SYNTHESIS OF TWO ISOMERIC 16,17-CYCLOPROPANO DERIVATIVES OF 5-PREGNENE*

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Simmons–Smith methylenation of the epimeric 5,16-pregnadien-3β,20-diols, as well as some reactions of these compounds carrying the cyclopropane ring in position 16,17 have been studied.

In the course of our studies[1] on participation of the cyclopropane ring in solvolytic reactions we became interested in steroid derivatives carrying the cyclopropane ring in position 16, 17. In this paper we describe Simmons–Smith methylenation of the epimeric 5,16-pregnadien-3β,20-diols as well as synthesis of the 16α,17α and 16β,17β cyclopropane derivatives of the 5-pregnene series, desired for further studies.

Compounds of this type have been prepared from the ketone *I* with diazomethane[2–6] or, recently[7] from this ketone on reaction with dimethylsulphoxonium methylide. However, formation of only one isomer – presumably the 16α,17α--compound – was reported. This configuration of the cyclopropane ring was now established by Tseikinskii and coworkers[8] by X-ray analysis. In the search for the 16β,17β isomer we therefore studied the Simmons–Smith methylenation of the allylic alcohols *II*, *III*, *IV* and *V* and prepared some of the already known[2–9] cyclopropane derivatives which were synthesized by different routes and the constants of which differed considerably from ours.

Reduction of the unsaturated ketone *I* to the allylic alcohols *III* and *V* was carried out first by Ercoli[10–12] with zinc in acetic acid and lead predominantly to 16,17 saturated products. Lithium aluminium hydride reduction was described by Shapiro[13] and by Benn[14] and afforded a mixture of diols *II* and *IV* from which the pure isomers were isolated with difficulties and in very low yields. We therefore studied this reaction in more detail. Reaction with lithium tri-tert-butoxyaluminium hydride gave exclusively 16,17-saturated compounds. Sodium borohydride reduction afforded a mixture of the 3-acetoxy derivatives *III* and *V* in 1 : 1 relation accompanied by about 10% of the 16,17-saturated products. This mixture could be easily separated by column chromatography over silica gel. Lithium aluminium hydride reduction

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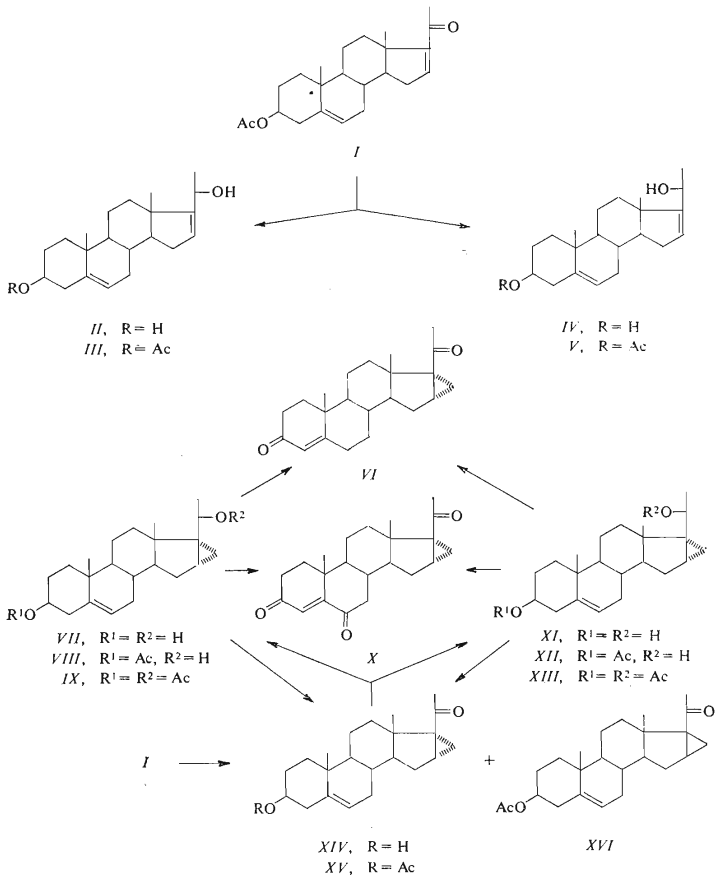
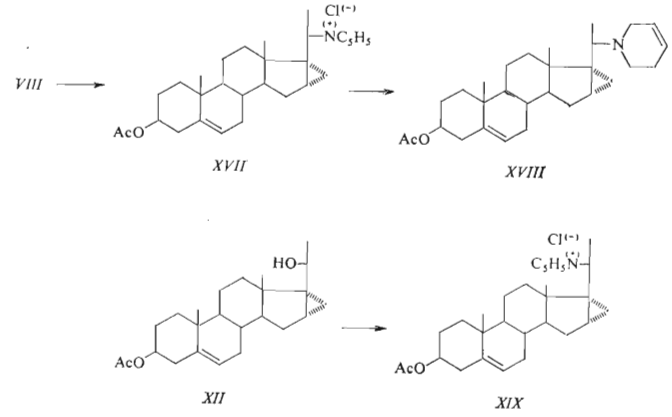
gave a mixture of diols *II* and *IV* in 1 : 1 relation as reported, but was almost quantitatively separated into its components without difficulties by chromatography over silica gel in benzene–ether.



