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HYDROBORATION—IV

HYDROBORATION OF 7-DEHYDROCHOLESTEROL*

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Abstract—It has been demonstrated that the hydroboration of 7-dehydrocholesterol takes place according to a 1:2 mechanism, leading to an allylic boron compound in which boron atom is in the 6α position. Treatment of this boron compound with acetic acid or acetic anhydride–acetic acid, leads through protonolysis and simultaneous migration of the double bond, to Δ^6-3β hydroxy cholestene.

THE discovery by Brown[1] that diborane, in the presence of ethers, adds to double-bonds and the development of the hydroboration reaction[2], has led to the investigation of this reaction with substituted olefines, olefines conjugated with ketones[3] and conjugated dienes. Brown *et al.*[4] ascertained that the reaction of diborane with cyclic and non-cyclic conjugated dienes takes place by two consecutive additions of diborane, the second addition proceeding more rapidly than the first.

By oxidation of the alkyl borons obtained, Brown *et al.* succeeded in isolating saturated diols or unsaturated alcohols.

In the case of α,β-unsaturated β, β-disubstituted ketones it has been shown that the reaction proceeds through two consecutive 1:2 additions, the addition to the carbonyl group preceding the addition to the double-bond.

Sondheimer *et al.*[5] have examined the hydroboration of 7-dehydrocholesterol (I) and report the isolation of Δ^6-3β-hydroxycholestene (II) in 10 to 35% yield. In this reaction, the authors assume that diborane acts as a reducing agent, and in accordance with 1:4 reduction the thermodynamically more stable Δ^6-3β-hydroxy-5 α-cholestene is produced.

The reaction of 7-dehydrocholesterol with diborane differs from the hydroboration of conjugated dienes in that Brown *et al.* did not report cases of 1:4 reduction.[4]

Davies reporting on the same reaction,[6] assumes that Δ^6-3β-hydroxy-5 α-cholestene is formed by a 1:4 monohydroboration of the diene system, followed by acid hydrolysis.

In the present work, the mechanism of Δ^6-3β-hydroxy-5α-cholestene formation during the hydroboration of 7-dehydrocholesterol was investigated. As the 7-8 double-bond in the cholesterol system is regarded as unreactive, it was assumed that the diborane reacts only with the double bond in the 5-6 position, forming a organoboron

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[1] H. C. Brown and B. C. Subba Rao, *J. Org. Chem.* **22,** 1136 (1957).
[2] H. C. Brown, *Tetrahedron*, **12,** 117 (1961). H. C. Brown, *Hydroboration* Benjamin, New York (1962).
[3] L. Caglioti and G. Cainelli, *R. C. Accad. Lincei* (8) **29,** 555 (1960).
[4] G. Zweifel, K. Nagase, H. C. Brown, *J. Amer. Chem. Soc.* **84,** 183 (1962).
[5] Y. Mazur, M. Nussim and F. Sondheimer, *Proc. Chem. Soc.* 314 (1959).
[6] Davies, Annual Reports on the Progress of Chemistry, 198 (1959).

allyl compound with the boron atom at position 6 and retaining the double bond in the 7-8 position.

This compound, by protonolysis with simultaneous migration of the double-bond, could yield the Δ^6-3β-hydroxy-5 α-cholestene, a reaction not new in the chemistry of the organometallic compounds.[7]

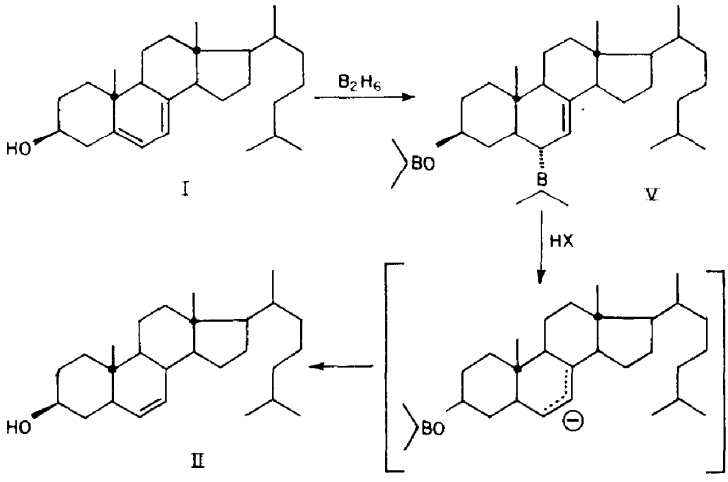

Fig. 1

This hypothesis, was proved by boronation of the dehydrocholesterol in THF(*) with a large excess of diborane. Alkaline hydrogen peroxide treatment of the reaction product yielded diol (III) in a 70–75% yield without even a trace of II (by thin layer chromatographic examination). The allyl alcohol on oxidation with chromic acid, yielded an unsaturated diketone (IV), the UV spectrum of which exhibits a maximum at 246 mμ in agreement with expectations for such a chromophore.

