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Synthesis of Steroidal Cyclopropanes

By **R. Ikan** * and **A. Markus**, Department of Organic Chemistry, Natural Products Laboratory, Hebrew University of Jerusalem, Israel
Z. Goldschmidt, Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel

22,23-Methylenestigmast-5-en-3β-ol (IX), 24,25-methylenecholest-5-en-3β-ol (VII) and 24,25-methylenelanost-8-en-3β-ol (XI) were synthesized by treating stigmasterol, desmosterol, and lanosterol with dichlorocarbene and reducing the adducts (VIII) and (VI) formed. Desmosteryl acetate (V) was synthesized by a novel method from 3β-acetoxychol-5-en-24-oic acid (I), the essential steps being preparation of the diazo-ketone (II), its photochemical Wolff rearrangement to the methyl ester (III), a Grignard reaction of (III) with methylmagnesium iodide and dehydration of the product.

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Most of the natural steroidal cyclopropanes reported to date (*e.g.* cycloartenol, 24-methylenecycloartenol, cycloeucalenol, and pollinasterol have the cyclopropane ring attached to the steroid nucleus.[1] In connection with our work on the utilization of natural sterols and their derivatives by insects,[2] we have synthesized some sterols bearing a cyclopropane system in the side chain. Djerassi and his co-workers [3,4] report that some of the naturally occurring C_{30} marine sterols (gorgosterol and acansterol) possess this rare structural feature. Furthermore, Schmitz and Pattabhiraman [5] have isolated a C_{29} marine sterol possessing a cyclopropyl side chain (23-demethylgorgosterol). We now describe the synthesis of 22,23-methylenestigmast-5-en-3β-ol (IX), 24,25-methylenecholest-5-en-3β-ol (VII), and 24,25-methylenelanost-8-en-3β-ol (XI). Dichlorocarbene adducts of stigmasterol, desmosterol, and lanosterol were prepared in high yield by treatment of the sterols with chloroform in the presence of concentrated aqueous sodium hydroxide and catalytic amounts of triethylbenzylammonium chloride.[6] The adducts were reduced with lithium–tetrahydrofuran–t-butyl alcohol.[7] This reaction sequence could also be applied in the triterpenoid series. Thus lanosterol was converted into its 24,25-methylene homologue in 50% overall yield.[8]

Since substantial quantities of desmosterol were required for the preparation of 24,25-methylenecholest-5-en-3β-ol, we devised a new method for its preparation in high overall yield, based on homologation of the readily available 3β-acetoxychol-5-en-24-oic acid by photochemical Wolff rearrangement [9] of the diazo-ketone (II). Subsequent Grignard reaction and smooth dehydration of the resulting alcohol (IV) with acetic acid–acetic anhydride [10] provided pure desmosterol (Scheme).

EXPERIMENTAL

M.p.s were determined on a Thomas-Hoover apparatus. Optical rotations were measured for solutions in chloroform, with a Perkin-Elmer polarimeter model 141. N.m.r. spectra were recorded for solutions in [^{2}H]chloroform with Varian T-60 and HA-100 spectrometers. I.r. spectra were recorded on a Perkin-Elmer 137 spectrometer for Nujol mulls, and u.v. spectra on a Unicam SP 800 spectrophotometer for solutions in ethanol. Mass spectra were recorded on a Hitachi–Perkin-Elmer RMU-6D spectrometer.

Methyl 3β-Acetoxychol-5-ene-24-carboxylate (III).—To a solution of 3β-acetoxychol-5-en-24-oic acid (I) (10 g) in dry benzene (100 ml), oxalyl chloride (3·5 g) was added dropwise. The mixture was refluxed for 3 h, benzene was removed under reduced pressure, and the residue was triturated with dry light petroleum, leaving 3β-acetoxychol-5-en-24-oyl chloride (9 g). This was dissolved in benzene (100 ml) and added dropwise at 5 °C to a dry ethereal solution of diazomethane [from nitrosomethylurea (40 g)]. The mixture was left overnight at room temperature and then evaporated, leaving the diazo-ketone (II) as yellowish crystals (9 g), $\lambda_{max.}$ 253 (ε 19,500) and 310 nm (8500), $\nu_{max.}$ 2100 ($CO{\cdot}CHN_2$) and 1725 cm^{-1} (CO_2Me). The diazo-ketone (9 g) was dissolved in tetrahydrofuran (160 ml) and methanol (40 ml) and irradiated through Pyrex vessel with a Hanovia Q-81 high-pressure burner immersion lamp until no more nitrogen was evolved. The solution was concentrated *in vacuo*, and the residue crystallized from acetone to give the *ester* (III), m.p. 88—89° (9 g, 84%), $[\alpha]_D$ −49·0° (*c* 1·0), $\nu_{max.}$ 1725 cm^{-1} (Found: C, 75·4; H, 9·6%; M^+, 384. $C_{28}H_{44}O_4$ requires C, 75·6; H, 9·9%; *M*, 384).