All four allylic alcohols *II*, *III*, *IV* and *V* have been subjected to the Simmons–Smith methylenation. In all cases only the 16α,17α adducts were formed as followed from spectral and chemical evidence, though the constants differed from the literature records[2–7], and no 16β,17β adduct was detected. The influence of the allylic hydroxyl on the stereochemistry of the methylene addition is well known[15–19]. But evidently in the 20α as well as in the 20β alcohol the freely rotating hydroxyl group always adopts a conformation which is convenient for formation of the 16α,17α adduct. We therefore repeated the methylenation of the ketone *I* with dimethylsulphoxonium methylide as described by Steinberg[7] and succeeded in isolation of the desired 16β,17β adduct *XVI* by careful work up of the mother liquors after isolation of the main product *XV*. Reduction of the ketone *XV* with lithium tri-tert-butoxyaluminium hydride afforded the monoacetates *VIII* and *XII* identical with the products obtained on Simmons–Smith methylenation of the allylic alcohols *III* and *V*. Jones' oxidation of the diols *VII* and *XI* gave the 6-oxo-16α,17α-cyclopropanoprogesterone (*X*); under mild conditions the known[6,9] 16α,17α-cyclopropanoprogesterone (*VI*) was isolated as the main product. Attempts to prepare a tosylate or a mesylate of the alcohols *VIII* or *XII* led to formation of pyridinium salts *XVII* or *XIX*, respectively. Analogous reactions have already been observed[20–22]. The pyridinium chloride *XVII* gave on reaction with sodium borohydride the amine *XVIII* in accordance with the proposed structure.



EXPERIMENTAL

Melting points were determined on a Kofler block. Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane. The ^{1}H NMR spectra were recorded on the Tesla 60 MHz instrument in deuteriochloroform unless otherwise stated and corrected to tetramethylsilane. The chemical shift is given in ppm. The mass spectra were recorded on the mass spectrometer AEI 902. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin layer chromatography (TLC), and by infrared and ^{1}H NMR spectra. Plates with 200 × 200 × 0·7 mm silica gel layer were used for preparative TLC. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulphate, and evaporation of the solvent *in vacuo*. Ligroin refers to the fraction of b.p. 40–62°C.

5,16-Pregnadiene-3β,20α-diol (*II*)

A solution of the ketone *I* (8 g) in tetrahydrofuran (80 ml) was treated dropwise under stirring with a solution of lithium aluminium hydride (5 g) in tetrahydrofuran (120 ml) in the course of 30 min. The mixture was allowed to stand at room temperature for 30 min and then heated to 70°C for 5 h. The excess hydride was decomposed with wet ether and ethyl acetate, and the organic layer was worked up. The residue after evaporation of the solvents was chromatographed on a silica gel column (1 kg) in benzene–ether (19 : 1). Fractions with the lipophilic component were combined, solvents removed, and the residue (2·9 g) was crystallized from ethyl acetate to yield 2·55 g of the diol *II*, m.p. 191°C, $[\alpha]_D^{20}$ −86° (*c* 0·9); literature[10–12,14] records m.p. 180 to 188°C, $[\alpha]_D^{20}$ −86°.

5,16-Pregnadiene-3β,20α-diol 3-Acetate (*III*)

Solid sodium borohydride (500 mg) was added to a solution of the ketone *I* (1 g) in 99% methanol (100 ml) and allowed to stand at room temperature for 30 min. The excess hydride was decomposed with water and 2% hydrochloric acid, and the product was isolated with ether. The ethereal solution was worked up and ether removed to yield 1 g of a crude product consisting according to the TLC of two main components. The mixture was chromatographed over silica gel (200 g) in benzene–ether (19 : 1). Fractions with the lipophilic component were combined, solvents removed, and the residue (300 mg) was crystallized from ethyl acetate to yield 220 mg of the acetate *III*, m.p. 138–139°C, $[\alpha]_D^{20}$ −89° (*c* 1·79); literature[10–12] records m.p. of the monohydrate 98 to 99°C.

5,16-Pregnadiene-3β,20β-diol (*IV*)

Fractions with the polar component after isolation of the diol *II* were combined, solvents were distilled off, and the residue (2·9 g) was crystallized from ethyl acetate to yield 2·1 g of the diol *IV*, m.p. 171°C, $[\alpha]_D^{20}$ −66° (*c* 0·90) in accordance with the literature[10–12,14].

5,16-Pregnadiene-3β,20β-diol 3-Acetate (*V*)

Further elution of the chromatography after isolation of the acetate *III* with the same solvent mixture afforded fractions with the polar component. Working up, evaporation of the solvents, and crystallization from ethyl acetate gave 200 mg of the acetate *V*, m.p. 152–153°C, $[\alpha]_D^{20}$ −73° (*c* 1·79); literature[10–12] records m.p. 145–146°C.

