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STEROIDS—LII[1]

SYNTHESIS AND REACTIONS OF A C_6-METHYLENE STEROID*

W. Z. CHOW, D. C. HUANG and HUANG-MINLON
Institute of Organic Chemistry, Academia Sinica, Shanghai

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Abstract—Reaction of 3β-acetoxy-5α,6α-oxido-6β-methyl-25D-spirostane (III) with *p*-toluenesulfonic acid in benzene affords the C_6-methylene compound (IV) (R = Ac) and the by-products, V, VIa, VIb and VII. The structure of IV has been elucidated. The structure and configuration at C_5 of the rearrangement product (IX) were determined by a series of reactions as shown in the text. The assignment of configuration at C_5 to compounds XIII and XVI is based on the results of molecular rotation comparison, ORD measurement, and stereochemical considerations.

ON A cleavage with acid, the 16β-methyl 16α,17α-oxide (I) afforded a mixture of the 16-methylene and $\Delta^{15(16)}$-16 methyl compounds (II)[2], whereas the 6β-methyl 5α,6α-oxide (III) underwent rearrangement on treatment with boron trifluoride[3] or formic acid[4] to give the A-bomo compound (VIa). On cleavage of the oxide ring of compound I with acid, the ratio of the products (16-methylene compound to $\Delta^{15(16)}$-16-methyl compound) varied with the acid used; *p*-toluenesulfonic acid led essentially to the 16-methylene compound, while concentrated hydrochloric acid afforded mainly the $\Delta^{15(16)}$-16-methyl compound.[2]

Cleavage of the epoxide ring of III with *p*-toluenesulfonic acid furnished the unsaturated IV (R = Ac) in good yield. The existence of a methylene group in this compound was demonstrated by its IR absorption spectrum (920, 1645, 3080 cm^{-1}) and NMR spectrum (5·2τ, 5·35τ)†. Treatment of IV (R = Ac) with monoperphthalic acid gave VIII. Cleavage of VIII with dilute sulfuric acid did not afford a 1,2-glycol but a carbonyl compound instead. By analogy with the rearrangement of the 6β-methyl 5α,6α-oxide (III),[3] we considered the carbonyl compound to be an A-homo-derivative (IX, R = H) resulting from the rearrangement (XVII → XVIII). The carbonyl band of IX (R = H) appeared at a rather low frequency, namely, 1680 cm^{-1}, probably due to the intramolecular hydrogen bonding of this group with the C_6-CH_2OH, as the frequency of the carbonyl group increased to 1695 cm^{-1} on acetylation (IX, R = Ac). On treatment with basic alumina, IX (R = Ac) underwent a base-catalysed β-elimination at C_3 to furnish the α,β-unsaturated ketone (X, R = Ac), Hydrolysis of X (R = Ac) with aqueous methanolic potassium carbonate furnished a hydroxyl-free substance regarded as XI. Its formation may be considered as a result of an intramolecular Michael addition.

* Preliminary communication, *Acta Chimica Sinica* **28**, 394 (1962); **30**, 93 (1964).

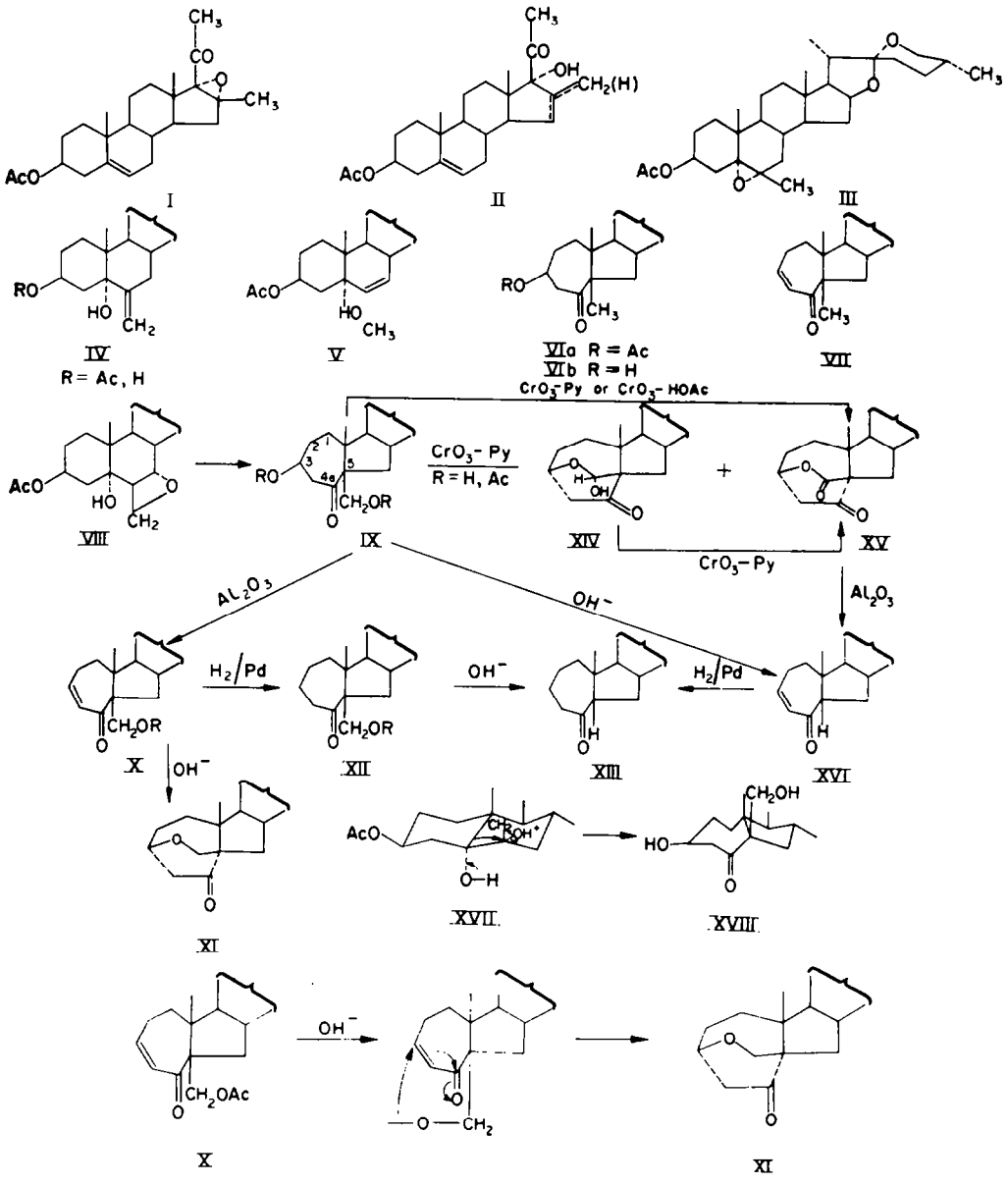
† The NMR spectrum indicated that the product also contained a very small amount of V.