Reduction of this ketone with sodium in liquid ammonia gave a product which on reoxidation with chromic acid yielded the 5α-cholestan-3-6-dione.

These results prove that hydroboration of the 7-dehydrocholesterol in at least 75% yield takes place in accordance with the 1:2 mechanism, producing a boron compound in which boron atom is the 6α position.

In order to demonstrate that organoboron compounds of type V on acid treatment can produce the Δ^6-3β-hydroxycholestene, the reaction mixture of 7-dehydrocholesterol with diborane in diglyme was refluxed with acetic acid, or with acetic anhydride containing traces of acetic acid.

This reagent was also used in β-elimination reactions of organoboron compounds carrying a β oxygen function.[8] The yield of Δ^6-3β-hydroxy- (or acetoxy) cholestene varied from 30 to 40%, but the mother liquors after crystallization, and thin layer chromatographic examination, showed the presence of other monoalcoholic isomers which could result from an equilibrium of the various isomers of the kind taken into

* THF: Dry Tetrahydrofuran.

[7] W. G. Young, M. Eisner, *J. Amer. Chem. Soc.* **63**, 2113 (1941).

[8] L. Caglioti, G. Cainelli, G. Maina and A. Selva, *Gazz. Chim. Ital.* **92**, 309 (1962).

consideration in the case of magnesium.[7] It has, therefore been demonstrated that the reaction of diborane with 7-dehydrocholesterol—at least for the 75%— has a 1:2 course. The Δ^6-3β-hydroxycholestene does not form directly in the reaction: this is noteworthy, as it appears that 3β hydroxy-Δ^6-5α cholestene reacts easily and quantitatively with diborane.

