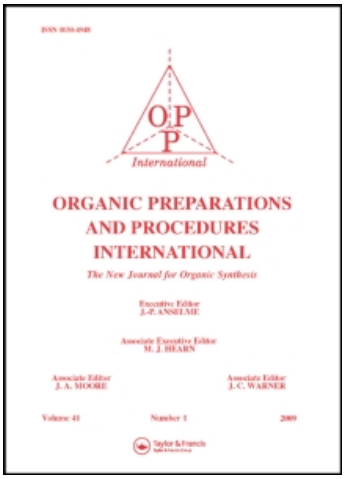

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THE SYNTHESIS OF STEROLS WITH MODIFIED SIDE CHAINS BY THE WITTIG REACTION

J. E. Herz[a]; S. M. Cruz[a]
[a] Departamento de Quimica, Centro de Investigacion del IPN, Mexico, DF, MEXICO

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THE SYNTHESIS OF STEROLS WITH MODIFIED SIDE CHAINS BY THE WITTIG REACTION

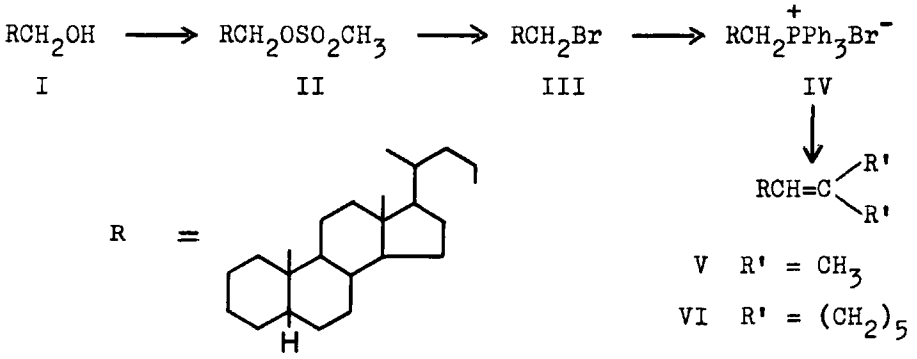
Submitted by (9/4/74)

J. E. Herz and S. Cruz M.

Departamento de Quimica
Centro de Investigacion del IPN
Apartado Postal 14-740
Mexico, D. F., MEXICO

The detailed preparation of two steroidal triphenyl phosphonium salts and their reactions with several ketones[1] is described.