[1] Part LI: Y. L. Wu, W. Z. Chow, C. C. Hou and Huang-Minlon, *Scientia Sinica* in the press.

[2] Huang-Minlon, C. H. Wu, S. W. Ching and Y. C. Chen, *Acta Chimica Sinica* **27**, 89 (1961); *Scientia Sinica* **11**, 1659 (1962); and the Refs cited therein.

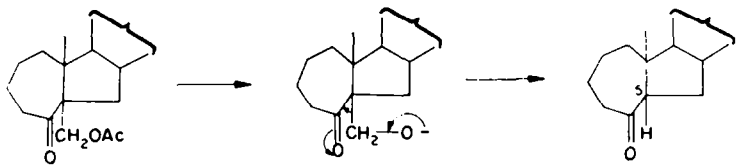
[3] D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4657 (1960).

[4] W. Z. Chow and W. S. Chu, *Acta Chimica Sinica* **28**, 385 (1962).



Compound XI showed an IR carbonyl band at a rather high frequency (1710 cm^{-1}), probably due to strain in the bicyclo-ring system. Since hydrolysis of X (R = Ac) did not give the corresponding free alcohol, an attempt was made to saturate the double bond of X (R = Ac) before hydrolysis with the hope of obtaining the C_5-CH_2OH compound. Hydrogenation of X (R = Ac) with Pd-C gave XII (R = Ac), which on saponification furnished only XIII in which the C_5-CH_2OH group was eliminated. The structure of this compound was established by its elemental analyses and spectral data. Its formation is regarded as proceeding through a retroaldol elimination.[5]

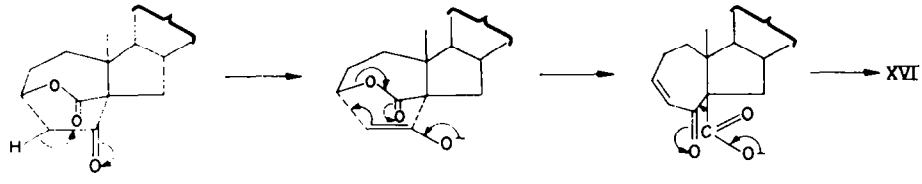
[5] D. H. R. Barton and P. de Mayo, *J. Chem. Soc.* 887 (1954).



XII XIII

Oxidation of IX (R = H) with chromic acid-pyridine at 25° for 2 hr. afforded a mixture of the hemiacetal (XIV) and the lactone (XV), separable by preparative TLC on alumina.[6] However, attempted separation of the mixture by column chromatography on alumina yielded only the hemiacetal (XIV) and the α,β-unsaturated ketone (XVI) (*vide infra*). Further oxidation of XIV with chromic acid–pyridine at 25° for 3 hr gave the lactone (XV), identical with the product obtained from a prolonged. oxidation of IX (R = H) with chromic acid–pyridine or chromic acid–acetic acid. The ready formation of the hemiacetal (XIV) and the lactone (XV) from IX having a $C_{3\beta}$-OH group established the β-orientation of the C_5-CH_2OH group on IX. The acetate of compound XIV and XV all showed an IR carbonyl band at a rather high frequency (1720 cm^{-1}), probably due to strain in the bicyclo-ring system (as for XI).

