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SYNTHESIS OF 27-NOR-25-OXOCHOLEST-5-EN-3β-YL ACETATE AND 27-NOR-25-OXOCHOLESTANOL FROM PREGNENOLONE

R. TSCHESCHE,* B. GOOSSENS, G. PIESTERT and A. TÖPFER
Institut für Org. Chemie und Biochemie der Universität Bonn, D-5300 Bonn, Max-Planck-Straße 1

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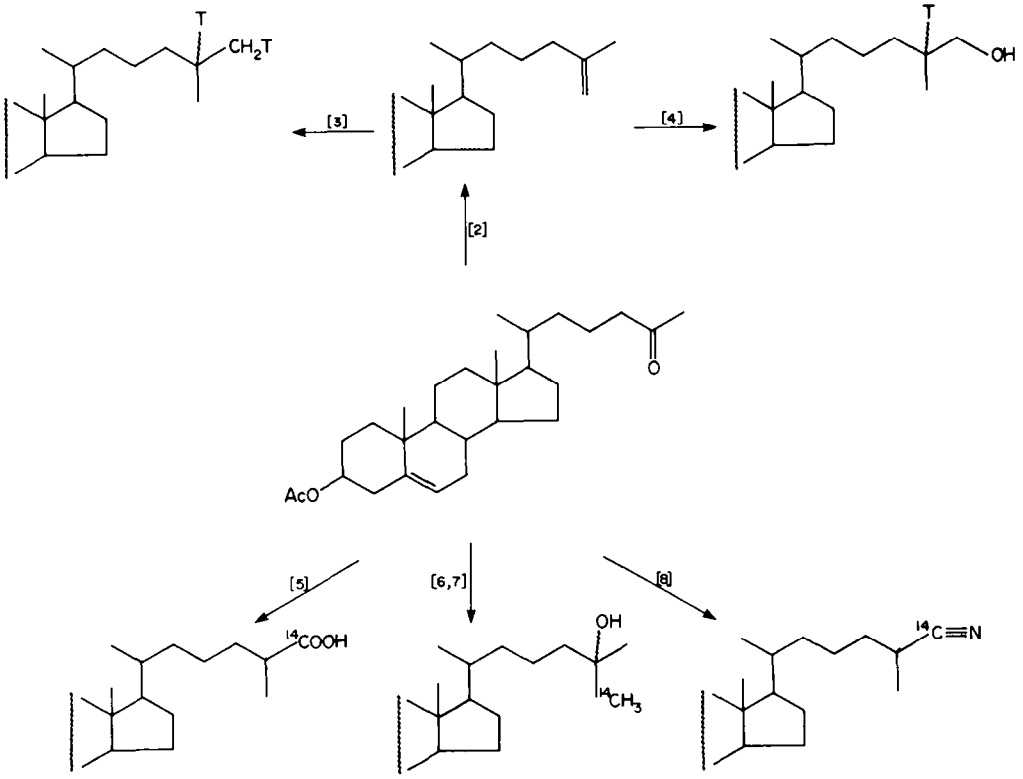
Abstract—Grignard-reaction of pregnenolone-3β-acetate with pentan-2-one ethylene ketal-5-magnesium bromide and subsequent dehydration yielded 27-nor-25-oxocholesta-5,20 (22)-dien-3β-yl acetate which was hydrogenated to 27-nor-25-oxocholest-5-en-3β-yl acetate and 27-nor-25-oxocholestan-3β-yl acetate.

27-Nor-25-oxocholesterol, which was first obtained by Ruzicka *et al.*[1] as by-product during oxidative degradation of cholesterol dibromide with chromium trioxide in glacial acetic acid, is the key-substance for introducing functional groups into the positions 25 and 26 (or 27) of the cholesterol skeleton, thus realizing a specific labelling of the cholesterol side-chain with tritium and carbon-14.[2-8]

The previously described method of Ruzicka[1] for the preparation of 27-nor-25-oxocholesterol requires an extensive separation process due to the many reaction products and gives rather poor yields. For our research work on the biogenesis of plant steroids we needed 25-(*R,S*)-25,26-$^3H_2$-cholesterol and were interested in the synthesis of 25-(*R,S*)-26-aminocholesterol and cholest - 5 - ene - 3β - ol - 26 - aldehyde via 25 - (*R,S*) - 25 - nitrilocholesterol, using 27 - nor - 25 - oxocholest - 5 - en - 3β - yl acetate as starting material.

