A Novel Skeletal Rearrangement During Reduction of 6β-Bromo-4β,5-epoxy-5β-cholestan-3β-ol with Lithium Aluminium Hydride

By D. J. COLLINS, J. J. HOBBS, and R. J. RAWSON

(Department of Veterinary Physiology, University of Sydney, N.S.W., Australia)

TREATMENT of 6β-bromo-4β,5-epoxy-5β-cholestan-3β-ol (I)[1] with lithium aluminium hydride in tetrahydrofuran for 15 hr. under reflux gave 92% of a new diol, m.p. 160°, $[\alpha]_D$ −52°, which we have shown to be 4,5-seco-4,6-cyclo-6β-cholestane-3β,5α-diol (II). No steroids with this novel carbon skeleton have previously been reported, although several compounds which have the A-nor-3,5-seco-3,6-cyclo-structure are known.[2—6]

Mild reduction of (I) with lithium aluminium hydride in ether gave the expected bromohydrin (III), m.p. 150—153°, $[\alpha]_D$ +21°, which was cleanly converted into (II) under conditions used for the direct reduction of (I) → (II).

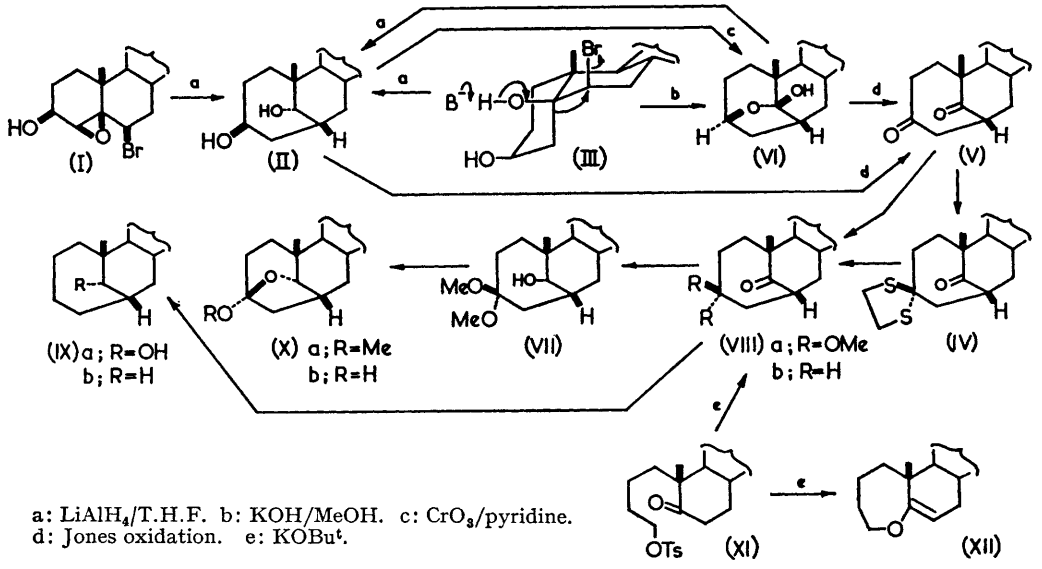
Jones oxidation of (II) yielded the diketone (V), m.p. 72—73°, $[\alpha]_D$ +15°, which upon treatment with alkali showed no change in its u.v. spectrum (λ_{max} 295 mμ, ε 43), or its optical rotation. Integration of a broad, incompletely resolved band centred at τ 7·4 in the n.m.r. spectrum indicated the presence of five protons on carbon atoms adjacent to carbonyl groups.

Mild oxidation of (II) with chromium trioxide in pyridine gave the hemiketal (VI), m.p. 180—182°, $[\alpha]_D$ +30°, (H-3 resonance at τ 5·6, W_H 14 c./sec.), identical with the product from treatment of the bromohydrin (III) with base. Jones oxidation of (VI) gave the diketone (V). Selective 3,3-ethylenedithioketalisation of (V) to (IV), and desulphurisation with W_2 Raney nickel afforded the 5-monoketone (VIIIb), $[\alpha]_D$ −69°, which upon Wolff–Kishner reduction yielded the new hydrocarbon (IXb) as an oil, $[\alpha]_D$ −47°.