A benzene solution of XV, upon standing for 3 days with basic alumina, furnished an α,β-unsaturated ketone formulated as XVI, according to its elemental analyses and spectral data, and the formation of this compound was pictured as follows:



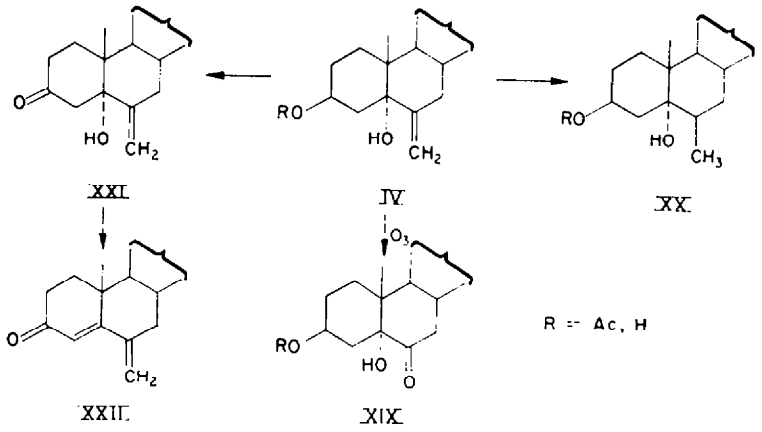
XV

Compound XV underwent this double elimination reaction so readily that even during the alumina column chromatographic separation of the oxidation products of IX, it was completely converted into the α,β-unsaturated ketone (XVI), as mentioned above. Hydrogenation of the double bond of XVI gave XIII, identical with that obtained from XII through basic elimination of its C_5-CH_2OAc group. Basic treatment of 1X (R = H) eliminated not only the C_3-hydroxyl group but also the C_5-hydroxymethyl group to give XVI, identical with that obtained from XV by treatment with alumina.

The structures of the various transformation products as postulated above pointed to the existence of a C_6-methylene group in IV, which was confirmed by the following chemical degradations; ozonization of IV (R = Ac) afforded the known 6-ketone (XIX R = Ac)[7] and formaldehyde (isolated as its 2,4-dinitrophenylhydrazone). Catalytic hydrogenation of IV (R = Ac) with Pt furnished the 6β-methyl derivative,

[6] V. Černy, J. Joska and L. Lábler, *Coll. Czech. Chem. Commun.* **26**, 1658 (1961).

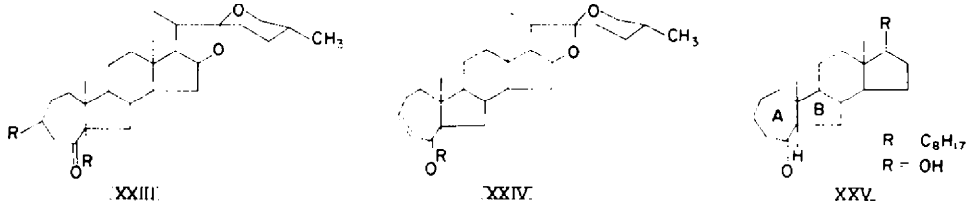
[7] B. Ellis, D. N. Kirk, V. Petrow and (Mrs) B. Waterhouse, *J. Chem. Soc.* 2828 (1960); T. W. Wang and Huang-minlon, *Acta Pharm. Sinica* **9**, 265 (1962).



(XX, R = Ac), which upon basic hydrolysis gave the known XX (R = H).[8] The C_3-hydroxyl IV (R = H) obtained from basic hydrolysis of IV (R = Ac) was oxidized with chromic acid–pyridine to yield the 6-methylene-3-one (XXI). Subsequent dehydration with base furnished a compound formulated as XXII according to its elemental analyses and spectral data.

Three known compounds, viz. VIa, VIb and VII[3] were isolated by alumina chromatography from the mother liquor of IV (R = Ac). Compound VIb probably resulted from hydrolysis of VIa during the isolation of IV, while VII probably came from VIa through elimination of the β-acetoxy group under acidic reaction conditions.[3] These results can be explained as involving the cleavage of epoxide ring in the 6β-methyl 5α,6α-oxide (III) by *p*-toluenesulfonic acid with the formation of a C_6 carbonium ion, followed by different electron shifts to form a mixture of the 6-methylene, Δ^6-6-methyl and A-homo-compounds (IV (R = Ac), V and VIa).

By analogy with the fact that the molecular rotation of C_{10} methyl steroids, such as testosterone ($[M]_D$ +340°) and its 19-nor anolag (C_{10}-H) ($[M]_D$ +184°), were of the same sign,[9] it was postulated that the C_5 hydrogen in XIII and XVI was β-oriented by a similar molecular rotational comparison with the configurationally known C_5-substituted analogs (XXIII, R′ = OH, Ac and H; R = CH_3, CH_2OH and CH_2OAc) and XXIV (R = CH_3 and CH_2OH) (Table 1).



The configuration at C_5 of XIII is so stable toward acidic or basic treatment that it remained unchanged even when heated with 2·5% sulfuric acid in dioxan for 24 hr or with 6% potassium hydroxide in dioxan (containing a small amount of EtOH) for

[8] D. Burn, B. Ellis, V. Petrow (Mrs.) I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4092 (1957).

