5,7-CYCLO-B-HOMOPREGNANE DERIVATIVES WITH AN OXYGEN FUNCTION IN POSITION 21*

A. MIRONOWICZ,** L. KOHOUT and J. FAJKOŠ

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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Synthesis of the isomeric 5,7-cyclo-B-homopregnane derivatives carrying an oxygen function in position 21 is described and structure of these compounds established by spectral means.

In a recent paper[1] of this series we described the synthesis of analogues of androgens with the 5,7-cyclo-B-homosteroid skeleton. In the course of our studies of the relationship between the structure and pharmacodynamical activity analogues of gestagens and corticoids of this type were of potential interest. In this paper we describe the synthesis of such analogues of progesterone and cortexone.

We set out from pregnenolone acetate (*I*) which was submitted to Simmons–Smith methylenation. The reaction mixture contained mainly unchanged starting material which was separated in the form of the 5,6-epoxide. The cyclosteroid fraction was separated by careful chromatography into the isomers *III* and *V* the yields being 5% of the 5β-compound *III* and 6·5% of the 5α-isomer *V*. Their structure follows from the NMR evidence; the data are presented in Table I. The acetates were hydrolysed to the alcohols *II* and *IV* respectively. Their oxidation afforded the diones *VI* and *VII* which may be regarded as analogues of progesterone. In order to prepare the analogues of cortexone the acetates *III* and *V* were treated with lead tetraacetate in acetic acid–acetic anhydride solution and the resulting 21-acetates *IX* and *XIII* were hydrolysed to the diols *VIII* and *XII*. Oxidation with N-bromo acetamide[2] in tert-butanol gave the desired ketones *X* and *XIV* which were also characterised as the acetates *XI* and *XV*.

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** Present address: Academy of Agriculture, Wroclaw, Poland.

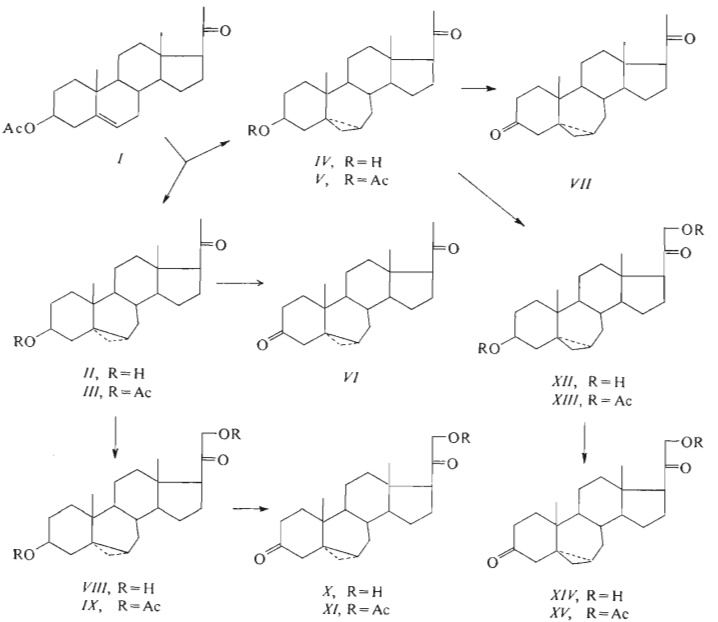

TABLE I

Chemical Shift Values (p.p.m.) for 19-Methyl Signals[a]

Compound	19-H	Δ
5α-Cholestan-3β-ol[3]	0·81	0
5,7α-Cyclo-B-homo-5α-cholestan-3β-ol[4]	0·88	+0·07
5,7β-Cyclo-B-homo-5β-cholestan-3β-ol[4]	1·21	+0·40
3β-Hydroxy-5α-pregnan-20-one	0·81	0
3β-Hydroxy-5,7α-cyclo-B-homo-5α-pregnan-20-one (*IV*)	0·88	+0·07
3β-Hydroxy-5,7β-cyclo-B-homo-5β-pregnan-20-one (*II*)	1·07	+0·26

[a] Solvent deuteriochloroform, tetramethylsilane as internal reference, Varian HA-100 instrument.

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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 tetrachloromethane 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, water, drying with magnesium sulphate, and evaporation of the solvent. The mass spectra were recorded on the mass spectrometer AEI MS 902.