Cholest-5-ene-3β,25-diol (IV).—To the Grignard reagent prepared from magnesium (3 g) and methyl iodide (19·2 g) in ether (50 ml), the ester (III) (8 g) in dry benzene (50 ml) was added dropwise, and the mixture was refluxed for 1 h. Ether was distilled off and the solution was then refluxed for a further 4 h and set aside overnight at room temperature. Hydrochloric acid (5%) was added and the product was extracted with benzene. Removal of the benzene and recrystallization of the residue from acetone yielded the diol (IV) (5·4 g, 73%), m.p. 176—177° (lit.,[11] 179—180°), $\nu_{max.}$ 3350 cm^{-1} (OH), $[\alpha]_D$ −41·6° (*c* 1·0) (lit.,[11] −40·4°) (Found: C, 80·7; H, 11·3%; M^+, 402. Calc. for $C_{27}H_{46}O_2$: C, 80·6; H, 11·4%; *M*, 402).

Cholesta-5,24-dien-3β-yl Acetate (V).—The diol (IV) (3 g), acetic acid (270 ml) and acetic anhydride (27 ml) were refluxed for 20 h.[10] The cooled solution was concentrated

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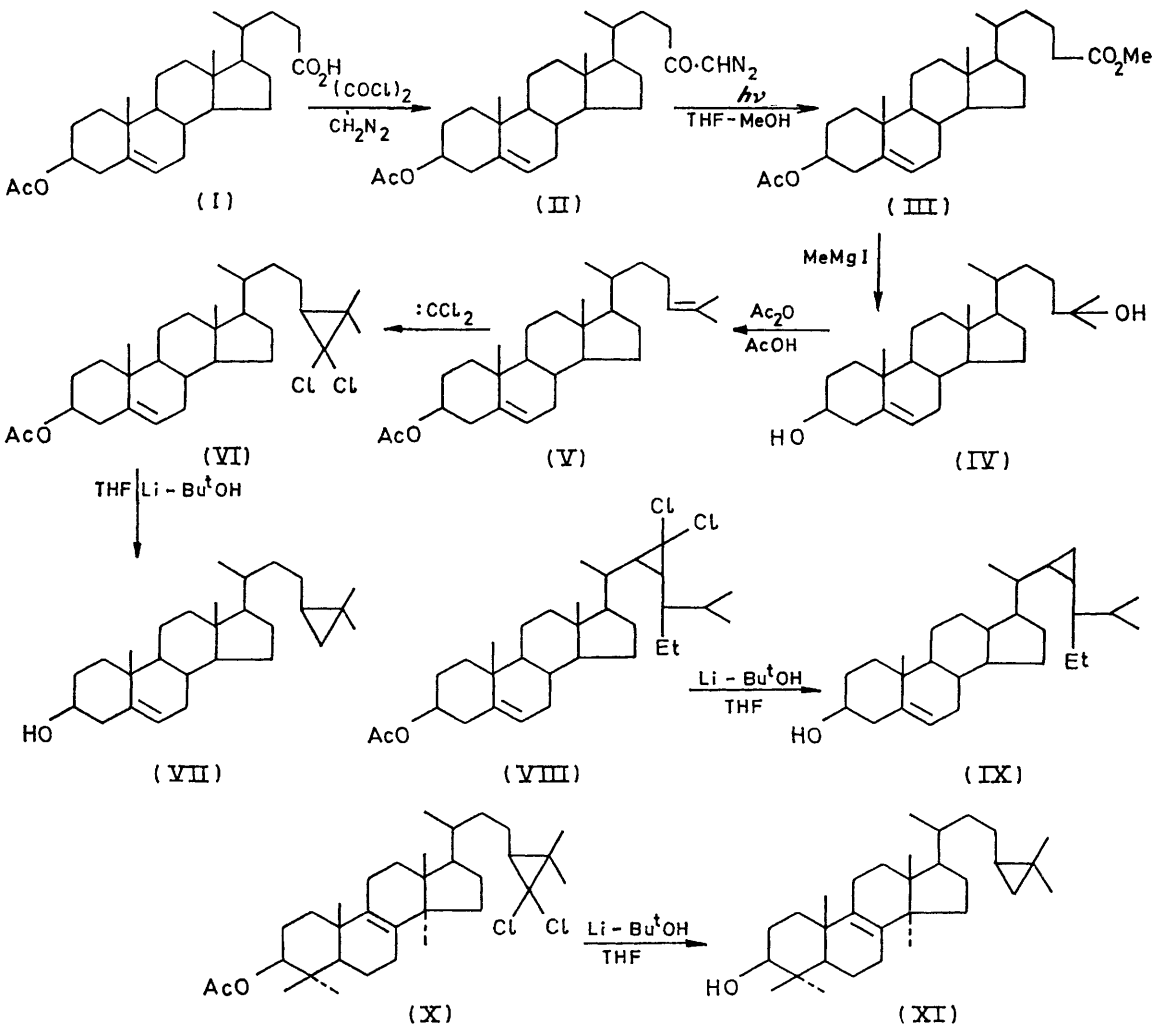
in vacuo and the residue treated with water (500 ml). The product (2·5 g, 78·4%) had m.p. 89—90° (from acetone) (lit.,[11] 92—93°), $[\alpha]_D$ −42·0° lit.,[11] −40·6°), $\nu_{max.}$ 1720 cm^{-1}, δ 5·4 (H-6) and 5·2 p.p.m. (H-24) (Found: C, 81·4; H, 10·5%; M^+, 366. Calc. for $C_{29}H_{46}O_2$: C, 81·7; H, 10·7%; *M*, 366).

