1**). *Syn*-(**1**) was obtained from (**2**) in good yield (77—87%) through formation of the bromohydrin,[5] followed by cyclization with Bu^{t}OK in THF (1 h at 25 °C). The integrated ^{1}H n.m.r. spectra‡ of both isomers were consistent with their structural assignments.

Reactions of *syn*- and *anti*-(**1**) with Bu^{t}SNa in aqueous dioxan gave the respective products of *trans*-stereospecific ring-opening (**3a**,**b**), acetylation of which gave the corresponding triacetates (**4a**,**b**). In order to distinguish between the isomers (**3a**) and (**3b**) reaction with acetone in the presence of *p*-toluenesulphonic acid was carried out (16 h at 25 °C.) In accord with the precedent that acetonide formation occurs selectively with *cis*-diols,[6] only (**3a**), the isomer derived from *anti*-(**1**) underwent transformation to an acetonide, confirming the *cis*- relationship between the 8- and 9- hydroxy groups. Further confirmation was provided by reaction with the potassium triacetylosmate reagent of Criegee[7] which gave a precipitate with (**3a**) but not with (**3b**). It follows, therefore, that in (**3a**) the steric relation of substituents is *trans-cis-trans*, whereas in (**3b**) it is *trans-trans-trans*. This assumes, of course, that attack of the sulphur nucleophile on the oxide ring affords the *trans*-product. Previous studies with other polycyclic oxides[8,9] support this concept. The n.m.r. spectra‡ of (**4a**,**b**) are consistent with these assignments and in close agreement with those of known closely related compounds.[10]

All the reactions gave good yields (70–90%) of the products and appear to be both regiospecific and stereospecific, however, minor amounts of other isomers may be formed. The observed stereochemical preferences are consistent with the expected properties of these ring systems. Thus, epoxidation of cyclic olefins by peracids is known to be susceptible to the *cis*- directing effect of axial allylic and homoallylic hydroxy groups.[11] Drieding models of (**2**) show essentially equal distances between either hydroxy group and the centre of the double bond. Apparently, the 8-hydroxy group is dominant, since *anti*-(**1**) is formed. The stereochemistry of bromohydrin formation is dominated by the large steric demand of the bromo group which directs axial attack on the diequatorial conformer of (**2**). Experiments on the comparative reactivity and biological properties of *syn* and *anti*-(**1**) are in progress.

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† The terms *syn*- and *anti*-are proposed for the diastereomers in which the 7-hydroxy function is *cis*- and *trans*-, respectively, to the oxide ring. For each diastereomer a pair of enantiomers is possible, the partial structure of only one of which is depicted. In addition, for each enantiomer there are two conformers in dynamic equilibrium in which the hydroxy groups are both either diaxial (*ax*,*ax'*) or diequatorial (*eq*,*eq'*).

‡ N.m.r. spectra were taken on Varian T-60 and Bruker 270 MHz spectrometers in [$^2H_6$]-Me_2SO relative to Me_4Si. *Anti*-(**1**): δ 5·22 (d, $J_{9,10}$ 4·5, H-10), 4·76 (d, $J_{7,8}$ 8·25, H-7), 3·96 (d, $J_{8,9}$ *ca.* 0, H-8), and 3·88 (d, H-9); *syn*-(**1**): δ 4·97 (d, $J_{9,10}$ 4·5, H-10), 4·92 (d, $J_{7,8}$ 6·0, H-7), 3·99 (d, $J_{8,9}$ *ca.* 0, H-8), and 3·88 (d, H-9); (**4a**): δ ($CDCl_3$) 6·83 (d, $J_{7,8}$ 10·0, H-7), 6·43 (d, $J_{8,9}$ 2·8, H-8), 5·99 (d, $J_{9,10}$ 4·0, H-9), and 5·28 (d, H-10); (**4b**): δ ($CDCl_3$) 6·96 (d, $J_{7,8}$ 8·25, H-7), 5·69 (apparent d, $J_{9,10}$ *ca.* 2, H-9), and 5·32 (two overlapping d, $J_{8,9}$ *ca.* 2, H-8,10).

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