Treatment of (V) with methanol and toluene-*p*-sulphonic acid produced the 3-ketal (VIIIa), m.p. 107—107·5°, $[\alpha]_D$ −52°, reduced with sodium borohydride to the noncrystalline 5α-alcohol (VII). Mild acid treatment of (VII) gave the cyclic ketal (Xa) m.p. 68·5°, $[\alpha]_D$ +52°, whose n.m.r. spectrum showed the presence of one methoxyl group (τ 6·61). Formation of (Xa) defines the stereochemistry at C-5 in (VII). More vigorous acid hydrolysis of the hydroxyketal (VII) afforded the cyclic hemiketal (Xb), m.p. 190—192°, $[\alpha]_D$ +49°, isomeric with

(VI). The n.m.r. spectra of (Xa) and (Xb) showed the 5β-protons as doublets at τ 6·12 (*J* 6·9 c./sec.), and τ 6·09 (*J* 7·3 c./sec.), respectively.

stereochemistry at C-5 in (II) is specified by the ready formation of a cyclic sulphite with thionyl chloride in pyridine.



a: $LiAlH_4$/T.H.F. b: KOH/MeOH. c: CrO_3/pyridine.
d: Jones oxidation. e: $KOBu^t$.

Stability of the diketone (V) and the monoketone (VIIIb) to alkali is in accord with the assigned structures in which the ring junction at C-6 is not epimerisable. Dreiding molecular models show that bond formation between C-4 and C-6 in a 4,5-seco-steroid can only occur to give the 6,10-*cis*-bicyclo[4,3,1]-derivative, and that ring-B is then constrained in the boat conformation. Thus, the 6-hydrogen must have the β-quasi-axial configuration.

Mechanistic considerations originally led to the structure of (II). Thus, the stereochemistry and environment of the initially formed *cis*-bromohydrin (III) are such that attack of the basic reagent on the 5β-hydroxyl group may be expected to result in an *anti*-periplanar migration–elimination reaction [(III), arrows; *cf.* the pinacolic-type rearrangements observed by Mazur and Nussim[7] during reaction of some steroid glycol monotosylates with potassium t-butoxide]. The intermediate ketol [which can only be isolated as the hemiketal (VI)] thus produced is then further reduced to (II). The

All of the above compounds, together with a number of other derivatives of (II), gave satisfactory microanalyses, and their i.r., n.m.r., and mass spectra are consistent with the assigned structures.

Further evidence for the novel bicyclo[4,3,1]-decane structure of rings-A and -B was obtained by an independent synthesis of the ketone (VIIIb). Reaction of the keto-tosylate (XI) (prepared by standard methods from cholest-4-en-3-one) with potassium t-butoxide gave mainly the cyclic enol ether (XII), m.p. 84—86°, $[\alpha]_D$ −27°, accompanied by the ketone (VIIIb). Reduction of the latter gave the crystalline 5α-alcohol (IXa), identical with material obtained by sodium borohydride reduction of the 5-ketone (VIIIb) obtained from (II).

We gratefully acknowledge the support of this work by the Ford Foundation through a grant to Professor C. W. Emmens.

(*Received, December 29th*, 1966; *Com.* 1034.)

[1] D. J. Collins and J. J. Hobbs, *Austral. J. Chem.*, 1965, **18**, 1049.
[2] W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Amer. Chem. Soc.*, 1960, **82**, 614.
[3] S. A. Julia, A. Eschenmoser, H. Heusser, and N. Tarköy, *Helv. Chim. Acta*, 1953, **36**, 1885.
[4] G. I. Fujimoto and K. D. Zwahlen, *J. Org. Chem.*, 1960, **25**, 445.
[5] A. Yogev and Y. Mazur, *J. Amer. Chem. Soc.*, 1965, **87**, 3520.
[6] G. I. Fujimoto and J. Pavlos, *Tetrahedron Letters*, 1965, 4477.
[7] Y. Mazur and M. Nussim, *J. Amer. Chem. Soc.*, 1961, **83**, 3911.