16α,17α-Cyclopropanopregn-4-ene-3,20-dione (*VI*)

a) *From* 16α,17α-*cyclopropanopregn*-4-*ene*-3β,20α-*diol* (VII): The diol *VII* (200 mg) in acetone (40 ml) was treated with excess Jones' reagent[23] and allowed to stand at room temperature for 5 min. The excess reagent was removed with methanol, the mixture was diluted with water, and the product was taken into ether. After working up and evaporation of the solvent the residue (190 mg) was chromatographed over silica gel (20 g) in ligroin–ether (1 : 1). Fractions with the lipophilic component were worked up, solvents removed and the residue was crystallized from ethyl acetate to afford 60 mg of the dione *VI*, m.p. 195–196°C, $[\alpha]_D^{20}$ +201° (*c* 1·19) in accordance with the literature[2,9]. ^{1}H NMR spectrum: 0·70–0·93 (mt, cyclopropane protons), 0·975 (s, 18-H), 1·03 (s, 19-H), 1·96 (s, 21-H), 3·49 (mt, $W_{1/2}$ = 20 Hz, 3α-H), 5·34 (mt, $W_{1/2}$ = = 8 Hz, 6-H). IR spectrum: 3 610, 1 048 (hydroxyl), 3 085 (cyclopropane), 1 365, 1 676 cm^{-1} (CH_3—CO-cyclopropane group).

b) *From* 16α,17α-*cyclopropanopregn*-4-*ene*-3β,20β-*diol* (XI): The diol *XI* (50 mg) in acetone (8 ml) was oxidized with Jones' reagent as described above. Similar working up afforded a mixture of the ketones *VI* and *X*. It was separated by preparative TLC on the plate in ligroin–ether (4 : 1). The zone with the lipophilic component was worked up to yield after evaporation of the solvent 20 mg of the dione *VI*, m.p. 194°C, identical with the sample prepared as under *a*).

16α,17α-Cyclopropanopregn-5-en-3β,20α-diol (*VII*)

a) *From* 5,16-*pregnadien*-3β,20α-*diol* (II): Zn–Cu couple was prepared by adding zinc dust (2 g) into a solution of cupric acetate monohydrate (50 mg) in acetic acid (2 mg) at 50–60°C and shaking until the solution decolorized. Fresh acetic acid (2 ml) was added and the sedimented zinc was decanted with eight portions (10 ml each) of ether. The couple was then covered with ether (8 ml), treated with diiodomethane (2 ml) and refluxed for 2 h in a nitrogen atmosphere under stirring. The olefin *II* (500 mg) in diiodomethane (3 ml) and ether (25 ml) was then added and refluxed under similar conditions for 2 h. After cooling off the mixture was poured into 10% sodium hydrogen carbonate solution, the product taken into ether, and the ethereal solution was washed with 5% hydrochloric acid, a sodium hydrogen carbonate solution, water, 10% sodium thiosulphate solution, water, dried and evaporated. The residue was chromatographed over silica gel (50 g) in ligroin (500 ml) and then in ligroin–ether (2 : 1). Fractions with the adduct were combined, solvents removed, and the residue (280 mg) was crystallized from ethyl acetate to afford 220 mg of the cyclopropano derivative *VII*, m.p. 227–228°C, $[\alpha]_D^{20}$ −45° (0·81; in chloroform–1% pyridine); literature[2] records m.p. 177–179°C, $[\alpha]_D^{20}$ −51°. Mass spectrum: $M^{+\cdot}$ 330. ^{1}H NMR spectrum: 0·28–0·64 (mt, cyclopropane protons), 0·93 (s, 18-H), 1·00 (s, 19-H), 1·19 (d, *J* = 6 Hz, 21-H), 3·36 (mt, $W_{1/2}$ = 28 Hz, 3α-H), 4·28 (q, *J* = 6 Hz, 20-H), 5·34 (mt, $W_{1/2}$ = = 7·5 Hz, 6-H). IR spectrum (KBr): 3 490, 1 081, 1 050 (hydroxyl), 3 070, 3 035, 3 005 (double bond and cyclopropane ring), 1 668 cm^{-1} (double bond). For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·68% C, 10·06% H.

b) *From* 16α,17α-*cyclopropanopregn*-5-*en*-3β,20α-*diol* 3-*acetate* (VIII): A solution of the acetate *VIII* (35 mg) in methanol (10 ml) was refluxed with a solution of potassium hydroxide (100 mg) in methanol (2 ml) for 90 min. After cooling off the mixture was poured in water and the product extracted into ethyl acetate. The organic layer was washed with water, dried, and solvent was distilled off. The crude product was purified by preparative TLC on one plate in ligroin–ether (1 : 1). Working up of the corresponding zone and crystallization from ethyl acetate yielded 8·5 mg of the diol *VII*, m.p. 224–225°C, $[\alpha]_D^{20}$ −44° (*c* 1·12 in chloroform–1% pyridine).

c) *From* 3β-*hydroxy*-16α,17α-*cyclopropanopregn*-5-*en*-20-*one* (XIV): A solution of the ketone *XIV* (280 mg) in ether (28 ml) was treated with lithium aluminium hydride (500 mg) and allowed

to stand 30 min at room temperature. The mixture was decomposed with ethyl acetate, diluted with ether, and the ethereal solution was worked up. The residue after evaporation of ether was chromatographed on a silica gel column (50 g) in ligroin–ether (4 : 1) and fractions with the product were worked up. The residue after evaporation of the solvents (134 mg) was crystallized from ethyl acetate to give 73 mg of the diol *VII*, m.p. 224—225°C, $[\alpha]_D^{20}$ —45° (*c* 1·18; in chloroform–1% pyridine).

