5,7-CYCLO-B-HOMOPREGNANE DERIVATIVES WITH AN OXYGEN FUNCTION IN POSITION 17α*

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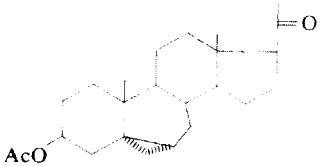
Synthesis of the isomeric 5,7-cyclo-B-homopregnane derivatives carrying an oxygen function in position 17α is described.

In the last paper[1] of this series we described synthesis of the isomeric 5,7-cyclo-B--homopregnane derivatives with an oxygen function in 21 position. In connection with these studies, compounds with an oxygen function at $C_{(17)}$ were of interest. In this paper we describe the synthesis of the isomeric 5,7-cyclo-B-homopregnane derivatives with a hydroxyl group in 17 position.

Identical reaction sequence was applied in the both isomeric series starting from the previously described ketones *I* or *VIII*, respectively: They were transformed into the enolacetates *II* and *IX* which on reaction with peracid afforded the epoxides *III* and *X*. Alkaline hydrolysis yielded the desired derivatives *IV* and *XI*. The reaction sequence was carried out without isolation of the intermediates.

Two methods of enolacetylation have been used with different results. Relatively low yields of the final products were obtained when this reaction was carried out in acetic anhydride under the presence of *p*-toluenesulphonic acid at 140°C. When a mild method[2] (ethyl acetate, acetic anhydride, perchloric acid, room temperature) was used, higher yields were obtained. We therefore studied the enolacetylation step more closely. When the crude diol *XI* obtained by the vigorous enolisation method was acetylated, besides the acetate *XII*, a new product was isolated by careful chromatography. Physicochemical evidence pointed to structure *XX* for this compound. Evidently, cleavage of the cyclopropane ring took place and the epoxide *XX* was formed through the intermediates *VIII*–*XVII*–*XVIII*–*XIX*. The attempts to isolate the intermediates were unsuccessful because of a very close polarity of the components in the reaction mixture. To prove our assumption analogous reaction was carried

* Part CLXXV in the series On Steroids; Part CLXXIV: This Journal *39*, 2828 (1974). Part XIV in the series B-Homosteroids; Part XIII: This Journal *39*, 1780 (1974).



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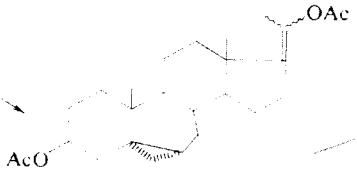

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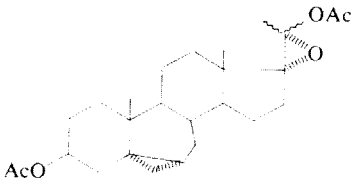

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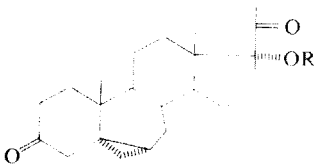

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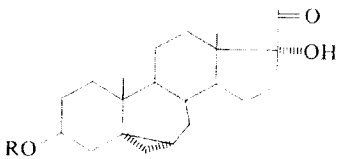
VII, R = Ac



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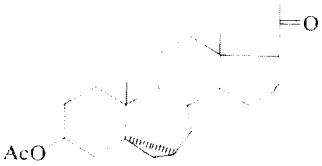
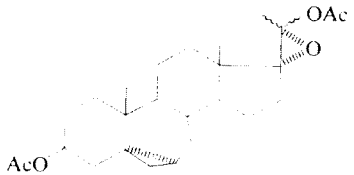
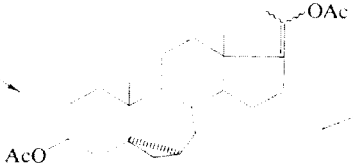
V, R = Ac