3β-Hydroxy-5,7β-cyclo-B-homo-5β-pregnan-20-one (*II*)

A solution of the acetate *III* (115 mg) in methanol (10 ml) was treated with a solution of potassium carbonate (115 mg) in water (1·5 ml) and allowed to stand at room temperature for 20 hours. Methanol was removed under reduced pressure and the product taken into ether. The ethereal solution was washed with water, dried, and ether distilled off. The residue (105 mg) was crystallised from methanol to yield 55 mg of the alcohol *II*, m.p. 219—221°3C, $[\alpha]_D^{20}$ +17° (*c* 1·04). IR: 3615 (hydroxyl), 3070 (cyclopropane), 1700, 1360 cm^{-1} (17β-acetyl). NMR: 0·14 (dd, J = = 9 Hz, J' = 4·5 Hz, one cyclopropane proton), 0·32 (dt, J = 4·5 Hz, J' = 2 Hz, one cyclopropane proton), 0·55 (s, 18-H), 1·07 (s, 19-H), 2·08 (s, 21-H) 2·45 (broad t, 17α-H), 3·72 (broad mt, W = 32 Hz, 3α-H). For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·35% C, 10·67% H.

3β-Acetoxy-5,7β-cyclo-B-homo-5β-pregnan-20-one (*III*)

0·7% Zn–Cu couple was prepared by adding zinc dust (52 g) into a solution of cupric acetate monohydrate (1·2 g) in acetic acid (50 ml) at 50—60° and shaking until the solution decolorised. Acetic acid (50 ml) was added and the sedimented zinc was decanted with eight portions of ether (80 ml each). The couple was transferred to an autoclave, a solution of the olefin *I* (15 g) in ether (250 ml) and diiodomethane (46 ml) were added, and heated to 100°C for 6 hours. After cooling off to room temperature the remaining metal was filtered off, washed with ether, and the filtrate was poured into 5% sodium hydrogen carbonate. The ethereal layer was washed with water, 5% hydrochloric acid, a sodium hydrogen carbonate solution, 10% sodium thiosulphate, water dried, and evaporated. The residue was chromatographed over silica gel (150 g) in ether–ligroin (1 : 4). Fractions containing the starting olefin and the desired product (identical polarity) were combined and evaporated to yield 8 g of an oil. It was dissolved in ether (200 ml) and treated with a solution of perphthalic acid (8 g) in ether (80 ml). After 18 hours at room temperature the excess peracid was removed with a sodium carbonate solution. The ethereal layer was washed with water, dried, and ether distilled off. The residue (8·5 g) was chromatographed on a silica gel column (400 g) in ether–ligroin (19 : 1). Fractions containing the lipophilic component were combined and evaporated, and the residue (845 mg) was crystallised from ligroin to yield 750 mg of the acetate *III*, m.p. 340—342°C, $[\alpha]_D^{20}$ +3° (*c* 2 . 10). Mass spectrum: M^+ 372. IR: 3065 (cyclopropane), 1735, 1247, 1033 (acetate), 1709, 1360 cm^{-1} (17β-acetyl). NMR: 0·24 (dd, J = = 9 Hz, J' = 4·5 Hz, one cyclopropane proton), 0·35 (dt, J = 4·5 Hz, J' = 1·5 Hz, one cyclopropane proton), 0·55 (s, 18-H), 1·08 (s, 19-H), 1·98 (s, 3β-acetate), 2·07 (s, 21-H), 2·45 (mt,

17α-H), 4·82 (broad mt, $W = 32$ Hz, 3α-H). For $C_{24}H_{36}O_3$ (372·5) calculated: 77·37% C, 9·74% H; found: 77·06% C, 9·64% H.

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

The acetate *V* (215 mg) in methanol (20 ml) was treated with a solution of potassium carbonate (215 mg) in water (2·5 mg) and set aside at room temperature for 20 hours. Methanol was distilled off under reduced pressure, the product extracted into ether, the ethereal solution was washed with water, dried, and ether was distilled off. The residue (200 mg) was crystallised from acetone to yield 162 mg of the alcohol *V*, m.p. 148–152°C, $[\alpha]_D^{20}$ +33° (*c* 0·72). IR: 3625, 1038 (hydroxyl), 3075 (cyclopropane), 1709, 1355 cm^{-1} (carbonyl). NMR: −0·07 (dd, $J = 8·5$ Hz, $J' = 4·5$ Hz, one cyclopropane proton), 0·30 (t, $J = 4·5$ Hz, one cyclopropane proton), 0·57 (s, 18-H), 0·88 (s, 19-H), 2·08 (s, 21-H), 2·47 (broad t, 17α-H), 3·85 (broad mt, $W = 27$ Hz, 3α-H). For $C_{22}·H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·58% C, 10·44% H.

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

Elution of the chromatography after isolation of the 5β-isomer *III* with ether–ligroin (19:1) afforded fractions with the polar adduct. Working up and evaporation yielded 1·93 g of a product which was crystallised from methanol–water to afford 950 mg of the acetate *V*, m.p. 81–85°C, $[\alpha]_D^{20}$ +63° (*c* 1·28). Mass spectrum: M^+ 372. IR: 1738, 1248, 1300 (acetate), 1709, 1360 (carbonyl), 3070 cm^{-1} (cyclopropane). NMR: −0·07 (dd, $J = 4$ Hz, $J' = 4·5$ Hz, one cyclopropane proton), 0·29 (t, $J = 4·5$ Hz, one cyclopropane proton), 0·56 (s, 18-H), 0·87 (s,19-H), 1·99 (s, 21-H), 2·08 (s, 3β-acetate), 2·47 (broad t, 17α-H), 5·39 (broad mt, $W = 30$ Hz, 3α-H). For $C_{24}H_{36}O_3$ (372·5) calculated: 77·37% C, 9·47% H; found: 77·45% C, 9·60% H.