16α,17α-Cyclopropanopregn-5-en-3β,20α-diol 3-acetate (*VIII*)

a) *From* 5,16-*pregnadiene*-3β,20α-*diol* 3-*acetate* (III): The olefin *III* (750 mg) was submitted to the Simmons–Smith methylenation as described above for methylenation of the olefin *II*. Similar working up afforded 700 mg of a product which was chromatographed on a silica gel column (60 g) in ligroin–ether (4 : 1). The corresponding fractions afforded after working up and evaporation of the solvents 500 mg of a residue which on crystallization from ethyl acetate gave 380 mg of the cyclopropano derivative *VIII*, m.p. 181—184°C (literature[7] records m.p. 149—151°C), $[\alpha]_D^{20}$ —71° (*c* 0·98). Mass spectrum: *m/z* 312 (M — 60). ^{1}H NMR spectrum: 0·31—0·75 (mt, cyclopropane protons), 0·91 (s, 18-H), 1·02 (s, 19-H), 1·18 (d, J = 6 Hz, 21-H), 2·00 (s, acetate), 4·05—4·78 (mt, 3α-H and 20-H), 5·33 (mt, $W_{1/2}$ = 8 Hz, 6-H). IR spectrum: 3 620 (hydroxyl), 3 075 (cyclopropane ring), 1 729, 1 259 (acetate), 1 671 cm^{-1} (double bond). For $C_{24}H_{36}O_3$ (372·5) calculated: 77·37% C, 9·74% H; found: 77·35% C, 9·38% H.

b) *From* 3β-*hydroxy*-16α,17α-*cyclopropanopregn*-5-*en*-10-*one* 3-*acetate* (XV): The ketone *XV* (350 mg) in tetrahydrofuran (20 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride (700 mg) and allowed to stand at room temperature for 20 h. The mixture was diluted with water, the excess hydride was removed with 2% hydrochloric acid and the product was taken into ether. The ethereal solution was worked up and ether removed. The residue consisted according to the TLC of two components. They were separated by column chromatography over silica gel (50 g) in ligroin–ether (9 : 1). Fractions with the lipophilic component were combined, solvents distilled off and the product (130 mg) was crystallized from methanol to yield 82 mg of the alcohol *VIII*, m.p. 181—184°C.

16α,17α-Cyclopropanopregn-5-ene-3β,20α-diol 3,20-Diacetate (*IX*)

The alcohol *VIII* (56 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) and allowed to stand at room temperature for 20 h. The excess anhydride was decomposed with ice and water and the product was taken into ether. Usual working up and crystallization of the residue from methanol yielded 29 mg of the diacetate *IX*, m.p. 196—198°C, $[\alpha]_D^{20}$ —19° (*c* 3·82). Literature[2] records m.p. 180—182°C, $[\alpha]_D^{20}$ —28°. ^{1}H NMR spectrum (Varian 100 MHz instrument): 0·37—0·55 and 0·61—0·75 (two mt, cyclopropane protons), 0·97 (s, 18-H), 1·03 (s, 19-H), 1·22 (d, J = 6 Hz, 21-H), 1·96 and 2·02 (two s, acetates), 4·59 (mt, $W_{1/2}$ = 23 Hz, 3α-H), 5·28 to 5·53 (mt, 6-H and 20-H). IR spectrum: 3·075 (cyclopropane), 3 040 (double bond), 1 740, 1 248 . . cm^{-1} (acetate). For $C_{26}H_{38}O_4$ (414·6) calculated: 75·32% C, 9·24% H; found: 75·40% C, 9·23% H.

16α,17α-Cyclopropanopregn-4-ene-3,6,20-trione (*X*)

a) *From* 16α,17α-*cyclopropanopregn*-5-*ene*-3β,20α-*diol* (VII): Elution of the chromatography after isolation of the dione *VI* under *a*) with the same solvent mixture yielded fractions with the polar component. Working up, evaporation of the solvents, and crystallization from ethyl acetate gave 60 mg of the trione *X*, m.p. 230—232°C, $[\alpha]_D^{20}$ +49° (*c* 0·91). Mass spectrum: M$^{+\cdot}$ 340.

^{1}H NMR spectrum: 0·98 (s, 18-H), 1·15 (s, 19-H), 1·90 (s, 21-H), 6·16 (s, 6-H). IR spectrum: 3 085 (cyclopropane), 1 681, 1 609 cm^{-1} (α,β-unsaturated oxo group). For $C_{22}H_{28}O_3$ (340·5) calculated: 77·61% C, 8·29% H; found: 77·84% C, 8·23% H. Identical trione *X* was obtained as the sole product on protracted oxidation (15 min) with excess Jones' reagent under analogous conditions.

b) *From* 16α,17α-*cyclopropanopregn*-5-*ene*-3β,20β-*diol* (XI): Working up of the zones with the polar component after isolation of the dione *VI* under *b*) afforded a product which on crystallization from ethyl acetate gave 20 mg of the trione *X*, m.p. 230—232°C. Identical trione *X* was obtained as the sole product on protracted oxidation (15 min) of the diol *XI* with excess Jones' reagent under analogous conditions.