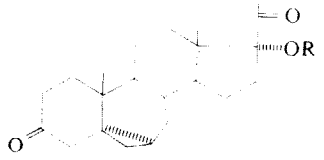
VIII



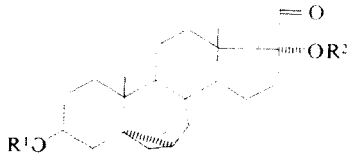
X



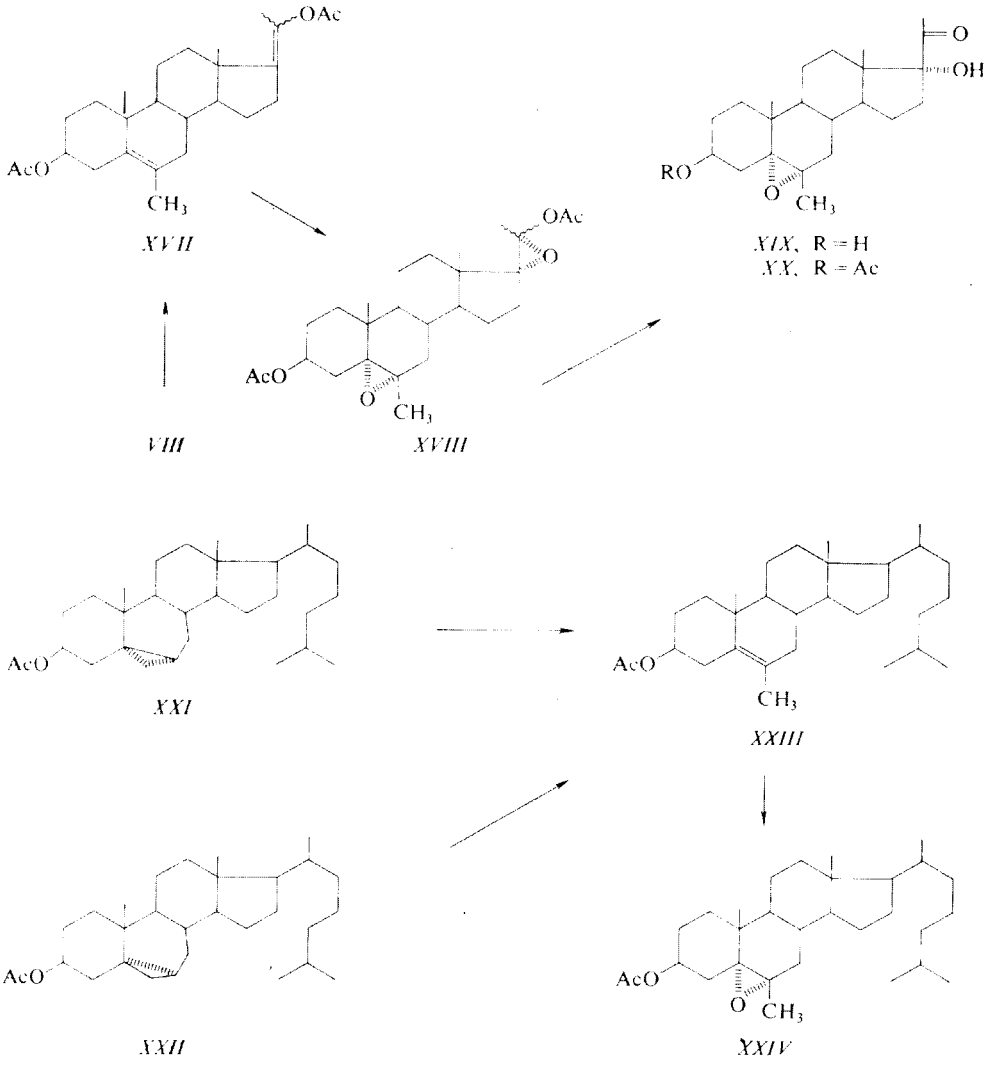
IX



XV, R = H
XVI, R = Ac



XI, $R^1 = R^2 = H$
XII, $R^1 = Ac$, $R^2 = H$
XIII, $R^1 = R^2 = Ac$
XIV, $R^1 = H$, $R^2 = Ac$



out in the cholestane series where the both isomeric 5,7-cyclo-B-homocholestanes *XXI* and *XXII* when exposed to the drastic enolisation conditions afforded the known olefin[3] *XXIII* in good yield; peracid oxidation gave the α-epoxide[4] *XXIV*.

