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ON THE CONVERSION OF SUBSTITUTED EPOXIDES TO HALOHYDRINS

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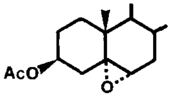
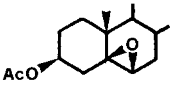
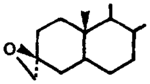
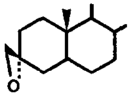
Abstract: Di- and trisubstituted steroidal epoxides are shown to be converted smoothly to halohydrins in high yield by triphenylphosphine-halogen complexes, under non-acidic and non-eliminating conditions.

In a previous paper[1], we reported a new method, using triphenylphosphine-halogen complexes in anhydrous dichloromethane, to convert epoxides to halohydrins under mild and non-acidic conditions. A borderline S_N2 mechanism for the oxirane-ring opening was suggested[1] by us, mainly on the grounds of the halohydrin distribution resulting from the cleavage of an unsymmetrically substituted epoxide, namely 1-methylcyclohexene oxide which displays both secondary and tertiary oxirane-ring-forming carbon atoms.

Recently, a Polish group reported[2] that trisubstituted steroidal epoxides, when treated with triphenylphosphine-iodine complex under our experimental conditions, undergo deoxygenation and afford the corresponding alkenes rather than the expected halohydrins. On the basis of these results, the authors suggested the epoxide cleavage to go through an intermediate tertiary carbonium ion which eventually is not readily accessible for nucleophilic attack, thus leading to triphenylphosphine oxide elimination to give alkenes. This is rather uncommon in epoxide chemistry[3] and even surprising if one considers that the steroidal substrates tested[2] have epoxide functions which are not expected to suffer from any sensible steric hindrances. Therefore, we repeated the reported experiments and our results are summarized in the Table. They show unambiguously that trisubstituted epoxides give without exception halohydrins, by $Ph_3P\text{-}Hal_2$ complexes, in a quite stereoselective manner. Only traces of accompanying elimination products could be detected in some instances.

The cleavage of (3R)- and (3S)-spiro-[5α-cholestane-3,2'-oxiran] by $Ph_3P\text{-}I_2$ complex is of particular significance. In fact, in these substrates, the oxirane ring is formed by both a primary and a tertiary carbon atoms, the latter being the C-3 carbon atom of the steroidal skeleton which is well known[4]

Table - Reactions of Substituted Cholestane Epoxides with Ph_3P - Hal_2.

Epoxide	Hal	% Yield	Halohydrin	
	I	90	3β-OAc; 5α-OH; 6β-I, m.p. 145-147 °C	(a),(i)
	Br	94	3β-OAc; 5α-OH; 6β-Br, m.p. 140-142 °C	(b),(i)
	I	93	3β-OAc; 5α-I; 6β-OH,	(c)
	Br	95	3β-OAc; 5α-Br; 6β-OH, m.p. 159-161 °C	(d),(h)
	I	90	3β-OH; 3α-CH_2I, m.p. 82-85 °C	(e),(i)
	Cl	92	3β-OH; 3α-CH_2Cl, m.p. 119-120 °C	(f),(i)
	I	88	3α-OH; 3β-CH_2I, m.p. 108-112 °C	(g),(i)

Significant ^{1}H-N.M.R. signal (, $CDCl_3$): a) 4.16 (1H, *m*, $w_{\frac{1}{2}}$ = 8 Hz, C6-H); b) 4.18 (1H, *m*, $w_{\frac{1}{2}}$ = 8 Hz, C6-H); c) (crude) 4.27 (1H, *m*, $w_{\frac{1}{2}}$ = 8 Hz, C6-H); d) 4.14 (1H, *m*, $w_{\frac{1}{2}}$ = 8 Hz, C6-H); e) 3.56 (2H, *s*, CH_2I); f) 3.70 (2H, *s*, CH_2Cl); g) 3.30 (2H, *s*, CH_2I); h) C-6 ketone, m.p. 154-155 °C; i) unaffected by Jones reagent.

to be reasonably unaffected by steric hindrance and prone to undergo nucleophilic attack. In our opinion, the nearly quantitative formation from any of these epoxides of the sole iodohydrin with a tertiary hydroxyl group at C-3, geminal with a iodomethyl group and having the same C-3 configuration as the parent epoxide, speaks in favour of the non-existence of a carbocation at C-3, hence in favour of S_N2-like cleavage of the oxirane ring. This appears even more compelling if one considers that chloride ion, smaller than iodide, leads to the same results[1].

We have also considered alternative routes to the formation of traces of alkenes accompanying in some instances the main reaction products, halohydrins. Actually, we carried out experiments under strictly anhydrous conditions (in a dry-box) and could conclude that no elimination of triphenylphosphine oxide, induced by halide ions[3], occurs in the reaction mixture before it is worked-up. Also slight excesses of halide ions added to the reagents turned out to be totally ineffective and, apparently, the alkenes are formed only from the free halohydrins according to known chemistry.

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