16α,17α-Cyclopropanopregn-5-ene-3β,20β-diol (*XI*)

a) *From* 5,16-*pregnadiene*-3β,20β-*diol* (IV): The olefin *IV* (500 mg) was submitted to the Simmons–Smith methylenation as described above for preparation of the cyclopropano derivative *VII* under *a*). Similar working up gave 350 mg of a crude product which on crystallization from ethyl acetate yielded 235 mg of the diol *XI*, m.p. 186—187°C, $[\alpha]_D^{20}$ —43° (*c* 1·64 in chloroform–methanol 1 : 1). ^{1}H NMR spectrum: 0·28—0·71 (mt, cyclopropane protons), 0·95 (s, 18-H), 0·90 (d, J = 7 Hz, 21-H), 1·01 (s, 19-H), 3·41 (mt, $W_{1/2}$ = 22 Hz, 3α-H), 4·40 (q, J = 6·5 Hz, 20-H), 5·32 (mt, $W_{1/2}$ = 8 Hz, 6-H). IR spectrum (KBr): 3 420, 1 090, 1 060, 1 048 (hydroxyl), 3 080, 3 030, 3 020 (double bond and cyclopropane ring), 1 660 cm^{-1} (carbonyl). For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·72% C, 10·35% H.

b) *From* 16α,17α-*cyclopropanopregn*-5-*ene*-3β,20β-*diol* 3-*acetate* (XII): The acetate *XII* (20 mg) was refluxed with a solution of potassium hydroxide (100 mg) in methanol (5 ml) for 90 min. Methanol was distilled off *in vacuo* and the residue was diluted with water. The product was taken into ether and the ethereal solution was washed with water, dried and solvent removed. The crude product was purified by preparative TLC (one plate in ligroin–ether 1 : 1) to yield after working up of the corresponding zone 16 mg of a product. Crystallization from methanol afforded 3·5 mg of the diol *XI*, m.p. 183—187°C, $[\alpha]_D^{20}$ —43° (*c* 1·19).

c) *From* 3β-*hydroxy*-16α,17α-*cyclopropanopregn*-5-*en*-20-*one* (XIV): Elution of the chromatography after isolation of the diol *VII* under *c*) afforded fractions with the polar product. Working up and removal of the solvents gave 68 mg of a product which on crystallization from methanol yielded 27 mg of the diol *XI*, m.p. 185—187°C, $[\alpha]_D^{20}$ —43° (*c* 0·72).

16α,17α-Cyclopropanopregn-5-ene-3β,20β-diol 3-Acetate (*XII*)

a) *From* 5,16-*pregnadiene*3β,20β-*diol* 3-*acetate* (V): The diol *V* (750 mg) was submitted to the Simmons–Smith methylenation as described for preparation of the diol *VII* under *a*). Similar working up yielded 700 mg of a product which was chromatographed on a silica gel column (60 g) in ligroin–ether (19 : 1; 300 ml) and then ligroin–ether (4 : 1). The corresponding fractions were worked up and the residue after evaporation of solvents was crystallized from ethyl acetate to yield 500 mg of the alcohol *XII*, m.p. 155°C (literature[7] records m.p. 140—144°C), $[\alpha]_D^{20}$ —69° (*c* 0·97). Mass spectrum: *m/z* 312 (M — CH_3COOH). ^{1}H NMR spectrum: 0·28—0·72 (mt, cyclopropane protons), 0·91 (d, J = 7 Hz, 21-H), 0·96 (s, 18-H), 1·03 (s, 19-H), 2·01 (s, acetate), 4·37 (q, J = 6·5 Hz, 20-H), 4·51 (mt, $W_{1/2}$ = 22 Hz, 3α-H), 5·32 (mt, $W_{1/2}$ = 8 Hz, 6-H). IR spectrum: 3 615 (hydroxyl), 3 075 (cyclopropane), 3 030, 3 020, 1 669 (double bond), 1 738, 1 248 cm^{-1} (acetate). For $C_{24}H_{36}O_3$ (372·5) calculated: 77·37% C, 9·74% H; found: 77·23% C, 9·68% H.

b) *From* 3β-*hydroxy*-16α,17α-*cyclopropanopregn*-5-*en*-20-*one* 3-*acetate* (XV): Elution of the chromatography after isolation of the alcohol *VIII* under *b*) afforded fractions with the polar alcohol. Working up gave a crude product (176 mg) which was crystallized from methanol to yield 111 mg of the alcohol *XII*, m.p. 153–155°C, $[\alpha]_D^{20}$ −67° (*c* 1·12).

16α,17α-Cyclopropanopregn-5-ene-3β,20β-diol 3,20-Diacetate (*XIII*)

The diol monoacetate *XII* (295 mg) in pyridine (10 ml) was acetylated with acetic anhydride (0·6 ml) for 18 h at room temperature. The mixture was decomposed with ice and water, and the product was isolated with ether. Usual working up and crystallization from methanol gave 169 mg of the diacetate *XIII*, m.p. 137–138,5°C, $[\alpha]_D^{20}$ 0° (*c* 0·66). ^{1}H NMR spectrum: 0·46–0·66 (mt, cyclopropane protons), 0·90 (d, J = 6 Hz, 21-H), 0·91 (s, 18-H), 1·02 (s, 19-H), 2·00 (s, acetates), 4·52 (mt, $W_{1/2}$ = 30 Hz, 3α-H), 5·23–5·64 (broad mt, 6-H and 20β-H). IR spectrum: 3 080 (cyclopropane), 1 731, 1 245 (acetate), 3 025, 1 668 cm^{-1} (double bond). For $C_{26}H_{38}O_4$ (414·6) calculated: 75·32% C, 9·24% H; found: 74·91% C, 9·18% H.