The dione-acetates *VII* and *XVI* which were required for biological assays were obtained from the diols *IV* and *XI* by Jones' oxidation followed by acetylation.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 80°C/0·2 Torr. Optical measurements were carried out in chloroform with an error of ±1°. The infrared spectra were recorded on the Zeiss UR 10 spectrometer in chloroform unless otherwise stated. The NMR spectra were recorded on the Varian HA-100 instrument in chloroform and corrected to tetramethylsilane (7·25 p.p.m.) unless otherwise stated. The chemical shift is given in p.p.m. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin-layer chromatography (TLC), and by infrared spectra. Ligroin of b.p. 40–60°C was used as solvent. Working up of an ethereal solution means extraction with 5% hydrochloric acid, water, 5% sodium hydrogen carbonate solution, water, drying with magnesium sulphate, and evaporation of the solvent. The mass spectra were recorded on the mass spectrometer AEI MS 902.

3β,17α-Dihydroxy-5,7β-cyclo-B-homo-5β-pregnan-20-one (*IV*)

A) The ketone[1] *I* (1·8 g) was dissolved in acetic anhydride (40 ml), *p*-toluenesulphonic acid was added (600 mg) and 30 ml of the mixture were distilled off within 2·5 hours. The mixture was evaporated to dryness under reduced pressure, the residual acetic anhydride was decomposed with ice and pyridine, and the product was taken into ether. The ethereal solution was worked up, and the residue after evaporation of the solvent was dissolved in ligroin–ether (9 : 1), and filtered over alumina column (50 g). The oily product (crude enolacetate *II*) was dissolved in benzene (40 ml), treated with a solution of perphthalic acid (3·3 g) in ether (30 ml) and allowed to stand at room temperature for 20 hours. The reaction mixture was diluted with ether, the excess peracid was removed with 5% sodium carbonate solution and the ethereal solution was washed with water, dried, and the solvent distilled off. The mixture of isomeric epoxides *III* was dissolved in ethanol (133 ml) at 60°C, treated with a solution of sodium hydroxide (750 mg) in ethanol (40 ml) and water (80 ml). After 30 minutes at the same temperature the reaction mixture was cooled off to room temperature, solvents were removed under reduced pressure, and the residue was treated with water. The product was extracted with ethyl acetate and the organic layer was washed with water, dried, and the solvent was removed. Crystallisation from dioxan (33 ml) and ethyl acetate (40 ml) gave 560 mg of the diol *IV*, m.p. 251–254°C, $[\alpha]_D^{20}$ −81° (chloroform–methanol 1 : 1; *c* 0·50). IR (nujol): 3490, 3340, 3065, 1690 cm^{-1}. For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·51% C, 10·09% H.

B) The ketone *I* (1·8 g) in ethyl acetate (46 ml) was treated with acetic anhydride (4·8 ml) and 72% perchloric acid (0·05 ml) and allowed to stand at room temperature for 6 hours. The acids were removed with a sodium hydrogen carbonate solution, and the solvent was distilled off. The residue, crude enol acetate *II*, was dissolved in benzene (40 ml) and treated with perphthalic acid and then hydrolysed with ethanolic sodium hydroxide as given in the previous experiment. Crystallisation from dioxan–ethyl acetate afforded 1·2 g of the diol *IV*, m.p. 252–254°C, $[\alpha]_D^{20}$ −83° (chloroform–methanol 1 : 1; *c* 0·50).

3β-Acetoxy-17α-hydroxy-5,7β-cyclo-B-homo-5β-pregnan-20-one (*V*)

Diol *IV* (60 mg) in pyridine (2·5 ml) was acetylated with acetic anhydride (1·5 ml) for 18 hours at room temperature. The reaction mixture was decomposed with ice, the product was isolated with ether, and the ethereal solution was worked up. The residue was crystallised from methanol to yield 20 mg of the monoacetate *V*, m.p. 203–204°C, $[\alpha]_D^{20}$ −73° (*c* 2·00). IR: 3610, 3510, 3070, 1721, 1710, 1690, 1357, 1254 cm^{-1}. For $C_{24}H_{36}O_4$ (388·5) calculated: 74·19% C, 9·34% H; found: 73·97% C, 9·24% H.