[9] W. Klyne, *J. Chem. Soc.* 2923 (1952).

TABLE 1. MOLECULAR ROTATION $[M]_D$

	$R = CH_3$	$R = CH_2OH$	
XXIII (R′ = OH)	−477°	−494°	
		$R = CH_2OAc$	
XXIII (R′ = OAc)	−385°	−462°	
		$R = CH_2OH$	
XXIII (R′ = H)	−514°	−469°	
XXIV	−669°	−597°	
XIII			−335° (C_5–H)
XVI			−368° (C_5–H)
Testosterone	+340° (C_{10}–CH_3)		+184° (C_{10}–H)
Progesterone	+631° (C_{10}–CH_3)		+441° (C_{10}–H)

2·5 hr. These results agreed well with the fact that the A/B *cis*-fusion in A-homo-B-nor-steroid (XXV, R = OH) is completely stable.[10] Thus, the C_5–H configuration of XIII was further confirmed.

Supporting evidence in favour of the 5β-H of XIII is also provided by its positive Cotton effect, similar to that shown by the *cis* ketone (XXV, R = C_8H_{17} or OH)[10] but different from that of the *trans*-isomer (as XXV, R = C_8H_{17} but with 5α-H)[10] which is characterized by a negative Cotton effect.

EXPERIMENTAL

All m.ps were uncorrected The UV spectra were measured with a Unicam Sp 500 spectrophotometer and the IR spectra with Zeiss UR 10 spectrophotometer. The NMR spectra were measured in $CDCl_3$ using TMS as internal standard at 60 Mc/s. We are indebted to Prof. D. H. R. Barton, F.R.S. for the measurement of NMR spectrum. Our thanks are due to Dr. Huang-liang for determination of optical rotatory dispersion with the JASCO ORD/UV-5 spectrophotometer.

3β-Acetoxy-6-methylene-25D-spirostane-5α-ol (IV, R = Ac)

To a solution of III (10 g) in dried benzene (300 ml) was added *p*-toluenesulfonic acid (350 mg). The reaction mixture was refluxed for 30 min, and benzene (about 80 ml) was distilled off. After cooling, water was added, and the benzene layer was washed with water to neutrality and dried (Na_2SO_4). The solvent was removed under red. press. (The temp of water bath did not exceed 40°.) The residue was washed with a small amount of MeOH and ethyl acetate to yield almost colorless crystals (4·65 g), m.p. 228–231°. Recrystallization from $CHCl_3$–MeOH gave 4·38 g of IV (R = Ac), m.p. 237–239°, $[\alpha]_D$ −105° (*c*, 1·33, $CHCl_3$), $\nu_{max}^{CCl_4}$ 920, 1645, 3080 cm^{-1} (>=CH_2) 1730, 1250 cm^{-1} (ester), 3430–3460, 3590 cm^{-1} (hydroxyl). (Found: C, 73·86; H, 9·28. $C_{30}H_{46}O_5$ requires: C, 74·09; H, 9·50%.)

Concentration of the mother liquor gave a brown oily residue (about 5 g), which was chromatographed over 90 g neutral alumina (grade III). From the pet. ether–benzene (9:1) eluate, a semi-solid (0·25 g) was obtained. Trituration with MeOH afforded 0·15 g, solid, which was recrystallized from acetone to furnish needles (VII), m.p. 205–207°, $[\alpha]_D^{18}$ −158·7° (*c*, 0·63, $CHCl_3$), λ_{max}^{EtOH} 226 mμ (6400), ν_{max}^{Nujol} 1675 cm^{-1} (α,β-unsaturated ketone). The residue from the mother liquor was recrystallized several times to give plates (VIa), m.p. 199–202°, $[\alpha]_D^{18}$ −85·1° (*c*, 0·74, $CHCl_3$), ν_{max}^{Nujol} 1700 cm^{-1} (carbonyl), 1735, 1260 cm^{-1} (ester). From the benzene–ethyl acetate (9:1) eluate was obtained a semi-solid (0·7 g), which as recrystallized from $CHCl_3$–MeOH to give plates (VIb; 230 mg), m.p. 234–236°. Further recrystallization from ethyl acetate raised the m.p. to 244–246°, $[\alpha]_D^{18}$ −111·2° (*c*, 0·562, $CHCl_3$), ν_{max}^{Nujol} 1690 cm^{-1} (carbonyl), 3450, 3600 cm^{-1} (hydroxyl). This compound (50 mg) was acetylated with pyridine (1 ml) and acetic anhydride (0·6 ml). The resulting acetate was recrystallized from acetone m.p. 204–206°, undepressed on mixing with VIa (R = Ac), $[\alpha]_D$ −79·7° (*c*, 0·94, $CHCl_3$). VIa, VIb or VII showed no m.p. depression when admixed with the corresponding

[10] Y. Mazur and M. Nussim, *J. Amer. Chem. Soc.* **83**, 3911 (1961).

authentic sample.[8] Each of the 3 compounds also showed identical spots on TLC (basic Al_2O_3, grade III, developed with ethyl acetate–benzene (1:9), spotted with conc H_2SO_4) and identical IR spectra with the corresponding authentic sample.