3β-Hydroxy-16α,17α-cyclopropanopregn-5-en-20-one (*XIV*)

A solution of the acetate *XV* (400 mg) in methanol (40 ml) was treated with a solution of potassium carbonate (400 mg) in water (4 ml) and allowed to stand at room temperature for 4 h. Methanol was distilled off under reduced pressure, the residue was diluted with water, and the product was taken into chloroform. The extract was washed with water, dried, and solvent removed. Crystallization from methanol afforded 270 mg of the alcohol *XIV*, m.p. 216–218°C, $[\alpha]_D^{20}$ +39° (*c* 1·96) in accordance with the literature[2]. ^{1}H NMR spectrum: 0·02 (mt) and 0·67–0·92 (mt, cyclopropane protons), 0·97 (s, 18-H), 1·02 (s, 19-H), 1·95 (s, 21-H), 2·62 (s, 3β-hydroxyl), 3·41 (mt, $W_{1/2}$ = = 25 Hz, 3α-H), 5·33 (mt, $W_{1/2}$ = 8·5 Hz, 6-H). IR spectrum: 3 615, 1 047 (hydroxyl), 3 085 (cyclopropane), 1 679, 1 367 cm^{-1} (carbonyl). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·28% H; found: 79·81% C, 9·84% H.

3β-Hydroxy-16α,17α-cyclopropanopregn-5-en-20-one 3-Acetate (*XV*)

a) *From* 3β-*hydroxypregna*-5,16-*dien*-20-*one* 3-*acetate* (I): A suspension of trimethyloxosulphonium iodide[24] (15·2 g) in dimethyl sulphoxide (152 ml) was stirred in a nitrogen atmosphere at room temperature until the iodide dissolved. The solution was then treated dropwise with a solution of sodium hydride (2·8 g) in dimethyl sulphoxide (56 ml) in the course of 30 min. The mixture was stirred at room temperature for additional 30 min, treated with a solution of the ketone *I* (10 g) in benzene (152 ml), and stirred in a nitrogen atmosphere for 3 h. The mixture was poured in water and the product was taken into chloroform. The organic layer was worked up and solvent removed. The residue (10 g) was dissolved in pyridine (50 ml) and acetic anhydride (30 ml) and allowed to stand at room temperature for 20 h. The excess anhydride was decomposed with ice and water and the product was isolated with ether as usual. Working up and crystallization from methanol afforded 6·07 g of the acetate *XV*; crystallization of the mother liquors gave additional 2·72 g of the acetate *XV* and 550 mg of a mixture of two compounds. They were separated by column chromatography over silica gel (200 g) in benzene–ether (49 : 1). Fractions with the lipophilic compound afforded after working up 320 mg of the acetate *XV*, to rise the yield to 9·11 g; m.p. 199–201°C, $[\alpha]_D^{20}$ +28° (*c* 4·29) in accordance with the literature[2–7]. Mass spectrum: m/z 310 (M − CH_3COOH). ^{1}H NMR spectrum: 0·66–0·92 (mt, cyclopropane protons), 1·00 (s, 18-H), 1·05 (s, 19-H), 1·96 (s, 21-H), 2·04 (s, acetate), 4·61 (mt, $W_{1/2}$ = 20 Hz, 3α-H), 5·40 (mt, $W_{1/2}$ = 8 Hz, 6-H). IR spectrum: 3 085, 3 040 (cyclopropane and double bond),

1 739, 1 248, 1 035 (acetate), 1 690 cm^{-1} (carbonyl). For $C_{24}H_{34}O_3$ (370·5) calculated: 77·79% C, 9·25% H; found: 78·06% C, 9·47% H.

b) *From* 16α,17α-*cyclopropanopregn*-5-*ene*-3β,20α-*diol* 3-*acetate* (VIII): A solution of the alcohol *VIII* (27 mg) in acetone (10 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 5 min. The excess reagent was removed with methanol, the mixture was diluted with water and the product was taken into ether. The ethereal solution was worked up and the residue after evaporation of the solvent was crystallized from methanol to yield 12 mg of the ketone *XV*, m.p. 199–201°C, $[\alpha]_D^{20}$ +28° (*c* 1·16).

c) *From* 16α,17α-*cyclopropanopregn*-5-*ene*-3β,20β-*diol* 3-*acetate* (XII): The alcohol *XII* (40 mg) was oxidized with Jones' reagent in acetone (10 ml) as described under *b*). Similar working up and crystallization from methanol yielded 22 mg of the ketone *XV*, m.p. 199–201°C, $[\alpha]_D^{20}$ +29° (*c* 1·12).

d) *From* 3β-*hydroxy*-16α,17α-*cyclopropanopregn*-5-*en*-20-*one* (XIV): The alcohol *XIV* (80 mg) in pyridine (2 ml) was acetylated with acetic anhydride (1·5 ml) for 18 h at room temperature. The mixture was decomposed with ice and water, the product was taken into ether and the ethereal solution was worked up. Crystallization from methanol afforded 55 mg of the acetate *XV*, m.p. 199–201°C, $[\alpha]_D^{20}$ +29° (*c* 1·15).