17α-Hydroxy-5,7β-cyclo-B-homo-5β-pregnan-3,20-dione (*VI*)

A solution of the diol *IV* (500 mg) in acetone (70 ml) and dioxan (100 ml) was treated with excess Jones' reagent. After 10 minutes at room temperature the excess oxidising agent was removed with methanol, the mixture was diluted with water, and the product extracted into ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallised from methanol to yield 340 mg of the ketone *VI*, m.p. 231—233°C, $[\alpha]_D^{20}$ —32° (*c* 2·60). IR: 3615, 3510, 3075, 1705, 1695, 1420, 1355 cm^{-1}. For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 77·12% C, 9·38% H.

17α-Acetoxy-5,7β-cyclo-B-homo-5β-pregnan-3,20-dione (*VII*)

The alcohol *VI* (300 mg) in acetic acid (15 ml) was acetylated with acetic anhydride (5ml) under the presence of *p*-toluenesulphonic acid (400 mg) at room temperature for 3 hours. The mixture was diluted with dichloromethane, washed with water, a sodium hydrogen carbonate solution, water, the organic layer was dried, and solvent removed. Crystallisation from methanol gave 195 mg of the acetate *VII*, m.p. 217—220°C, $[\alpha]_D^{20}$ —51° (*c* 1·32). IR: 3075, 1729, 1708, 1353, 1256 cm^{-1}. Mass spectrum: M^+ 386. NMR: 0·17 to 0·42 (m, two cyclopropane protons), 0·71 (s, 18-H), 1·28 (s, 19-H), 2·03 (s, acetate), 2·11 (s, 21-H), 3·01 (d, J_{gem} = 15·5 Hz, 4-H, one proton). For $C_{24}H_{34}O_4$ (386·5) calculated: 74·59% C, 8·87%H; found: 74·51% C, 8·73% H.

3β, 17α-Dihydroxy-5,7α-cyclo-B-homo-5α-pregnan-20-one (*XI*)

A) The ketone[1] *VIII* (1·9 g) in acetic anhydride (40 ml) was treated with *p*-toluenesulphonic acid (600 mg) similarly as described for the 5β-isomer *IV*. Working up, filtration over alumina and evaporation of the solvent left 1·6 g of oily enol acetate *IX* which was transformed with monoperphthalic acid in benzene to the mixture of epoxides *X*. The epoxides were hydrolysed with sodium hydroxide (800 mg) in ethanol (170 ml)-water (80 ml) at 60°C for 30 minutes. Working up and crystallisation from dioxan (33 ml) and ethyl acetate (40 ml) afforded 650 mg of the diol *XI*, m.p. 235—237°C, $[\alpha]_D^{20}$ —21° (*c* 1·50 in chloroform–methanol 1 : 1). IR (nujol): 3440, 3305, 3065, 1702, 1350 cm^{-1}. For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·53% C, 9·75% H.

B) The ketone *VIII* (1·9 g) in ethyl acetate (46 ml) was treated similarly as given for the preparation of the 5β-isomer *IV*. Identical working up, epoxidation, and hydrolysis afforded a product which on crystallisation from dioxan–ethyl acetate gave 1·1 g of the ketone *XI*, m.p. 235—237°C, $[\alpha]_D^{20}$ —22° (*c* 1·45 in chloroform–methanol 1 : 1).

3β-Acetoxy-17α-hydroxy-5,7α-cyclo-B-homo-5α-pregnan-20-one (*XII*)

The crude diol *XI* (900 mg) obtained from the ketone *VIII* according to the *A* was acetylated with acetic anhydride (7 ml) in pyridine (10 ml) for 6 hours at room temperature. Usual working up yielded a product (800 mg) which was chromatographed on a silica gel column (100 g) in benzene–ether (19 : 1). Fractions containing the lipophilic product were combined, evaporated, and the residue was crystallised from n-heptane to yield 310 mg of the acetate *XII*, m.p. 139—140°C, $[\alpha]_D^{20}$ —28° (*c* 1·72). IR: 3610, 3510, 3073, 1718, 1690, 1358, 1257 cm^{-1}. For $C_{24}H_{36}O_4$ (388·5) calculated: 74·19% C, 9·34% H; found: 74·12% C, 9·43% H.

