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SIMPLE SYNTHESIS OF 3β,24-DIHYDROXYCHOL-5-EN-7-ONE BY OXIDATIVE CLEAVAGE OF THE SIDE CHAIN OF CHOLESTEROL

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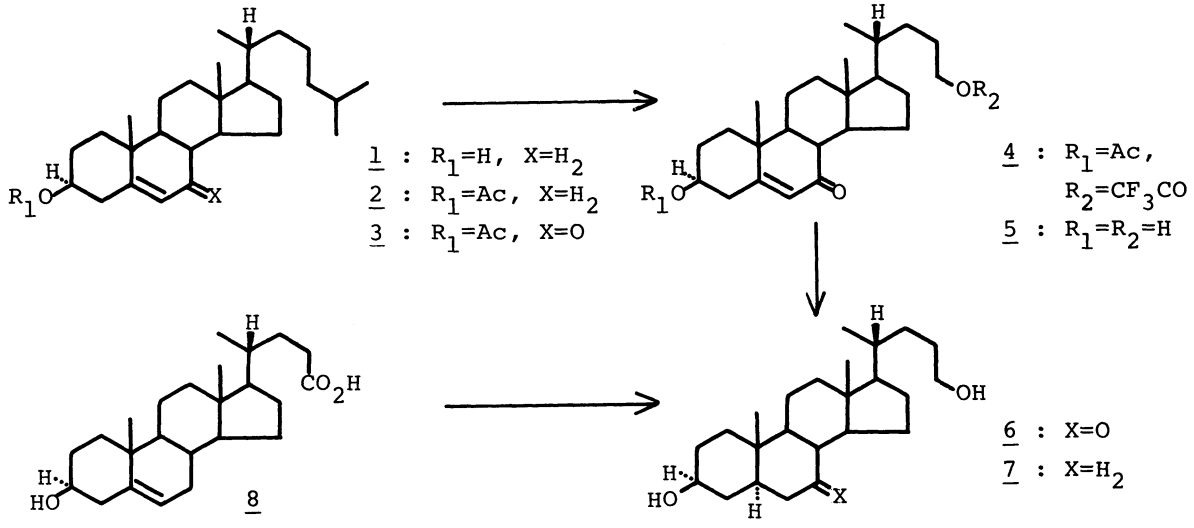
A Potential steroidal synthon, 3β,24-hydroxychol-5-en-7-one, has been prepared in facile manner from cholesterol by oxidative cleavage of the side chain with a mixture of 30% aqueous hydrogen peroxide, trifluoroacetic anhydride, and sulfuric acid.

Due to the lack of an efficient method for selective functionalization of its nonactivated 17-side chain, utilization of cholesterol (1) as starting material in the synthesis of other important steroids with 17-side chain has not been satisfactory. The methods reported so far involved oxidative functionalization of the side chain in 23% yield at best by chromic acid,[1] by photolysis,[2] and by trifluoroperacetic acid,[3,4] using substrates with appropriately protected steroidal portion. In the present work, a method is described for the synthesis of 3β,24-dihydroxychol-5-en-7-one (5) from cholesterol (1) via 7-oxocholest-5-en-3β-yl acetate (3) by oxidation with a mixture of aqueous hydrogen peroxide, trifluoroacetic anhydride, and sulfuric acid, followed by methanolysis.

To a stirred solution of trifluoroacetic anhydride (17.0 ml) and 98% sulfuric acid (7.0 ml) was added 30% aqueous hydrogen peroxide (1.7 ml) dropwise below 0 °C. To this mixture was then added 7-oxocholest-5-en-3β-ol acetate (3), 1.0 g



(2.26 mmol), prepared from cholesterol (1) by two step sequence via the acetate (2),[5,6] in one portion at 0 °C and the stirring was continued for 4.5 h at the same temperature. The suspension first formed gradually dissolved into clear orange solution. The mixture was then treated with triethylamine (36 ml) at -15 °C and the mixture was concentrated under reduced pressure. The residue was taken up with benzene and usual work-up gave crude 7-oxochol-5-en-3β,24-diol 3-acetate 24-trifluoroacetate (4)[7] which was directly treated with methanol (40 ml) containing potassium carbonate (1.56 g) to give 3β,24-dihydroxychol-5-en-7-one (5),[8] 160 mg (19% from (3)), mp 208.5 - 210 °C, $[\alpha]_D$ -106.9° (c 0.20, EtOH), after purification by silica gel column chromatography.

In order to confirm the structure of the product, 5 was hydrogenated on 10% palladized carbon[9] to give the saturated ketol (6), mp 205 - 207 °C, which was further reduced with zinc in diethyl ether saturated with hydrogen chloride[10] to give 5α-cholane-3β,24-diol (7), mp 198 - 200 °C, $[\alpha]_D$ +14.0° (c 0.31, EtOH). The compound obtained was identical in all respects with an authentic material, mp 200 - 202 °C (mixed mp 198 -200 °C), $[\alpha]_D$ +13.3° (c 0.54, EtOH), prepared from 3β-hydroxy-5-cholen-24-oic acid (8) by sequential reduction using 10% palladized carbon followed by lithium aluminum hydride.

The compound (5) thus obtained may be especially useful for the synthesis of a pharmaceutically important chenodeoxycholic acid being clinically used in the treatment of gallstone[11] as well as pavoninins, recently discovered shark-repelling steroids.[12] Although the yield in the present method needs more improvement in the key stage, the reaction was simple and by-products could be easily removed by a single column chromatography. Furthermore, the present method is more practical both in generating the peracid by using trifluoroacetic anhydride and dilute aqueous hydrogen peroxide and in quenching the excess peracid and the acidic additive by using triethylamine which greatly facilitate the work-up.

References

1) S. P. J. Mass and J. G. DeHeus, Rec. Trav. Chim., 77, 531 (1958).
2) A. Rotman and Y. Mazur, J. Chem. Soc., Chem. Commun., 1974, 15.
3) N. C. Deno and M. D. Meyer, J. Org. Chem., 44, 3383 (1979).
4) R. P. Manley, K. W. Curry, N. C. Deno, and M. D. Meyer, J. Org. Chem., 45, 4385 (1980).
5) W. G. Salmond, M. A. Barta, and J. L. Havens, J. Org. Chem., 43, 2057 (1978).
6) W. Mappus and C. -Y. Cuilleron, J. Chem. Res. (S), 1979, 42.
7) The pure 4 (mp 105 - 107 °C) could be isolated in 29% yield after flash chromatography (SiO_2) and subsequent methanolysis yielded 5 quantitatively.
8) All new compounds obtained gave satisfactory analytical (combustion and accurate mass) and spectral (IR, ^{1}H-NMR, mass) data.
9) Cf. P. Wieland, H. Ueberwasser, G. Anner, and K. Miescher, Helv. Chim. Acta, 36, 1231 (1953).
10) Cf. M. Toda and Y. Hirata, J. Chem. Soc., Chem. Commun., 1969, 919.
11) F. Sugata, Tokyo Tanabe Quarterly, 1980, 168.
12) K. Tachibana, M. Sakaitani, and K. Nakanishi, Science, 226, 703 (1984).

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