3β-Hydroxy-16β,17β-cyclopropanopregn-5-en-20-one 3-Acetate (*XVI*)

Elution of the chromatography after isolation of the adduct *XV* under *a*) with the same solvent mixture yielded fractions with the polar component. Combination and evaporation of the solvent and crystallization from ethyl acetate gave 171 mg of the acetate *XVI*, m.p. 161°C, $[\alpha]_D^{20}$ −128° (*c* 1·56). Mass spectrum: $M^{+\cdot}$ 370. ^{1}H NMR spectrum: 0·83 (s, 18-H), 1·03 (s, 19-H), 2·03 and 2·05 (two s, 21-H and acetate), 4·60 (mt, $W_{1/2}$ = 20 Hz, 3α-H), 5·36 (mt, $W_{1/2}$ = 8 Hz, 6-H). IR spectrum: 3 080, 3 035 (double bond and cyclopropane ring), 1 738, 1 247 (acetate), 1 693 cm^{-1} (carbonyl). For $C_{24}H_{34}O_3$ (370·5) calculated: 77·79% C, 9·25% H; found: 77·90% C, 8·82% H.

3β-Acetoxy-16α,17α-cyclopropanopregn-5-en-20α-yl-pyridinium Chloride (*XVII*)

a) *With pyridine and methanesulphonyl chloride*: A solution of the alcohol *VIII* (150 mg) in pyridine (5 ml) was cooled to 0°C and treated with methanesulphonyl chloride (0·3 ml). After 2 h at 0°C the mixture was poured into water and ice. The unreacted material was removed by extraction with ether and the aqueous layer was saturated with sodium chloride and extracted with chloroform. The chloroform extract was washed with 5% aqueous hydrochloric acid, water, 5% aqueous potassium hydrogen carbonate solution, water, dried and solvent removed. The residue (120 mg) was dissolved in methanol and the product was precipitated with ether. Yield 80 mg of the chloride *XVII*, m.p. 178–180°C (acetone), $[\alpha]_D^{20}$ −2° (*c* 1·77 in methanol). Mass spectrum: *m/z* 330 $(M - C_5H_5N{-}CH_3COOH)^{+\cdot}$. ^{1}H NMR spectrum: 0·92 (s, 18-H), 1·07 (s, 19-H), 1·46 (d, J = 7 Hz, 21-H), 1·99 (s, acetate), 4·49 (mt, $W_{1/2}$ = 19·5 Hz, 3α-H), 5·32 (mt, $W_{1/2}$ = 8 Hz, 6-H), 5·93 (mt, $W_{1/2}$ = 15 Hz, 20-H), 8·29 (dd, J = 7 Hz, J' = 7 Hz, two pyridine protons), 8·47 (dd, J = 7 Hz, J' = 15 Hz, one pyridine proton), 9·75 (d, J = 7 Hz, two pyridine protons). IR spectrum (KBr): 1 724, 1 260 (acetate), 1 631, 1 581, 786, 686 cm^{-1} (pyridinium chloride). For $C_{29}H_{49}ClNO_2$ (470·1) calculated: 7·54% Cl, 2·98% N; found: 7·02% Cl, 2·94% N.

b) *With pyridine and* p-*toluenesulphonyl chloride*: A solution of the alcohol *VIII* (217 mg) in pyridine (5 ml) was treated with *p*-toluenesulphonyl chloride (220 mg) and allowed to stand at

room temperature for 20 h. Fresh chloride (440 mg) was added and after 20 h the mixture was poured into ice and water and the product was isolated as described under *a*). The crude product was crystallized from acetone to yield 107 mg of the chloride *XVII*, m.p. 178–180°C, $[\alpha]_D^{20}$ 0° (*c* 0·74 in methanol).

16α,17α-Cyclopropano-20α-(1-(1,2,5,6-tetrahydropyridyl))-pregn-5-en-3β-ol 3-Acetate (*XVIII*)

The chloride *XVII* (180 mg) in water (2 ml) and methanol (150 mg) was treated with sodium borohydride (2 g) and allowed to stand at room temperature for 1 h. The mixture was poured into water and the product was taken into chloroform. The extract was washed with water, dried, and the solvent removed. The crude product was purified by preparative TLC (4 plates in ligroin–ether (2 : 3)). Working up of the corresponding zones yielded 48 mg of the amine *XVIII*, m.p. 135–137°C, $[\alpha]_D^{20}$ −26° (*c* 2·03). Mass spectrum: $M^{+\cdot}$ 437; basic peak: $C_7H_{12}N^{+\cdot}$ (*m/z* 110). ^{1}H NMR spectrum: 0·66 (d, J = 6·5 Hz, 21-H), 0·92 (s, 18-H), 1·04 (s, 19-H), 2·03 (s, acetate), 4·50 (mt, $W_{1/2}$ = 26 Hz, 3α-H), 5·34 (broad d, J = 5 Hz, 6-H), 5·68 (mt, protons in the heterocyclic ring). IR spectrum: 3 075, 3 035, 3 020, 1 665 (double bond and cyclopropane ring), 1 737, 1 248, 1 024 (acetate), 2 600–2 800 cm^{-1} (—N=). For $C_{29}H_{43}NO_2$ (437·6) calculated: 79·59% C, 9·90% H, 3·20% N; found: 79·47% C, 9·97% H, 3·38% N.

