The Backbone Rearrangement of Cholesterol: a Chemical Proof

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Summary Anhydrous HF transforms cholesterol into the two epimeric 17β-hydroxy-3-methyl-3-(4-fluoro-4-methyl)pent-1-yl-D-homo-5α-androstanes, through a backbone rearrangement followed by ring-expansion and hydride transfer.

BESIDES the expected addition products,[1,2] reaction of anhydrous HF with cholesterol (**1**) gives other compounds.[3] We report the structures of two of these, (A), m.p. 144°, and (E), m.p. 157—158°, isolated in 2% yields.

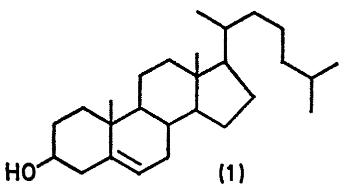
(A) and (E) are isomers, $C_{27}H_{47}OF$. ^1H and ^{19}F n.m.r. data show that they both contain the fragment $\cdot CH_2\cdot CFMe_2$ (methyl protons: doublet' at τ 8·65; *J* 21 Hz; fluorine: nonuplet; *J* 21 Hz). Spectroscopic arguments, which are omitted for the sake of brevity, lead to tentative structures (**2**) for (A) and (E). Both structures were confirmed by the synthesis of the degradation products (**3**).

Base-catalysed elimination of HF gave a mixture of olefins (**4**) and (**5**). $NaIO_4$–$KMnO_4$ oxidation[4] of the mixture afforded, *inter alia*, acid (**6**), which was submitted to two successive Barbier–Wieland degradations, leading to acid (**7**) [(**7A**) from (A), (**7E**) from (E)]. Physical arguments indicated that (**7A**) had an axial carboxyl group, (**7E**) an equatorial carboxyl group. The corresponding esters (**3A**) (m.p. 120—122°) and (**3E**) (m.p. 121·5°) were synthesized in following way.

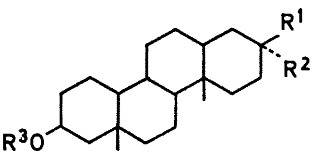
The mixture of the known[5] alcohols (**8a**) and (**8b**) was converted, by treatment with H_2SO_4–HCO_2H,[6] into acid (**8c**). The corresponding methyl ester (**8d**) was then submitted to a D-ring expansion by the usual treatment.† Ketone (**9A**) was obtained as a minor product. $NaBH_4$ reduction of (**9A**), followed by acetylation, gave a compound identical in every respect with (**3A**).

17β-Acetoxy-5α-androstan-3-one[7] was transformed into nitrile (**10a**) by standard procedures. The sequence (**10a**) → (**10d**) is straightforward. Methylenation (CH_2I_2–Zn)[8] of alcohol (**10d**) gave alcohol (**11a**), whose acetate (**11b**) was hydrogenolysed[9] to acetate (**12a**). The corresponding diol (**12b**) was oxidized to acid (**8e**), whose ester (**8f**) was submitted as above to ring-D expansion. $NaBH_4$ reduction of the minor product (**9E**), followed by acetylation, gave a compound identical in every respect with (**3E**).

These results fully confirm formulae (**2A**) and (**2E**), and imply that this acid-catalysed rearrangement of cholesterol (**1**) is one of the most extensive known to date and goes much further than the usual backbone rearrangements of steroids.[10–12]

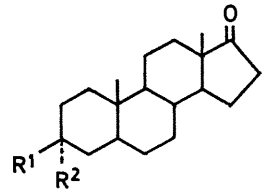


(1)

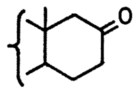


(2A) R^1 = Me; R^2 = $[CH_2]_3\cdot CFMe_2$; R^3 = H
(2E) R^1 = $[CH_2]_3\cdot CFMe_2$; R^2 = Me; R^3 = H
(3A) R^1 = Me; R^2 = CO_2Me; R^3 = Ac
(3E) R^1 = CO_2Me; R^2 = Me; R^3 = Ac

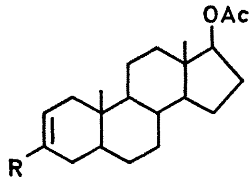
(4) $>CMe\cdot[CH_2]_3\cdot CMe{:}CH_2$
(5) $>CMe\cdot[CH_2]_2\cdot CH{:}CMe_2$
(6) $>CMe\cdot[CH_2]_2\cdot CO_2H$
(7) $>CMe\cdot CO_2H$



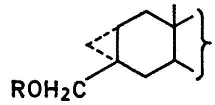
(8) a; R^1 = OH, R^2 = Me
b; R^1 = Me, R^2 = OH
c; R^1 = Me, R^2 = CO_2H
d; R^1 = Me, R^2 = CO_2Me
e; R^1 = CO_2H, R^2 = Me
f; R^1 = CO_2Me, R^2 = Me



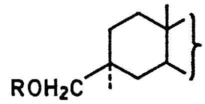
(9)



(10) a; R = CN
b; R = CO_2H
c; R = CO_2Me
d; R = CH_2OH



(11) a; R = H
b; R = Ac



(12) a; R = Ac
b; R = H

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† Cyanohydrin formation, reduction to amino-alcohol, and nitrous acid deamination.

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