

5 β ,7 β -Cyclosteroids

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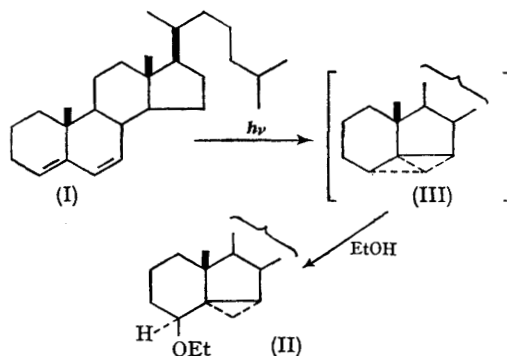
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ALTHOUGH derivatives of 3 α ,5 α -cyclosteroids¹ and 3 β ,5 β -cyclosteroids² are well known, little information is available concerning 5 α ,7 α -cyclosteroids³ and no examples of 5 β ,7 β -cyclosteroids have been recorded. We now report the first examples of 5 β ,7 β -cyclosteroids, prepared by both photochemical and nonphotochemical routes. Furthermore, we report synthetic routes to the first 3-substituted derivative of any 5,7-cyclosteroid, of interest because of their close relationship to naturally occurring variants.⁴

Irradiation of cholesta-4,6-diene (I)⁵ in absolute ethanol with a Vycor-filtered 450w Hanovia mercury arc for 18 hr. gave, after chromatography on silica gel, a saturated ether (II) (40%), † m.p. 93—94°, $[\alpha]_D^{25} -79.2^\circ$. The n.m.r. spectrum of (II) showed a typical ABX four-peak multiplet centred at $\tau 10.40$ with $J_{AB} 5.0$ and $J_{AX} 7.5$ c./sec. This peak was assigned to the 6 α -proton. The presence of the cyclopropyl geminal hydrogens was also demonstrated by the near-infrared maximum⁶ at 1.645 μ ($\epsilon 0.311$).

Chromatography of the crude irradiation product on alumina gave the olefinic product (IV), m.p. 112—113°, $[\alpha]_D^{25} -11.5^\circ$. The infrared spectrum showed an olefinic stretch at 6.12 μ and a cyclopropyl geminal hydrogen absorption at 1.646 μ

($\epsilon 0.312$). The ultraviolet absorption at λ_{max} 211 m μ ($\epsilon 11,300$) (in 95% EtOH) indicated that the olefinic function was conjugated with the cyclopropane. Chromatography of pure (II) on alumina showed that it was readily converted into (IV). Catalytic hydrogenation of (IV) over palladium on carbon resulted in the uptake of one mole of

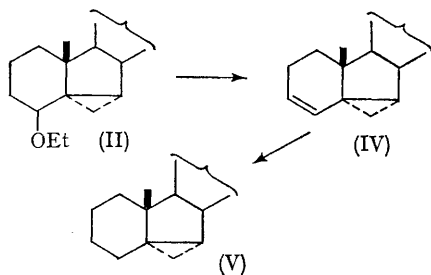


hydrogen and the formation of (V), m.p. 80—81°, $[\alpha]_D^{25} -18.2^\circ$. The n.m.r. spectrum of (V) showed an ABX four-peak multiplet (1 proton) at $\tau 10.30$ with $J_{AB} 5.0$ and $J_{AX} 8.0$ c./sec. At this

† Satisfactory elemental analyses have been obtained on all new compounds.

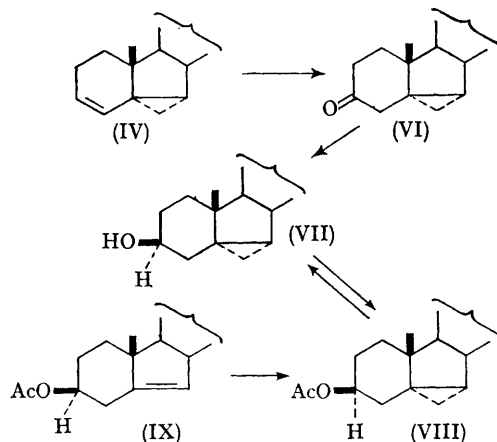
point the presence of the vinyl cyclopropane moiety was established, but neither the position nor the stereochemistry of these groups was known with assurance. By analogy with the findings of Dauben and Just⁴ it would be expected that the product should be formed from the photochemically generated intermediate (III). Addition of ethanol to (III) would be expected to occur across the bond between C-4 and C-6 according to the "twist" bent bond hypothesis⁷ to yield (II) with the stereochemistry shown.

Since the $5\beta,7\beta$ -cyclocholestanes represent a new class of modified steroids, a rigorous proof of structure was deemed desirable. The best approach to such a verification of structure was thought to be the independent synthesis of a derivative of our photo-product. We hydroborated (IV) and oxidized the hydroboration product to (VI), m.p. 121.0—122.5°, $[\alpha]_D^{25} + 44.9^\circ$, in 50% overall yield. This ketone had a carbonyl absorption at 5.80μ and a cyclopropyl geminal hydrogen stretching overtone peak at 1.644μ (ϵ 0.349). The position of the cyclopropyl C-H stretching showed that the carbonyl was not conjugated with the cyclopropyl group.⁶ The n.m.r. spectrum of (VI) showed the characteristic ABX four-peak multiplet centred at τ 10.14 with J_{AB} 5.5 and J_{AX} 8 c./sec. (1 proton). Reduction of (VI) with lithium aluminium hydride gave (VII) (87%), m.p. 148.5—149.3°, $[\alpha]_D^{25} - 25.0^\circ$.



Acetylation of (VII) with acetic anhydride in pyridine gave (VIII), m.p. 112.7—113.5°, $[\alpha]_D^{25} - 23.2^\circ$.

A direct synthesis of (VIII) involved addition of methylene to the known⁸ β -norcholesterol acetate (IX). The best analogy for additions to the double bond of (IX) is conversion into the epoxide.



Dauben and his co-workers have shown that epoxidation occurs exclusively from the α -side of the steroidal skeleton.⁹ Thus, methylene transfer should also occur from the α -side. Reaction of (IX) with Simmons-Smith reagent prepared from granular zinc-copper couple according to the procedure of LeGoff¹⁰ gave (VIII), $[\alpha]_D^{25} - 22.9^\circ$, mixture melting point with authentic (VIII) 112.0—113.2°. The β -norcholesterol acetate was extremely resistant to addition. Only 2% conversion of (IX) into (VIII) was observed after 3 days. Hydrolysis of the acetate obtained from the methylene transfer reaction gave an alcohol which was identical with (VII) in all respects.

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¹ For an interesting Review see N. L. Wendler in "Molecular Rearrangements", Vol. II, ed. P. de Mayo, Interscience, New York, 1964, pp. 1075—1080.

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⁶ P. G. Gassman and F. V. Zalar, *J. Org. Chem.*, 1966, **31**, 166.

⁷ For a discussion of the "twist" bent bond hypothesis see P. G. Gassman, preceding Communication.

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¹⁰ E. LeGoff, *J. Org. Chem.*, 1964, **29**, 2048.