24,25-*Dichloromethylenecholest-5-en-3β-yl Acetate* (VI).—To a solution of the acetate (V) (2 g) in chloroform (30 ml), triethylbenzylammonium chloride (0·2 g) (from equimolar quantities of triethylamine and benzyl chloride in acetone) was added. The mixture was stirred until the salt dissolved; aqueous sodium hydroxide (50%; 20 ml) was then added and stirring was continued for a further 3 days. Water was added and the product was extracted with chloroform; the extract was dried, filtered, boiled with charcoal–Celite (1 : 1), filtered again, and concentrated *in vacuo*. The residue was subjected to column chromatography on Florisil. Elution with hexane–benzene gave the *adduct* (VI), (1·5 g, 50%), m.p. 70—72°, $[\alpha]_D$ −38·3°, $\nu_{max.}$ 1740 cm^{-1} (CO_2Me) (Found: C, 70·6; H, 8·8; Cl, 14·4. $C_{30}H_{45}Cl_2O_2$ requires C, 70·9; H, 8·9; Cl, 14·0%).

24,25-*Methylenecholest-5-en-3β-ol* (VII).—To a stirred solution of the adduct (VI) (1 g) in dry tetrahydrofuran (20 ml), lithium flakes (1 g) and t-butyl alcohol (distilled over sodium) (18 ml) were added in portions during 6 h. The mixture was poured over ice, and the precipitate was filtered off. The product gave a negative halogen test. Recrystallization from methanol gave the *cyclopropane* (VII) (70%), m.p. 95°, $[\alpha]_D$ −28°, $\nu_{max.}$ 3350 cm^{-1} (OH) (no CO absorption), *m/e* 398 (M^+), 384 (*M* − cyclopropane CH_2), 383 [*M* − C(27)H_3], 380 (*M* − H_2O), 369 (*M* − CH_3 − CH_2), 365 (*M* − CH_3 − H_2O), 351 (*M* − CH_3 − CH_2 − H_2O), 338 (*M* − Me_2C), 314 (23,24-cleavage + loss of H_2O), 300 (22,23-cleavage + loss of H_2O), and 258 (*M* − side chain − H_2O), δ − 0·1 to 0·4 p.p.m. (cyclopropane protons [3,8]).



SCHEME

22,23-*Dichloromethylenestigmast-5-en-3β-yl Acetate* (VIII).—This *adduct*, prepared analogously to the adduct (VI), was obtained in 75% yield; m.p. 95—97°, $[\alpha]_D$ −57·9°, $\nu_{max.}$ 1740 cm^{-1} (AcO) (Found: C, 71·6; H, 9·3; Cl, 12·5%; M^+, 477. $C_{32}H_{52}Cl_2O_2$ requires C, 71·5; H, 9·5; Cl, 13·2%; *M*, 477).

22,23-*Methylenestigmast-5-en-3β-ol* (IX).—This was prepared like compound (VII); m.p. 132—134°, $[\alpha]_D$ −41·3°,

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$\nu_{max.}$ 3350 cm^{-1} (OH) (no CO absorption), *m/e* 426 (M^+), 412 ($M - CH_2$), 408 ($M - H_2O$), 396 (M − 2 terminal Me), 383 ($M - Me_2CH$), 369 ($M - Me_2CH - CH_2$), 328 (22,23-cleavage and loss of C_7 chain), 314 (loss of C_8 chain), and 255 (M − side chain − H_2O), δ 0·3—0·75 p.p.m. (cyclopropane protons [3]).

24,25-*Dichloromethylenelanost*-8-*en*-3β-*yl Acetate* (X).—Prepared analogously to the adduct (VI) (yield 70%), this had m.p. 162—163° (lit.,[8] m.p. 165—168°), $[\alpha]_D$ +55·2°, $\nu_{max.}$ 1740 cm^{-1} (OAc) (Found: C, 72·1; H, 9·9; Cl, 12·3. Calc. for $C_{32}H_{52}Cl_2O_2$: C, 71·9; H, 10·2; Cl, 12·9%).

24,25-*Methylenelanost*-8-*en*-3β-*ol* (XI).—Prepared analogously to compound (VII), this had m.p. 142—144° (lit.,[8] 144—147°), $[\alpha]_D$ +46·5° (lit.,[8] +51°), $\nu_{max.}$ 3350 cm^{-1} (OH) (no CO absorption), *m/e* 440 (M^+), 428 ($M - CH_2$), 425 [$M - C(27)H_3$], 422 ($M - H_2O$), and 407 (M − Me − H_2O), δ −0·1 to 0·4 p.p.m.

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