3β-Acetoxy-16α,17α-cyclopropanopregn-5-en-20α-yl-pyridinium Chloride (*XIX*)

a) *With pyridine and methanesulphonyl chloride*: The alcohol *XII* (190 mg) in pyridine (5 ml) was treated with methanesulphonyl chloride (0·38 ml) as described for the preparation of the chloride *XVII* under *a*). Similar working up and crystallization from acetone gave 145 mg of the chloride *XIX*, m.p. 195–200°C (subl., decomp.), $[\alpha]_D^{20}$ −47° (*c* 1·37 in methanol). Mass spectrum: $(M - CH_3COOH - C_5H_5N)^{+\cdot}$ 330. ^{1}H NMR spectrum: 0·27 (mt, $W_{1/2}$ = 5 Hz, one cyclopropane proton), 1·03 (s, 19-H), 1·23 (s, 18-H), 1·48 (d, J = 6·5 Hz, 21-H), 2·02 (s, acetate), 4·56 (mt, $W_{1/2}$ = 22 Hz, 3α-H), 5·35 (mt, $W_{1/2}$ = 8 Hz, 6-H), 5·84 (mt, $W_{1/2}$ = 32 Hz, 20-H), 8·40 (mt, $W_{1/2}$ = 15 Hz, three pyridine protons), 9·32 (mt, $W_{1/2}$ = 10 Hz, one pyridine proton), 9·79 (mt, $W_{1/2}$ = 11 Hz, one pyridine proton). IR spectrum (KBr): 1 731, 1 250 (acetate), 1 672 (double bond), 3 000–3 160, 1 632, 1 584, 787, 700 cm^{-1} (pyridinium chloride). For $C_{29}H_{40}ClNO_2$ (470·1) calculated: 7·54% Cl, 2·98% N; found: 8·28% Cl, 2·89% N.

b) *With pyridine and* p-*toluenesulphonyl chloride*: The alcohol *XII* (500 mg) in pyridine (10 ml) was treated with *p*-toluenesulphonyl chloride (500 mg) and set aside for 20 h. The mixture was worked up as described for preparation of the chloride *XVII* under *b*) to yield 320 mg of a product which on crystallization from acetone gave 65 mg of the chloride *XIX*, m.p. 195–200°C (decomp.).

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REFERENCES

1. Kohout L.: This Journal *46*, 1828 (1981).
2. Sandoval A., Rosenkranz G., Djerassi C.: J. Amer. Chem. Soc. *73*, 2383 (1951).

3. Wiechert R., Kaspar E.: Chem. Ber. *93*, 1710 (1960).
4. Ger. P. 1 107 663 (C.A. *56*, P 2492c).
5. Kocsis K., Ferrini P. G., Arigoni D., Jeger O.: Helv. Chim. Acta *43*, 2178 (1960).
6. Villotti R., Halpern O., Bowers A.: Gaz. Chim. Ital. *93*, 244 (1962).
7. Steinberg N. G.: J. Org. Chem. *44*, 2294 (1979).
8. Tseikinskii V. M., Rybakov V. B., Simonov V. I., Kamernitzky A. V., Ignatov V. N., Levina I. S.: Bioorg. Khim. *6*, 752 (1981).
9. Eberhardt U.: Pharmazie *30*, 280 (1975).
10. Ercoli A., de Ruggieri P.: Il Farmaco Scienza e Tecnica *7*, 11 (1952).
11. Ercoli A., de Ruggieri P.: Il Farmaco Scienza e Tecnica *7*, 129 (1952).
12. Ercoli A., de Ruggieri P.: Il Farmaco Scienza e Tecnica *7*, 287 (1952).
13. Shapiro E. L., Gould D., Hershberg E. B.: J. Amer. Chem. Soc. *77*, 2912 (1955).
14. Benn W. R.: J. Org. Chem. *28*, 3557 (1963).
15. Dauben W. G., Berezin G. H.: J. Amer. Chem. Soc. *85*, 468 (1963).
16. Schmidt O., Przewowsky K., Schulz G., Weichert R.: Chem. Ber. *101*, 939 (1968).
17. Gloor J., Schaffner K., Jeger O.: Helv. Chim. Acta *54*, 1864 (1971).
18. Dauben W. G., Fullerton D. S.: J. Org. Chem. *36*, 3277 (1971).
19. Amice P., Conia J. M.: C. R. Acad. Sci. Ser. C *271*, 948 (1970).
20. Wagner A. F.: *Thesis*. Princeton University, Princeton 1951.
21. Tadanier J.: J. Org. Chem. *31*, 2124 (1965).
22. Tadanier J.: Experientia *21*, 563 (1965).
23. Fieser L. F., Fieser M.: *Reagents for Organic Synthesis*, Vol. 1, p. 142. Wiley, New York 1967.
24. Corey E. J., Chaykovsky M.: J. Amer. Chem. Soc. *84*, 3782 (1962).

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