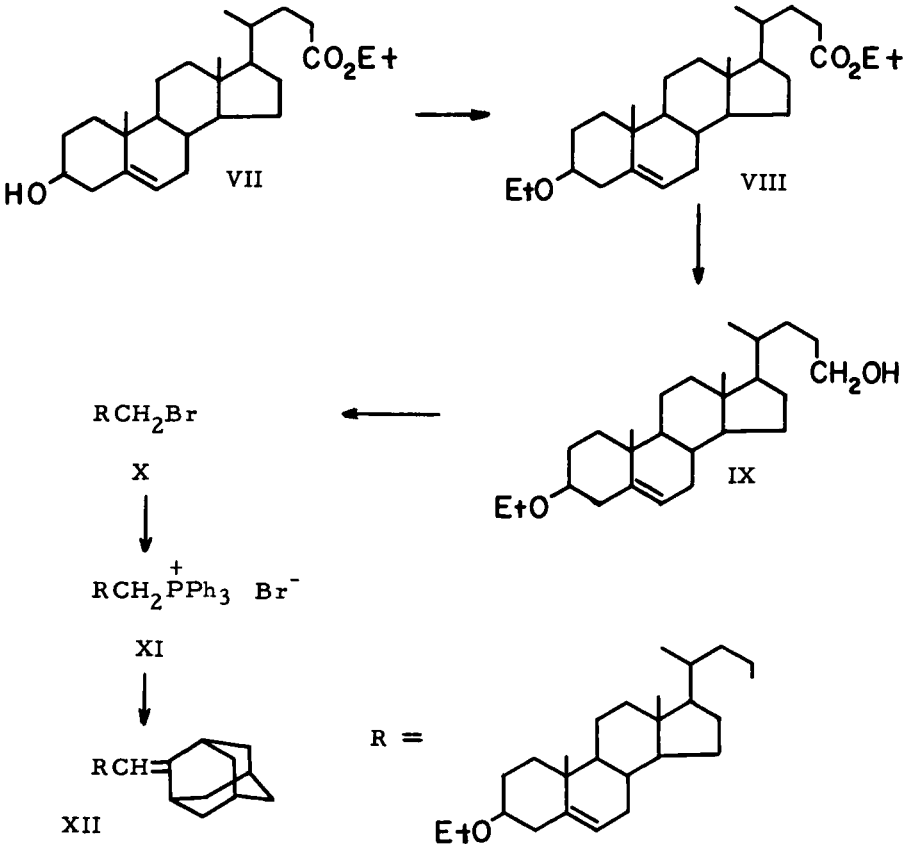
SCHEME I



EXPERIMENTAL

Melting points were determined on a Kofler Hotstage and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 421 in chloroform. NMR spectra were determined in deuterochloroform on a Varian A-60 spectrometer. Rotations

SCHEME II



were obtained in chloroform on a Perkin-Elmer Model 141 M polarimeter.

24-Cholanol methanesulfonate (II). - To a solution of 1.3 g of 5β-cholan-24-ol (I) in 12 ml anhydrous pyridine was added 1.5 ml methanesulfonyl chloride at 0°. After 5 hrs., the mixture was precipitated on ice, extracted with ether and the ethereal extract washed free of pyridine and evaporated. The residue was crystallized from ether-ethyl acetate, mp. 95°, $[\alpha]_D$ +30°,

IR 1360 cm^{-1}, 1170 cm^{-1}, yield 57%.

Anal. Calc. for $C_{25}H_{44}SO_3$: C, 70.70; H, 10.44; S, 7.54
Found: C, 70.85; H, 10.35; S, 7.42

24-Bromo-5β-cholane (III). - In a solution of 4.5 g (II) in 450 ml methyl ethyl ketone was suspended 11.5 g of LiBr and the mixture refluxed during 30 hrs. The mixture was then concentrated in vacuo and the residue taken up in CH_2Cl_2, washed with water, dried and evaporated. The product was crystallized from ether-acetone, yield 66%, mp. 83°, $[\alpha]_D$ + 25.6°.

Anal. Calc. for $C_{24}H_{41}Br$: C, 70.39; H, 10.09; Br, 19.51
Found: C, 71.00; H, 10.12; Br, 19.32

24-Cholanyl triphenylphosphonium bromide (IV). - This compound was prepared in a similar way as XI. Yield 57%, mp. 178°, $[\alpha]_D$ + 38.5°, NMR 7.8 ppm, m, (15H aromatic), IR 790 cm^{-1}, 760 cm^{-1}.

Anal. Calc. for $C_{42}H_{50}BrP$: C, 75.14, H, 8.34, Br, 11.90, P, 4.61
Found: C, 75.19, H, 8.44, Br, 11.78, P, 4.49

24-Cyclohexylidene-5β-cholane (V). - To a suspension of 1 g of IV in 20 ml of anh. ether was added dropwise, over a period of 20 min. 1 ml 1M phenyllithium in benzene-ether until the intense red color of the ylid had formed. The ylid solution was left agitating during 1 hr. at room temperature and 0.5 ml of dry cyclohexanone was added dropwise over a period of 15 min. The mixture was agitated at room temperature for 4 hrs. and left standing overnight. The solvent then was removed by evaporation and the residue extracted with a mixture of 90%

aq. methanol and the residue chromatographed on neutral alumina. The product, an oil, was eluted with pentane: yield 50%, $[\alpha]_D$ + 22.05°.

Anal. Calc. for $C_{30}H_{50}$: C, 87.73; H, 12.27
Found: C, 87.85; H, 12.46

5α-Cholest-24-ene (VI) was prepared in a similar way as V, by reaction of IV with acetone: yield 67% oil, $[\alpha]_D$ + 22.1°.