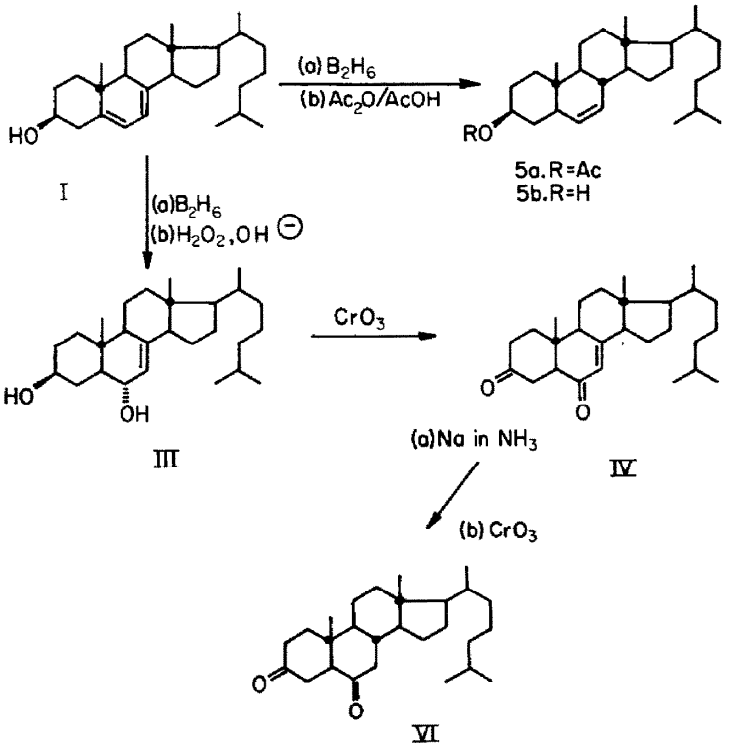

Fig. 2

EXPERIMENTAL

Δ^6,5α,3β-*Hydroxycholestene* (II) *from 7-dehydrocholesterol* (I). 7-dehydrocholesterol (2 g) in diglyme (40 ml) was treated at room temp, in an atmosphere of dry nitrogen, with excess gaseous diborane. After 1 hr, acetic anhydride (20 ml) was added and the mixture heated under reflux for 4 hr. The solution was evaporated *in vacuo* to dryness, ether added and the ethereal solution washed with 2N NaOH and then with water to neutrality and evaporated. The residue, dissolved in anhydrous ether (70 ml) was heated under reflux for 4 hr with $LiAlH_4$ (1 g). After cooling and addition of ethyl acetate; the reaction mixture was extracted with ether, washed with water and evaporated, yielding 1·7 g which was chromatographed on Alox Woelm act. II (50 g). Benzene–ether (9:1) eluted a crystalline product (700 mg) which was purified by recrystallization from dil. methanol: m.p. 118–119°, $[\alpha]_D^{20°} = -83°$ identical with 3β-hydroxy-5α-Δ^6-cholestene. (Found: C, 83·69; H, 11·82. $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%).

Examination of other chromatographic fractions and the mother liquors after crystallization by thin layer chromatography indicated according to polarity the presence of monoalcoholic isomers.

3β,6α-*Dihydroxy*-5α,Δ^7-*cholestene* (III) *from 7-dehydrocholesterol.* 7-Dehydrocholesterol (2 g) dissolved in diglyme (40 ml) was treated with excess diborane at 0°. After standing at room temp for 2 hr the reaction mixture was treated with 5% NaOH (20 ml) and 30% H_2O_2 (5 ml) and after a further 5 min, the mixture was extracted with ether, washed with water, a solution of 5% $FeSO_4$, and again with water and dried. Recrystallization of the residue (2·2 g) from ether–methanol yielded 1·4 g of

a crystalline product: m.p. 192°, $[\alpha]_D^{20°} = +48°$ ($c = 1{\cdot}1$). (Found: C, 81·03; H, 11·28. $C_{37}H_{46}O_2$ requires: C, 80·54; H, 11·52%). The IR spectrum in Nujol shows bands at 3200 cm^{-1}.

3β,6α-Diacetoxy-Δ⁶,5α-cholestene by acetylation of the 3β,6α-dihydroxy-Δ⁶,5α-cholestene. Acetylation of 3β,6α-dihydroxy-Δ⁶,5α-cholestene (200 mg) with acetic anhydride (5 ml) and pyridine (5 ml) followed by several recrystallization from ether–methanol gave a crystalline product, m.p. 114°; $[\alpha]_D^{20°} = +74°$ ($c = 0{\cdot}8$). (Found: C, 76·99; H, 10·20. $C_{31}H_{50}O_4$ requires: C, 76·50; H, 10·36%).

3,6-Diketo-Δ⁷,5α-cholestene IV)(*from 3β,6α-dihydroxy-Δ⁷,5α-cholestene.* 3β,6α-dihydroxy-Δ⁷,5α-cholestene (900 mg) was dissolved in acetone (100 ml) and 5 ml of Kiliani solution[9] added with stirring during 5 min at low temp. Methanol was added to destroy the excess reagent; the mixture evaporated *in vacuo* and then extracted with ether and washed with water. The residue after ether evaporation yielded, after several recrystallizations from ether–methanol, a crystalline product (550 mg); m.p. 212–214°; $[\alpha]_D^{20°} = +29°$. UV spectrum shows a maximum at 246 mη, log ε = 4·1. (Found: C, 81·25; H, 10·45. $C_{27}H_{42}O_2$ requires: C, 81·35; H, 10·62%).

3,6-Diketo-5α-cholestene from 3,6-diketo-Δ⁷,5α-cholestene. 3,6-Diketo-Δ⁷,5α-cholestene (350 mg) in tetrahydrofuran (15 ml) was added to lithium (1 g) in liquid ammonia (100 ml). The mixture was left 4 hr, methanol was added slowly and after concentration *in vacuo* the mixture was extracted with ether and washed with water. The ethereal solution was then acidificated with dil. H_2SO_4, washed with water to neutrality and evaporated. The residue (300 mg) dissolved in acetone (40 ml) was oxidized with 5 ml Kiliani solution in the usual manner. After extraction with ether and several recrystallizations of the residue from dil. methanol a crystalline product (130 mg) was obtained, m.p. 169–171°, $[\alpha]_D^{20°} = +5°$, identical with an authentic sample of 3,6-diketo-5α-cholestane. (Found: C, 80·69; H, 10·73. $C_{27}H_{44}O_2$ requires: C, 80·94; H, 11·07%).

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[9] R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 461 (1953).