3β-Acetoxy-6-methylene-α-epoxide-25D-spirostane-5α-ol (VIII)

To a solution of IV (R = Ac; 3 g) in $CHCl_3$ (50 ml) cooled to −7°, 37 ml of an ethereal solution of monoperphthalic acid (0·08 g per ml) was added and the temp was not allowed to exceed −3°. After the addition was complete, the reaction mixture was allowed to stand in a refrigerator overnight. The acidic compound was then removed with 5% Na_2CO_3 and the organic layer was washed with water to neutrality, dried and then concentrated under red. press. to give thin plates (2·7 g), m.p. 288–291°. Recrystallization from $CHCl_3$–MeOH furnished VIII, m.p. 289–291°, $[\alpha]_D$ −72·8° (*c*, 1·03, $CHCl_3$), $\nu_{max}^{CHCl_3}$ 1100 cm^{-1} (oxide), 1730, 1280 cm^{-1} (ester), 3450 cm^{-1} (hydroxyl). (Found: C, 71·40; H, 9·21; CH_3CO, 8·66; $C_{30}H_{46}O_6$ requires: C, 71·68; H, 9·22; CH_3CO, 8·55%.)

5β-Hydroxymethyl-A-homo-B-nor-25D-spirostane-3β-ol-4-α-one (IX R = H)

A mixture of VIII (2·7 g), dixoan (25 ml), MeOH (150 ml), and 2N H_2SO_4 (25 ml) was refluxed on a water bath for 3 hr. Removal of most of the solvent under red. press. followed by the addition of water afforded a crude product (2·27 g), m.p. 240–241°. Recrystallization from $CHCl_3$–MeOH furnished 1·67 g of IX (R = H), m.p. 244–246°. From the mother liquor 0·42 g of a second crop of product, m.p. 240–242° was obtained; $[\alpha]_D^6$ −108·1° (*c*, 0·832, $CHCl_3$), ν_{max}^{Nujol} 1680 cm^{-1} (carbonyl), 3450 cm^{-1} (hydroxyl). (Found: C, 72·78, H, 9·89; $C_{28}H_{44}O_5$ requires: c, 73·00; H, 9·63%.)

The acetate (IX; R = Ac) m.p. 166–168°, $[\alpha]_D^{15}$ −85° (*c*, 0·66, $CHCl_3$), ν_{max}^{Nujol} 1695 cm^{-1} (carbonyl) 1740, 1270 cm^{-1} (ester). (Found: C, 70·55; H, 9·00; $C_{32}H_{48}O_7$ requires: C, 70·56; H, 8·88%.)

Δ⁴-5β-Acetoxymethyl-A-homo-B-nor-25D-spirostene-4a-one (X, R = Ac)

To a solution of IX (R = Ac; 1·5 g) in dried benzene (150 ml) was added basic alumina (grade I–II; 15 g). After the reaction mixture was refluxed with stirring for 50 min, the alumina was filtered off and fully washed with hot benzene. The combined benzene solution was concentrated to dryness, and the solid residue was recrystallized from $CHCl_3$–ethyl acetate to give small needles (0·78 g), m.p. 205–207°. Analytical sample, m.p. 210–212°, $[\alpha]_D^9$ −123·6° (*c*, 0·752, $ChCl_3$), λ_{max}^{EtOH} 226 mμ (5500), ν_{max}^{Nujol} 1680 cm^{-1} (α,β-unsaturated ketone), 1740, 1250 cm^{-1} (ester). (Found: C, 74·44; H, 9·24; $C_{30}H_{44}O_5$ requires: C, 74·34; H, 9·15%.)

3β, 5β-Methylene-oxido-A-homo-B-nor-25D-spirostane-4a-one (XI)

A mixture of X (R = Ac; 150 mg), MeOH (12 ml), and 1·2 ml K_2CO_3aq (5 g K_2CO_3 in 30 ml water) was refluxed on a water bath for 30 min the crude mixture was concentrated under red. press. to give thin plates (80 mg), m.p. 218–227°. Recrystallization from $CHCl_3$–MeOH gave XI m.p. 225–227°, $[\alpha]_D$ −113·2° (*c*, 0·68, $CHCl_3$), ν_{max}^{Nujol} 1100 cm^{-1} (oxide), 1710 cm^{-1} (carbonyl). (Found: C, 76·34; H, 9·95; $C_{28}H_{42}O_4$ requires: C, 75·97; H, 9·56%.)

5β-Acetoxymethyl-A-homo-B-nor-25D-spirostane-4a-one (XII) (R = Ac)

To a solution of X (R = Ac; 200 mg) in MeOH (60 ml) was added 10% Pd–C (100 mg). The mixture was hydrogenated until no further H_2 uptake occurred. The catalyst was filtered off and washed with a small amount of $CHCl_3$. The filtrate was concentrated until crystallization commenced. The mixture was cooled and then filtered to furnish XII (R = Ac; 120 mg), m.p. 148–150°. A second crop of 40 mg m.p. 120–140°, was obtained from the mother liquor. The analytical sample melted at 152–153°, ν_{max}^{Nujol} 1685 cm^{-1} (keto), 1720, 1240 cm^{-1} (ester). Its UV spectrum showed only end absorptions. $[\alpha]_D^{11}$ −96·4° (*c*, 1·286, $CHCl_3$). (Found: C, 73·72; H, 9·63; $C_{30}H_{46}O_5$ requires: C, 74·03; H, 9·53%.)

