The Direct Formation of a *cis*-Bromohydrin from an 8β-Methyloestrane Derivative

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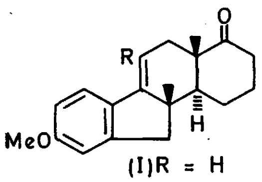
Summary The reaction of an 8β-methylœstrane has been shown to give in high yield a *cis*-bromohydrin.

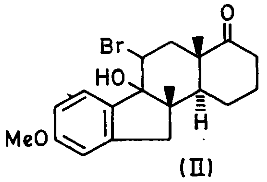
ISOLATED examples have been recorded for the *cis*-addition of electrophiles to double bonds.[1] Recent reports[2] on the addition of bromine to phenyl-substituted olefins would indicate that this non-stereospecific addition is, at least in part, the result of formation of an open or only partially bridged cation. We report now what we believe to be the first stereospecific *cis*-addition of hypobromous acid to a phenyl-substituted olefin.

The reaction of hypobromous acid (generated from *N*-bromoacetamide and perchloric acid in aqueous tetrahydrofuran[3]) with the totally synthetic 8β-methyloestrane[4] (I) resulted in the formation of the *cis*-bromohydrin (II), m.p. 210—230° (decomp.) in 72% yield.

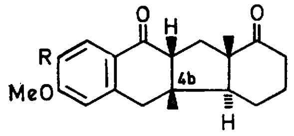
Proof for the assignment of (II) as a *cis*-bromohydrin derives from its reaction with base.[5] Treatment of (II) with NaH in ether at room temp.[6] afforded the product of a pinacol-type rearrangement (III), m.p. 206—210°. An improved procedure involved the use of potassium t-butoxide in t-butyl alcohol.[7] Hydrogenolysis of (III) then yielded (IV), m.p. 133—134°. The base peak in the mass spectrum of (IV) appeared at *m/e* 148 ($C_9H_8O_2$) corresponding to the fragment (V). This establishes the presence of a tetralone moiety.



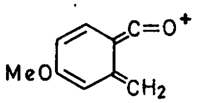
(I) R = H
(IX) R = Br



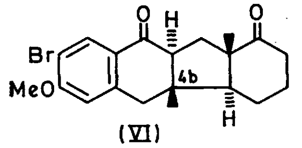
(II)



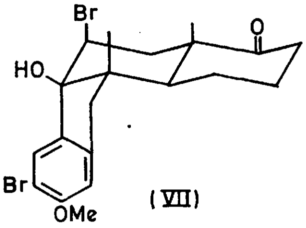
(III) R = Br
(IV) R = H



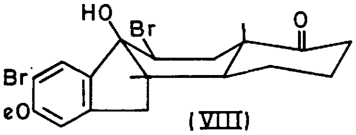
(V)



(VI)



(VII)



(VIII)

Silver-assisted solvolysis of (II) in acetone, on the other hand, gave (VI), m.p. 206—210° which is converted into (III) either thermally or by base. This was demonstrated both by n.m.r. and differential thermal analysis. Assignment of a *trans*-ring fusion to (VI) is based primarily on n.m.r. evidence. The C-4b methyl group in (III) resonates at τ 8·76 (relative to Me_4Si) whereas the same methyl group in (VI) is shifted to τ 9·14. The shielding of this methyl group by both the carbonyl group and phenyl ring in (VI) is particularly evident in models.

It is well established that in pinacol-type rearrangements, the migrating group should bear an *anti*-coplanar relationship to the leaving group.[8] Structure (VI) establishes that the bromine atom in (II) must be β-oriented otherwise (III) should be the solvolysis product. Thus two structures, those in which the bromine is β and the hydroxy-group either α or β, are possible for the bromohydrin. Models show that the structure in which the hydroxy-group is α would be rigid and the bromine and hydroxy-group truly diaxial. Reaction of a compound with this structure with base or silver ion would be expected to yield an epoxide or a rearrangement product derived therefrom. Thus, the diaxial bromohydrin may be discounted. Two possible conformations may be written for the *cis*-bromohydrin as shown in structures (VII) and (VIII). Since there was no evidence for migration of the *p*-methoxybenzyl moiety, (VII) cannot contribute significantly.

Positive bromine must attack the olefin from the β-face of the molecule producing a species containing three axial substituents in the C-ring.† This steric congestion is alleviated by the C-ring adopting a boat conformation (as in VIII) and the bromine, therefore, an equatorial configuration. The transition state must then involve a bromocarbonium ion in which there is no neighbouring bromine participation. The conformational change in the C-ring also reduces the methyl–methyl interaction and opens up the carbonium ion for capture by hydroxyl ion. These results parallel those recently described by Rolston and Yates[9] for the bromination of various styrenes, the hypobromous acid addition to (I) representing the limiting case.

Further evidence for a free carbonium ion intermediate derives from the reaction of (I) with *N*-bromosuccinimide in moist dimethyl sulphoxide.[10] This gave the bromostyrene (IX), m.p. 181—183°, in 80% yield. Dalton, Dutta, and Jones reported[10] only bromohydrin and dibromide formation under these conditions. The formation of (IX) must be due to steric inhibition to addition of Me_2SO to the tertiary carbon atom since normal attack by water on the sulphonium intermediate would be expected. It is also reasonable to conclude that water, presumably bound to solvent, has even greater steric requirements. Undoubtedly of greater significance is the preferred equatorial configuration of the bromine which results in an axial hydrogen on the same carbon ideally oriented for removal as a proton and formation of (VI).‡

Note added in proof: Compound (IV) has now been prepared in an unequivocal manner and will be described in the full paper.

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† It is noteworthy that catalytic reduction of (I) also occurs predominatly from the highly congested β-face.[4]

‡ Formation of an α-sulphonium intermediate followed by elimination cannot, however, be ruled out.

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