Anal. Calc. for $C_{27}H_{46}$: C, 87.49; H, 12.51
Found: C, 87.43; H, 12.53

Ethyl 3β-ethoxychol-5-enate (VIII). - To a solution of 1 g of VII[2] in 10 ml of ethyl orthoformate was added 0.56 ml 70% perchloric acid at room temperature:[3] yield 72% (from methanol), mp. 70°, $[\alpha]_D$ -47.2°; NMR 3.5 ppm (2H, q, ether), 4.17 ppm (2H, q, ester); IR 1730 cm^{-1}.

Anal. Calc. for $C_{28}H_{46}O_3$: C, 78.08; H, 10.76
Found: C, 77.95; H, 10.71

3β-Ethoxy-5-cholen-24-ol (IX). - To a solution of 0.8 g of VIII in anh. tetrahydrofuran was added 4 ml of a 70% solution of Red-Al[4] and the mixture heated to reflux for 1 hr., then hydrolyzed with 10% HCl. The solution was filtered, extracted with CH_2Cl_2 and the organic phase washed and evaporated. The product was crystallized from acetone to give 81% yield, mp. 150°, $[\alpha]_D$ -45.3°; NMR 3.4 ppm (q, 3β-OCH_2), 3.6 ppm (H_{24}), 5.4 ppm (H_6); IR 3620 cm^{-1}, 3420 cm^{-1}, 1735 cm^{-1}.

Anal. Calc. for $C_{25}H_{42}O_2$: C, 80.16; H, 11.03
Found: C, 80.15; H, 11.23

24-Bromo-3β-ethoxy-5-cholene (X)[5] - A solution of 2.038 g (8 mmoles) of triphenylphosphine in 20 ml of anhydrous ether was added to a solution of 1.7 g (4 mmoles) of IX and 2.58 g of carbon tetrabromide (8 mmoles) in 100 ml of anhydrous ether and left agitating overnight at room temperature. The mixture was then filtered and the filtrate evaporated. The residue was washed with a 1:1 mixture of 90% aqueous methanol and petroleum ether and recrystallized from acetone; yield 71%, mp. 139°, $[\alpha]_D$ -16.1°.

Anal. Calc. for $C_{26}H_{43}BrO$: C, 69.16; H, 9.60; Br, 17.70
Found: C, 69.36; H, 9.79; Br, 17.62

3β-Ethoxy-chol-5-enyl-24-triphenylphosphonium bromide (XI). - A solution of 1 g (2 mmoles) of X and 0.83 g (3 mmoles) of triphenylphosphine in 20 ml dry DMF was heated to reflux under nitrogen for 36 hrs. After cooling, the salt XI was precipitated by addition of ether, collected, and washed with ether. Yield 61%, mp. 230°, $[\alpha]_D$ -9.62°, NMR 7.8 ppm (15H, m, aromatic).

Anal. Calc. for $C_{44}H_{58}BrPO$: C 74.03, H 8.13, Br 11.19, P 4.30
Found: C 73.83, H 8.22, Br 11.28, P 4.21

24-(1-Adamantyliden)-3β-ethoxy-5-cholene (XII) was prepared from XI and 1-adamantanone as in V. Yield 65%, oil, $[\alpha]_D$ + 16.1°, NMR 5.0 ppm (H_{24}, t), 5.4 ppm (H_6).

Anal. Calc. for $C_{38}H_{56}O$: C, 85.65; H, 11.18
Found: C, 85.85; H, 11.25

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THE SPECTRAL CHARACTERIZATION OF endo-4-OXATRICYCLO[5,2,1,$O^{2,6}$]DEC-2-ENE

Submitted by (8/20/74)

Bradford P. Mundy

Department of Chemistry
Montana State University
Bozeman, Montana 59715

Characterization of the title compound by nmr resulted in a simple spectrum (δ values from tetramethylsilane, CCl_4 solvent) of broad singlets:

δ 1.44 [2H] (C-10); 2.76 [4H] (C-1,C-2,C-6,C-7);
3.30 [4H] (C-3,C-5); 6.01 [2H] (C-8,C-9).