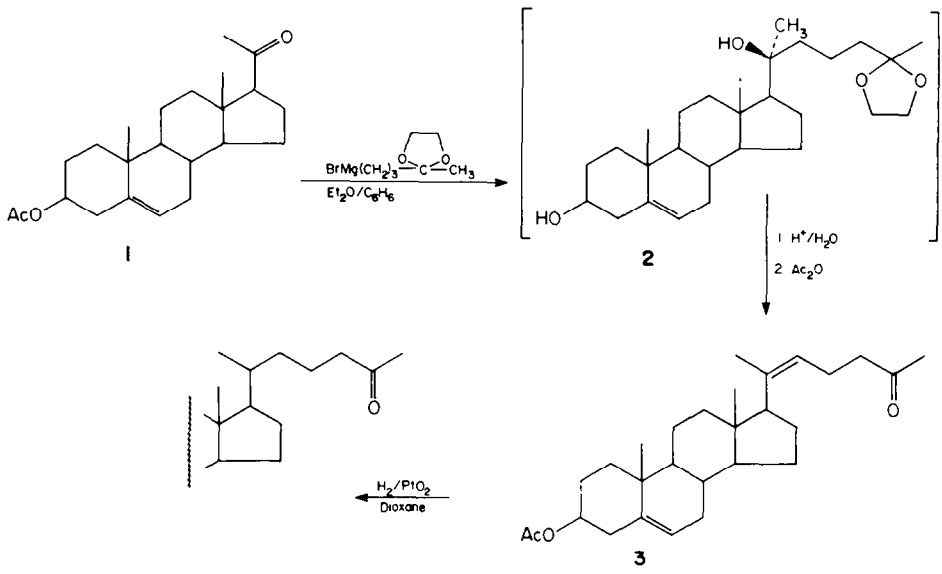
We therefore developed an alternative route for the synthesis of the desired 27 - nor - 25 - oxocholesterol involving the following conventional procedures:

Pregnenolone-3β-acetate (**1**) was converted by Grignard-reaction with pentane-2-one ethylene ketal-5-magnesium bromide into 27-nor-25-oxo ethylene ketal - cholest - 5 - ene - 3β,20α-diol (**2**). In order to avoid uncontrolled self-dehydration the crude product (without chromatographic purification) was acidic catalyzed dehydrated and hydrolyzed to 27 - nor - 25 - oxocholesta-5,20 (22) - dien - 3β - ol, which after usual acetylation and separation on silica gel yielded 27 - nor - 25 - oxocholesta - 5,20(22) - dien - 3β - yl acetate (**3**). According to Chaudhuri *et al.*[9] cholest - 5 - ene - 3β,20α - diol under the



([3]–[8] see references)

Scheme 1.



Scheme 2.

above mentioned dehydration conditions gives only cholesta-5,20(22)-dien-3β-ol, while the other four possible isomers—as opposed to the use of phosphorus oxychloride as dehydration agent[10]—are not formed. Structure proof of (3) was obtained from its NMR spectrum, which showed the presence of the 22 vinylic proton. Selective hydrogenation of the 20–22 double bond by a method analogous to that of Bergmann *et al.*[11] yielded after chromatographic purification and recrystallization 27 - nor - 25 - oxocholest - 5 - en - 3β - yl acetate (4), which showed no m.p. depression on admixture with an authentic specimen generously supplied from Schering corporation, USA.

Hydrogenation of (3) over a Pd–C catalyst caused both double bonds to be saturated and after chromatographic purification 27 - nor - 25 - oxocholestan - 3β - yl acetate (5) was produced, from which after saponification 27 - nor - 25 - oxocholestanol (6) was obtained.

EXPERIMENTAL

M.ps were taken on a LEITZ microscope heating stage. NMR spectra were obtained in $CDCl_3$ soln with TMS as the internal standard on a 60 MHz-VARIAN spectrometer. Mass spectra were determined on MS 9 (A.E.I.). Silica gel 60 PF 254/366 (E. Merck) was used for TLC and silica gel WOELM (0.063–0.1 mm) was taken for column chromatography.

5-Bromopentan-2-one was obtained according to T. Bacchetti *et al.*[12] 2-Acetylbutyrolactone as starting material was purchased from FLUKA AG, Switzerland.