A-Homo-B-nor-5β-25D-spirostane-4a-one (XIII)

(a) To a solution of XII (R = Ac; 300 mg) in MeOH (15 ml) was added 1·5 ml K_2CO_3aq (5 g of K_2CO_3 in 30 ml of water), and the reaction mixture was refluxed for 30 min. The crystalline product which separated on cooling was filtered to give XIII (190 mg), m.p. 166–168°. Concentration of the mother liquor under red. press. followed by the addition of water gave 50 mg of second crop of

material, m.p. 156–158°. The analytical sample melted at 171–173°, ν_{max}^{Nujol} 1700 cm^{-1} (keto), $[\alpha]_D^{31}$ −80·9° (*c*, 0·84, $CHCl_3$); $[\alpha]_{306}^{26}$ +270 (peak), $[\alpha]_{306}^{26}$ −1180° (trough), $[\alpha]_{330}^{26}$ −1200° (*c*, 0·18 in dioxan). (Found: C, 78·48; H, 10·16; $C_{27}H_{42}O_3$ requires: C, 78·21; H, 10·21%.)

(b) A hot solution of XVI (0·32 g) in dioxan (25 ml) was diluted with MeOH (50 ml). After cooling, the reaction mixture was hydrogenated in the presence of 10% Pd–C (200 mg) under ordinary press. and temp. until no further H_2 uptake occurred. Recrystallization of the product from $CHCl_3$–MeOH gave XIII (238 mg), m.p. 171–173°, and from the mother liquor a second crop of material (86 mg), m.p. 164–168° was obtained, ν_{max}^{Nujol} 1700 cm^{-1} (keto), $[\alpha]_D^{14}$ −80·0° (*c*, 0·525, $CHCl_3$). It showed no m.p. depression when admixed with the product obtained from (a).

*3β-Hydroxy-*A*-homo-*B*-nor-25*D*-spirostane-*4a*-one-5β-al (3 → 5)-lactol* (XIV)

Compound IX (R = H; 500 mg) was dissolved in pyridine (5 ml) by warming. The cooled solution was then gradually added to a pasty solution of chromic acid (500 mg) in pyridine (5 ml). After the reaction mixture was allowed to stand at room temp (25°) for 2 hr, it was poured into ice water and extracted with ethyl acetate. The organic layer was successively washed with water, 10% aqueous tartaric acid solution, and 5% $NaHCO_3$aq, and again with water to neutrality, dried, and concentrated to dryness under red. press. to yield 440 mg crude product. TLC (on alumina, grade III–IV, developed with benzene–ethyl acetate (9:1), spotted with conc. H_2SO_4 and baked with small flame) showed that the crude product consisted of two components with different polarities. The mixture was separated by preparative TLC with alumina.[6] (The grade of alumina and the solvent system used were similar to that mentioned above.) The more polar product was eluted with $CHCl_3$ identified as XIV (280 mg). Recrystallization form $CHCl_3$–MeOH gave 180 mg of pure material, m.p. 254–256, $[\alpha]_D^{28}$ −155·6° (*c*, 1·015, $CHCl_3$), ν_{max}^{Nujol} 1705 cm^{-1} (keto), 3370 cm^{-1} (hydroxyl). (Found: C, 73·49; H, 9·08; $C_{28}H_{42}O_5$ requires: C, 73·32; H, 9·23%.)

Acetylation of XIV (acetic anhydride and pyridine) furnished the acetate, m.p. 214–217°, $[\alpha]_D^{26}$ −138·6° (*c*, 1·745; $CHCl_3$), ν_{max}^{Nujol} 1720 cm^{-1} (keto), 1745, 1280 cm^{-1} (ester).

The above-mentioned less polar XV (70 mg) was eluted with $CHCl_3$. Two recrystallizations form $CHCl_3$–MeOH gave pure product, m.p. 280–281°, $[\alpha]_D^{22}$ −94·5° (*c*, 0·73, $CHCl_3$), ν_{max}^{Nujol} 1720 cm^{-1} (keto), 1745 cm^{-1} (lactone).

*3β-Hydroxy-*A*-homo-*B*-nor-25*D*-spirostane-*4a*-one-5β-carboxylic acid lactone* (XV)

(a) To a pasty solution of chromic acid (100 mg) in pyridine (1 ml) was added a solution of XIV (100 mg) in pyridine (1 ml). The reaction mixture was allowed to stand at room temp overnight (14 hr). The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed successively with water, dil HCl, $NaHCO_3$aq and again with water to neutrality, dried, and concentrated to yield a crude product, which was recrystallized from $CHCl_3$–MeOH to give 70 mg of XV, m.p. 275–279°, $[\alpha]_D^{26}$ −93·0 (*c*, 1·0, $CHCl_3$), ν_{max}^{Nujol} 1720 cm^{-1} (keto), 1745 cm^{-1} (lactone). The compound showed no m.p. depression when admixed with the lactone obtained in the previous experiment. Both samples showed the same spots on alumina TLC as well as identical IR spectra.

