Reactions of Dihalogenocarbenes with Ring B Steroid Olefins

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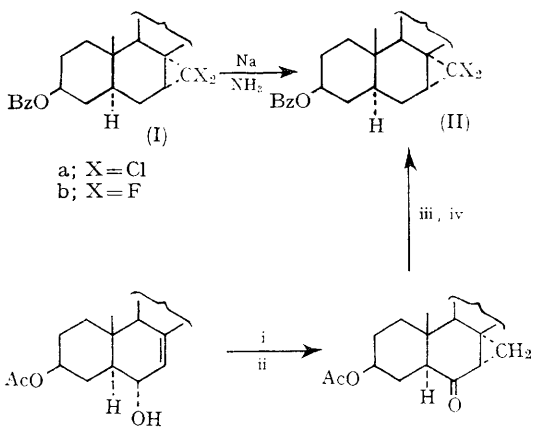
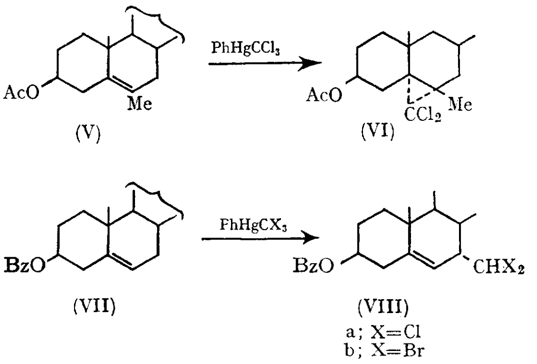
PREVIOUS studies[1-3] of the reaction of dihalogenocarbenes with steroid olefins have shown that non-activated double bonds, other than in ring A, fail to give addition, except in the case of difluorocarbene which surprisingly added β to the Δ^5-position.[1] Both dichloro- and dibromo-carbenes were inert in reactions with Δ^5-steroids bearing a 10β-methyl group, although α-attack occurred with 5,7-dienes,[2] and β-attack with 3,5-dienes.[1] These results seemed to preclude the general applicability of dichloro- and dibromo-carbene additions to more hindered positions either in steroids or other molecules.

We have found that use of phenyl(trihalogeno)-mercury precursors[4] results in effective addition to the highly hindered Δ^7-position[5] as well as to 6-substituted Δ^5-olefins, and the Δ^6-position. In a typical experiment cholest-7-en-3β-yl benzoate (3·3 mmoles) and the mercurial (50 mmoles) were heated for 2 hr. at 156° in glyme (70 ml.) in a sealed tube. Standard workup gave the dichloro-adduct (Ia)† (50%, m.p. 181—182·5°, $[\alpha]_D - 39°$). Similarly, the difluoro-adduct (Ib) (83%, m.p. 125—126°, $[\alpha]_D + 11°$) was obtained by using sodium chlorodifluoroacetate.[1,6] The $7\alpha,8\alpha$-assignment to (Ia) was confirmed by sodium–ammonia reduction to (II) which was identical with authentic material synthesized stereospecifically[7] by Simmons–Smith addition[8] to the 7-ene-$3\beta,6\alpha$-diol 3-acetate (III),[9] followed by oxidation to (IV), Wolff–Kishner reduction, and benzoylation. The stereochemistry of (Ib) is confirmed by the appearance of an unsplit C-19 methyl signal in the n.m.r. spectrum at 0·95 p.p.m.

These results, seemingly in conflict with β-attack[1] at Δ^5, are best explained by axial attack of the reagent *via* at least a partially charged transition-state.[10] A similar proposal has been made for cyanonitrene attack.[11] With Δ^7-olefins this occurs with formation of an axial 7α-bond and positive charge at the tertiary C-8 position. With the more nucleophilic 6-methyl-Δ^5-olefin (V), dichlorocarbene clearly gives an adduct, m.p. 158—159°, $[\alpha]_D - 12°$, which we assigned structure (VI) on the basis of its n.m.r. spectrum.‡ Under these sealed tube–mercurial conditions, cholesteryl benzoate fails to give addition, but the allylic insertion products (VIIIa), m.p. 215—217°, $[\alpha]_D - 70°$, and (VIIIb), m.p. 238—242°, $[\alpha]_D - 57°$ could be



(i) Simmons–Smith addition; (ii) Jones oxidation; (iii) Wolff–Kishner reduction; (iv) PhCOCl.



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† Satisfactory analyses were obtained for all new compounds.

‡ The α-stereochemistry is assigned on the basis of the chemical shift of the C-19 methyl group which is at either 1·15 or 1·22δ, the other sharp singlet being due to the 6-methyl group. Using a Zurcher value of +18 c./sec. for a 5α, 6α dichlorocyclopropyl group (derived in our laboratories from a study of compounds similar to those of Nazer[2]), one predicts a chemical shift of δ 1·22.

isolated along with recovered starting material.§ The low-field n.m.r. region of (VIIIa) shows aromatic protons and three one-proton bands at 6·12, 5·77, and 4·66 p.p.m., assigned respectively to the 7α-dichloromethyl proton, the C-6 proton, and the C-3 proton. The position and stereochemistry of attack were shown by zinc-dust reduction of both (VIIIa) and (VIIIb) to 7α-methylcholest-5-en-3β-yl benzoate, and conversion with lithium aluminium hydride into 7α-methylcholesterol, which was identical with an authentic sample.

We thank the National Institutes of Health for financial support and Dr. G. A. Thompson for an authentic sample of 7α-methylcholesterol.

(*Received, July 22nd,* 1968; *Com.* 981.)

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§ The insertion is stereospecific into the 7α-bond. No attempt has been made to maximize yields (20—40%), though this appears to be an attractive route to biologically interesting 7α-steroids.

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