5-Bromopentan-2-one ethylene ketal. 35 g 5-bromopentan-2-one, 16.5 g ethylene glycol and 50 mg *p*-toluene-sulfonic acid in 150 ml benzene were refluxed azeotropically for 48 hr. After cooling the mixture was washed with 1% $NaHCO_3$aq and water, dried over $MgSO_4$ and rectified *in vacuo*, yield: 35 g (85%) b.p.$_{17}$ 96–97°; NMR: ppm 1.25 (s, CH_3); ppm 1.6–2.0 (m, CH_2-3,-4); ppm 3.35 (t, CH_2-Br); ppm 3.86 (s, ethylene ketal).

27-Nor-25-oxocholesta-5,20(22)-dien-3β-yl acetate (3). The Grignard reagent was prepared by adding a quarter of a soln. of 17 g freshly (!) rectified 5 - bromopentan - 2 - one ethylene ketal in 80 ml abs. ether to 1.9 g of Mg turning in an atmosphere of N_2. After initiation of the reaction the remainder was added dropwisely while refluxing and stirring. After refluxing for 2 hr in order to achieve complete reaction 4 g of 1 dissolved in 80 ml dry benzene were added dropwisely. The mixture was stirred for 1 hr at room temp., then the solvent was distilled off until the b.p. reached 73°, and the volume of the soln. was kept constant by the addition of dry benzene. The mixture was then refluxed for 3 hr with stirring, after cooling ether was added and the Grignard complex was decomposed with ice water and HCl. The ether layer was washed with water and $NaHCO_3$aq, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The oily residue containing 2 was dissolved in 100 ml MeOH, boiled with 12 drops of conc. HCl for 15 min and kept at 50° for 2 hr. Then water was added till the mixture showed a weak opacity and kept for another 2 hr at 50° with stirring. After ether extraction, washing with water and $NaHCO_3$aq, drying over Na_2SO_4, the evaporated ether layer was acetylated, worked up in the usual manner and chromatographed on silica gel in the system methylene chloride/acetone 50:1. Crystallization yielded 2.4 g 27 - nor - 25 - oxocholesta - 5,20 (22) - dien - 3β - yl acetate, m.p. 106.5° (needles from MeOH); NMR: ppm 0.83 (s, CH_3-18); ppm 1.1 (s, CH_3-19); ppm 1.66 (d, CH_3-21); ppm 2.0 (s, CH_3COO); ppm 2.1 (s, CH_3-26); ppm 5.25 (H-22); MS: *m/e* (rel. intensity) 426 (10, M^+); 411 (5, M^+-CH_3); 366 (100, M^+-HOAc); 253 (45, M^+-side chain + 2H).

27 - Nor - 25 - oxocholest - 5 en - 3β - yl acetate (4). 1 g of (3) in 50 ml of abs dioxane and 1 ml glacial AcOH was hydrogenated in the presence of 0.1 g PtO_2 at room temp. and under atmospheric pressure for 5 hr. The filtrate was evaporated, chromatographed (methylene chloride/acetone 100:1) and recrystallized from acetone, yielded 780 mg; m.p. 139° (no m.p. depression on admixture with an authentic specimen; identic NMR, IR and MS).

27 - Nor - 25 - oxocholestan - 3β - yl acetate (5). 0.1 g of (3) in 5 ml abs. dioxane and 0.1 ml Ac_2O was hydrogenated in the presence of 30 mg Pd-C catalyst at room temp. and under atmospheric pressure for 36 hr. Work up as above gave 70 mg (5), m.p. 151.5°; NMR: ppm 0.65 (s, CH_3-18); ppm 0.83 (s, CH_3-19); ppm 2.0 (s. CH_3COO); ppm 2.1 (s, CH_3-26); no vinylic proton; MS: *m/e* (rel. intensity) 430 (34, M^+); 370 (100, M^+-HOAc).

27 - Nor - 25 - oxocholestanol (6). 30 mg of (5) were saponified with 5% methanolic KOH and after usual work up purified on silica gel (methylene chloride/acetone 33:1). Recrystallization from MeOH gave 18 mg (6), m.p. 135°; MS: *m/e* (rel. intensity) 388 (100, M^+) 370 (35, M^+-H_2O).

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(This paper is dedicated to Prof. Dr. K. H. SLOTTA in remembrance of his 80th birthday)