(b) To a pasty solution of chromic acid (500 mg) in pyridine (5 ml) was added a solution of IX (R = H; 0·5 g) in pyridine (5 ml), and the reaction mixture was allowed to stand at room temp overnight. The dark brown mixture was then filtered, and the pyridine solution was concentrated to dryness under red. press. (the temp of water bath did not exceed 40°). The residue was extracted with benzene and the benzene extract was washed successively with 10% HClaq, water, 5% NaHCOaq and again with water to neutrality, dried, and concentrated to give a crude product (0·43 g), m.p. 238–240°. Recrystallization from $CHCl_3$–MeOH furnished XV (0·16 g), m.p. 274–276°, and from the mother liquor a second crop of material (0·12 g), m.p. 240–246°, was obtained $[\alpha]_D^{23}$ −94·6° (*c*, 1·468, $CHCl_3$), ν_{max}^{Nujol} 1720 cm^{-1} (carbonyl), 1745 cm^{-1} (lactone). It showed no m.p. depression when admixed with the product from (a). Both samples showed the same spots on alumina TLC as well as identical IR spectra.

(c) To a solution of IX (R = H; 0·3 g) in acetic acid was gradually added a solution of chromic acid (0·17 g) in acetic acid (12 ml). After the reaction mixture was allowed to stand at room temp for 6 hr, isopropanol was added to decompose the excess chromic acid. Acetic acid was removed under red. press. and the residue was treated with water and filtered to give colorless crystals (0·23 g), m.p. 241–243°. Recrystallization from $CHCl_3$–MeOH furnished XV (0·15 g), m.p. 278–279°. From the

mother liquor, a further crop of the material (40 mg), m.p. 260–262° was obtained, $[\alpha]_D^{28}$ −92° (*c*, 1·022, $CHCl_3$), ν_{max}^{Nujol} 1720 cm^{-1} (carbonyl), 1745 cm^{-1} (lactone). The product showed no m.p. depression when admixed with the product from (b). Both samples showed the same spots on alumina TLC as well as identical IR spectra. (Found: C, 73·66; H, 8·86; $C_{38}H_{40}O_5$ requires: C, 73·65; H, 8·83%.)

Δ^3-A-homo-B-nor-5β-25D-spirostene-4a-one (XVI)

(a) A solution of XV (0·3 g) in a small amount of benzene was poured onto an alumina chromatographic column (25 g, grade II, neutral alumina) and washed with more benzene. The column was allowed to stand at room temp for 3 days, and then eluted with benzene. The product obtained was recrystallized from $CHCl_3$–MeOH to give XVI (0·17 g), m.p. 190–192°, $[\alpha]_D^{30}$ −95·9 (*c*, 0·93, $CHCl_3$), λ_{max}^{EtOH} 228 mμ (6600), ν_{max}^{Nujol} 1670 cm^{-1} (α,β-unsaturated ketone). The analytical sample melted at 194–196°. (Found: C, 78·87; H, 9·46; $C_{37}H_{40}O_3$ requires: C, 78·59; H, 9·77%.)

(b) A mixture of IX (R = Ac; 70 mg), t-butanol (3 ml) and potassium t-butoxide in t-butanol (1·5 ml; 0·3N) was refluxed for 1 hr, water was then added and the mixture was extracted with ether. Isolation of the product by preparative alumina TLC gave XVI, m.p. 191–192°. It showed no m.p. depression when admixed with the product obtained from (a). $[\alpha]_D^{23}$ −100° (*c*, 0·23, $CHCL_3$), λ_{max}^{EtOH} 226 mμ (6000), ν_{max}^{Nujol} 1675 cm^{-1} (α,β-unsaturated ketone).

(c) To a pasty solution of chromic acid in pyridine (1 g chromic acid in 10 ml pyridine) was added a solution of IX (R = H; 1·1 g) in pyridine (10 ml). Upon standing at room temp (25°) for 2 hr, the crude product was filtered through neutral alumina (30 mg grade II–III) to remove the brown residue. The filtrate was concentrated under red. press. to a small volume, and diluted with water to give a mixture (960 mg), which was separated by column chromatography on neutral alumina (30 g, grade II–III). From the benzene eluate, XVI (120 mg) was obtained, m.p. 190–192°. It showed no m.p. depression when admixed with the product obtained from (b). The benzene–ethyl acetate (8:2) eluate gave XIV. Recrystallization from $CHCl_3$–MeOH gave crystals (340 mg), m.p. 255–257°. From the mother liquor, a second crop of 127 mg, m.p. 251–253°, was obtained. The m.p. of this compound was not depressed on mixing with that obtained in the previous experiment.