3β, 17α-Diacetoxy-5,7α-cyclo-B-homo-5α-pregnan-20-one (*XIII*)

A solution of the diol *XI* (800 mg) in acetic acid (30 ml) and acetic anhydride (10 ml) was treated with *p*-toluenesulphonic acid (800 mg) and set aside for 2 hours. The mixture was decomposed

with ice containing 10 ml of pyridine, and the product was extracted with dichloromethane. The extract was worked up and solvent distilled off. The residue was crystallised from chloroform–methanol to yield 520 mg of the diacetate *XIII*, m.p. 189–191°C, $[\alpha]_D^{20}$ −22° (*c* 1·40). IR (tetrachloromethane): 3075, 1737, 1720, 1354, 1250 cm^{-1}. For $C_{26}H_{38}O_5$ (430·6) calculated: 72·52% C, 8·90% H; found: 72·24% C, 8·81% H.

3β-Hydroxy-17α-acetoxy-5,7α-cyclo-B-homo-5α-pregnan-20-one (*XIV*)

A solution of the diacetate *XIII* (480 mg) in methanol (150 ml) was refluxed with conc. hydrochloric acid (1 ml) for 2 hours. The mixture was diluted with ethyl acetate, washed with a sodium hydrogen carbonate solution, water, dried, and the solvent distilled off. The residue (420 mg) was crystallised from chloroform–methanol to yield 270 mg of the alcohol *XIV*, m.p. 199–200°C, $[\alpha]_D^{20}$ −29° (*c* 1·23). IR (tetrachloromethane): 3625, 3500, 3075, 1737, 1719, 1353, 1248 cm^{-1}. For $C_{24}H_{36}O_4$(388·5) calculated: 74·19% C, 9·34% H; found: 74·17% C, 9·29% H.

17α-Hydroxy-5,7α-cyclo-B-homo-5α-pregnan-3,20-dione (*XV*)

A solution of the diol *XI* (75 mg) in acetone (8 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 minutes. The excess reagent was removed with methanol, the mixture was diluted with water, and the product isolated with ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and solvent removed. The residue was crystallised from ethanol to yield 52 mg of the dione *XV*, m.p. 242 to 244°C, $[\alpha]_D^{20}$ +52° (*c* 1·54). IR: 3610, 3475, 3073, 1710, 1690, 1356 cm^{-1}. NMR: 0·18 (dd, $J = 5$ Hz, $J' = 9$ Hz, one cyclopropane proton), 0·38 (t, $J = 5$ Hz, one cyclopropane proton), 0·70 (s, 18-H), 0,97 (s, 19-H), 2·26 (s, 21-H), 2·80 (d, $J_{gem} = 16$ Hz, 4-H, one proton). For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·69% C, 9·41% H.

17α-Acetoxy-5,7α-cyclo-B-homo-5α-pregnan-3,20-dione (*XVI*)

a) *From* 3β-*hydroxy*-17α-*acetoxy*-5,7α-*cyclo*-B-*homo*-5α-*pregnan*-20-*one* (XIV): The alcohol *XIV* (320 mg) in acetone (20 ml) was oxidised with excess Jones' reagent and worked up in the usual way as described in the previous experiment. The crude product was chromatographed on a silica gel column (30 g) in ligroin–ether (9 : 1). The corresponding fractions were combined, evaporated, and the residue was crystallised from methanol to yield 284 mg of the dione *XVI*, m.p. 208–209°C, $[\alpha]_D^{20}$ −70° (*c* 1·54). IR: 3075, 1730, 1715, 1353, 1255 cm^{-1}. Mass spectrum: M^+ 386. NMR: 0·19 (dd, $J = 5$ Hz, $J' = 9$ Hz, one cyclopropane proton), 0·38 (t, $J = 5$ Hz, one cyclopropane proton), 0·62 (s, 18-H), 0·98 (s, 19-H), 1·39 (d, $J_{gem} = 16$ Hz, 4β-H, one proton), 2·03 (s, acetate), 2·12 (s, 21-H), 2·82 (d, $J_{gem} = 16$ Hz, 4α-H, one proton). For $C_{24}H_{34}O_4$ (386·5) calculated: 74·58% C, 8·87% H; found: 74·61% C, 8·87% H.

b) *From* 17α-*hydroxy*-5,7α-*cyclo*-B-*homo*-5α-*pregnan*-3,20-*dione* (XV): The alcohol *XV* (27 mg) in acetic acid (1·5 ml) was acetylated with acetic anhydride (0·5 ml) under the presence of *p*-toluenesulphonic acid (20 mg) for 3 hours at room temperature. The mixture was decomposed with ice, the product taken into dichloromethane, and the organic layer was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallised from ethanol to yield 11 mg of the acetate *XVI*, m.p. 207–209°C, $[\alpha]_D^{20}$ −71° (*c* 1·37).

3β-Acetoxy-5,6α-epoxy-6β-methyl-17α-hydroxy-5α-pregnan-20-one (*XX*)

Elution of the chromatography after isolation of the alcohol *XII* with the same solvent mixture afforded fractions with the polar component. Combination and evaporation of the corresponding

fractions gave 300 mg of the epoxide *XX*, m.p. 87–88°C (acetone–ligroin), $[\alpha]_D^{20}$ −52° (*c* 1·65). IR: 3610, 3505, 1728, 1706, 1690, 1252 cm^{-1}. Mass spectrum: M^+ 404. NMR: 0·65 (s, 18-H), 1·06 (s, 19-H), 1·26 (s, 6β-methyl), 2·03 (s, acetate), 2·24 (s, 21-H), 4·90 (m, W = 30 Hz, 3α-H). For $C_{24}H_{36}O_5$ (404·5) calculated: 71·25% C, 8·97% H; found: 71·00% C, 8·81% H.

3β-Acetoxy-6-methyl-5-cholestene (*XXIII*)

a) *From* 3β-*acetoxy*-5,7β-*cyclo*-B-*homo*-5β-*cholestane* (XXI): The acetate[5] *XXI* (150 mg) in acetic anhydride (20 ml) was refluxed under the presence of *p*-toluenesulphonic acid (200 mg) for 5 hours. The anhydride was distilled off under reduced pressure, the residue was decomposed with ice and pyridine, and the product was taken into ether. The ethereal solution was worked up and the product purified on two plates of silica gel (20 × 20 cm) in ligroin–benzene (1 : 1). Crystallisation from methanol afforded 73 mg of the olefin *XXIII*, m.p. 115–117°C, $[\alpha]_D^{20}$ −49° (*c* 1·34) in accordance with the literature[3]. IR (tetrachloromethane): 1734, 1243 cm^{-1}. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·02% C, 11·40% H.

b) *From* 3β-*acetoxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane* (XXII): The acetate[5] *XXII* (100 mg) in acetic anhydride (20 ml) was refluxed under the presence of *p*-toluenesulphonic acid (100 mg) for 5 hours. The mixture was worked up as described in the previous experiment and the product purified by preparative TLC. Crystallisation from methanol yielded 48 mg of the olefin *XXIII*, m.p. 114–116°C, $[\alpha]_D^{20}$ −48° (*c* 1·54).

3β-Acetoxy-5,6α-epoxy-6β-methyl-5α-cholestane (*XXIV*)

The olefin *XXIII* (150 mg) in benzene (4 ml) was treated with monoperphthalic acid (300 mg) in ether (3 ml) and allowed to stand for 18 hours at room temperature. The excess peracid was extracted into 5% sodium carbonate solution, the organic layer was washed with water, dried, and solvent removed. The residue was crystallised from methanol to yield 75 mg of the epoxide *XXIV*, m.p. 140–141°C, $[\alpha]_D^{20}$ −29° (*c* 1·26) in agreement with the literature[4]. NMR: 0·61 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26- and 27-H), 0·88 (d, J = 6 Hz, 21-H), 1·04 (s, 19-H), 1·24 (s, 6β-methyl), 2·01 (s, acetate), 4·89 (broad mt, 3α-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H, found: 78·63% C, 10·96% H.

The analyses were carried out in the Analytical Laboratory of this Institute by Mr V. Štěrba, Mrs V. Rusová and Mrs E. Sýkorová under the direction of Dr J. Horáček. The infrared spectra were recorded by Mr P. Formánek under the direction of Dr S. Vašíčková. The NMR spectra were recorded and interpreted by Dr M. Buděšínský. The mass spectra were recorded by Dr A. Trka.

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