3β-Acetoxy-25D-spirostane-5α-ol-6-one (XIX)

A solution of IV (R = Ac, 0·6 g) in $CHCl_3$ (12 ml) was ozonized at −70 to −80° for 25 min. The chloroform was partially removed under red. press. and the reaction mixture was steam distilled. When the distillate was passed into a solution of the 2,4-dinitrophenylhydrazine reagent, a precipitate immediately separated. It was filtered to give a derivative (0·23 g), m.p. 147–150°. Recrystallization from $CHCl_3$–MeOH gave 0·085 g, of product, m.p. 163–164°. It showed no m.p. depression when admixed with an authentic sample of formaldehyde 2,4-dinitrophenylhydrazone. After formaldehyde was removed, the residue was dried and chromatographed over grade II–III neutral alumina. From the ethyl acetate–benzene (1:9) eluate, 50 mg of crystals was obtained. Recrystallization from $CHCl_3$–MeOH gave XIX, m.p. 268–269°, $[\alpha]_D^5$ −117·4° (*c*, 0·46, $CHCl_3$), ν_{max}^{Nujol} 1710 cm^{-1} (carbonyl), 1740, 1260 cm^{-1} (ester), 3400, 3480 cm^{-1} (hydroxyl). This compound showed no depression of mixed m.p. when admixed with an authentic sample (m.p. 271–272°).[7]

3β-Acetoxy-6β-methyl-25D-spirostane-5α-ol (XX; R = Ac)

A solution of IV (R = Ac; 0·5 g) in acetic acid was hydrogenated in the presence of 60 mg PtO_2 under ordinary temp and press until H_2 uptake ceased and then worked up to give XX (R = Ac), m.p. 231–234°, $[\alpha]_D^{24}$ −96·6° (*c*, 0·80, $CHCl_3$), $\nu_{max}^{ClC_4}$ 1720, 1250 cm^{-1} (ester), 3450, 3600 cm^{-1} (hydroxyl). (Found: C, 73·73; H, 9·72; $C_{30}H_{48}O_5$ requires; C, 73·73; H, 9·90%.)

To a solution of XX (R = Ac; 70 mg) in MeOH (6 ml) was added 0·6 ml K_2CO_3aq (the same concentration as described before). The reaction mixture was refluxed on a water bath for 30 min and worked up in the usual way to give XX (R = H), m.p. 216–219°, $[\alpha]_D$ −76·6° (*c*, 0·6, $CHCl_3$), ν_{max}^{Nujol} 3300–3400 cm^{-1} (hydroxyl). It showed no m.p. depression when admixed with an authentic sample (217–218°).[8]

3β-Hydroxy-6-methylene-25D-spirostane-5α-ol (IV; R = H)

To a solution of IV (R = Ac; 0·3 g) in tetrahydrofuran (2 ml) and MeOH (20 ml) was added 2 ml K_2CO_3aq (5 g of K_2CO_3 in 30 ml water) and the reaction mixture was refluxed on a water bath

for 30 min and worked up to give 0·28 g of IV (R = H), m.p. 224–227°. Recrystallization from $CHCl_3$–MeOH gave IV (R = H) (0·24 g), m.p. 225–227°, $[\alpha]_D^{14}$ −94·4° (*c*, 1·29, $CHCl_3$), ν_{max}^{Nujol} 910, 1645, 3080 cm^{-1} (>=CH_2) 3300–3400 cm^{-1} (hydroxyl). (Found: C, 75·78; H, 9·97; $C_{28}H_{44}O_4$ requires: C, 75·63; H, 9·97%.)

6-methylene-25D-spirostane-5α-ol-3-one (XXI)

To a pasty solution of chromic acid (0·33 g) in pyridine (3·3 ml) was added a solution of IV (R = H; 0·33 g) in pyridine (3 ml), and the reaction mixture was allowed to stand overnight. The crude mixture was then filtered over grade II neutral alumina (15 g) to give an almost colorless solution. The solvent was removed under red. press. and the residue was treated with water to yield XXI (0·22 g) m.p. 196–199°. Recrystallization from $CHCl_3$–MeOH gave 0·15 g, of product, m.p. 265–267°. The analytical sample melted at 268–269°, $[\alpha]_D^{26}$ −101·3° (*c*, 1·195, $CHCl_3$), ν_{max}^{Nujol} 910, 1645, 3080 cm^{-1} (>=CH_2), 1710 cm^{-1} (ketone), 3400 cm^{-1} (hydroxyl).

6-Methylene-Δ⁴-25D-spirostene-3-one (XXII)

To a solution of XXI (0·2 g) in tetrahydrofuran (10 ml) and MeOH (10 ml) was added a solution (1·5 ml) KOH in EtOH (0·23 g KOH in 25 ml EtOH), and the reaction mixture was refluxed on a water bath for 2 hr. After cooling, acetic acid (2 drops) was added and the solvent was removed under red. press. Addition of water followed by filtration gave a pale yellow solid (0·18 g), m.p. 199–201°. Two recrystallizations from $CHCl_3$–MeOH gave 0·13 g m.p. 203–205°, $[\alpha]_D^{19}$ +145·7° (*c*, 1·05; $CHCl_3$), λ_{max}^{EtOH} 262 mμ (12300), ν_{max}^{Nujol} 900, 1625, 3080 cm^{-1} (>=CH_2), 1605, 1680 cm^{-1} (α,β-unsaturated ketone). (Found: C, 78·92; H, 9·87; $C_{28}H_{40}O_2$ requires: C, 79·20; H, 9·50%.)