5,7β-Cyclo-B-homo-5β-pregnan-3,20-dione (*VI*)

The alcohol *II* (530 mg) in acetone (20 ml) was treated with excess Jones'reagent and allowed to stand at room temperature for 10 minutes. The excess oxidising agent was removed with methanol, the reaction 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 ether distilled off. The residue (390 mg) was crystallised from methanol to yield 260 mg of the ketone *VI*, m.p. 202–204°C, $[\alpha]_D^{20}$ +54° (*c* 1·79). IR: 3070 (cyclopropane), 1710 (carbonyl), 1700, 1360 cm^{-1} (17β-acetyl). NMR: 0·22 (dd, $J = 9$ Hz, $J' = 4·5$ Hz, one cyclopropane proton), 0·32 (dt, $J = 4·5$ Hz, $J' = 1·5$ Hz, one cyclopropane proton), 0·57 (s, 18-H), 1·25 (s, 19-H), 1·25 and 2·98 (two dd, $J = 15·5$ Hz, J' 1·5 Hz, 4-H), 2·08 (s, 21-H). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·80% C, 9·60% H.

5,7α-Cyclo-B-homo-5α-pregnan-3,20-dione (*VII*)

A solution of the alcohol *III* (600 mg) in acetone (100 ml) was treated with excess Jones'reagent. After 10 minutes at room temperature the excess reagent was destroyed with methanol, the reaction mixture was diluted with water, and the product extracted with ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried and the solvent distilled off. The residue was crystallised from acetone to yield 340 mg of the ketone *IV*, m.p. 191–193°C, $[\alpha]_D^{20}$ +184° (*c* 1·31). IR: 3072 (cyclopropane), 1725 (3-carbonyl), 1710, 1356 cm^{-1} (17β-acetyl). NMR: 0·15 (dd, $J = 9$ Hz, $J' = 5$ Hz, one cyclopropane proton), 0·35 (t, $J = 5$ Hz, one cyclo-

propane proton), 0·59 (s, 18-H), 0·95 (s, 19-H), 1·37 and 2·78 (two d, $J = 16$ Hz, 4-H), 2·09 (s, 21-H). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·01% C, 10·03% H.

3β,21-Dihydroxy-5,7β-cyclo-B-homo-5β-pregnan-20-one (*VIII*)

The diacetate *IX* (900 mg) in methanol (170 ml) was refluxed with a solution of potassium carbonate (900 mg) in water (33 ml) under nitrogen for 20 minutes. Methanol was removed under reduced pressure, the residue was diluted with water, and the product taken into chloroform. The extract was washed with water, dried, and the solvent removed. The residue was crystallised from ethyl acetate to yield 700 mg of the alcohol *IX*, m.p. 209—214°C, $[\alpha]_D^{20}$ −2° (*c* 1·40). IR: 3065 (cyclopropane), 3615, 1076, 1063, 1038 (hydroxyl), 1705 cm^{-1} (carbonyl). NMR: 0·16 (dd, one cyclopropane proton), 0·33 (broad *t*, one cyclopropane proton), 0·68 (s, 18-H), 1·08 (s, 19-H), 3·75 (broad mt, 3-H), 4·16 (s, 21-H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 75·95% C, 9·92% H.

3β,21-Diacetoxy-5,7β-cyclo-B-homo-5β-pregnan-20-one (*IX*)

The acetate *III* (3·7 g) in acetic acid (77 ml) and acetic anhydride (2·6 ml) was heated to 75°C with lead tetraacetate (3·52 g) under stirring for 4 1/2 hours. Acetic acid was distilled off under reduced pressure, the residue extracted with chloroform and the extract was worked up. The residue was chromatographed on a silica gel column (300 g) in ligroin–ether (9 : 1). Fractions with the starting material afforded 2·6 g of the acetate *III*, fractions with the polar component were worked up to yield after crystallisation from methanol 920 mg of the diacetate *IX*, m.p. 152—154°C, $[\alpha]_D^{20}$ −45° (*c* 1·32). IR: 3070 (cyclopropane), 1735, 1245, 1032 (3-acetate), 1755, 1735, 1230, 1218 cm^{-1} (21-acetate). NMR: 0·16—0·43 (mt, two cyclopropane protons), 0·59 (s, 18-H), 1·09 (s, 19-H), 1·99 (s, acetate), 2·04 (s, acetate), 4·47 and 4·71 (two d, $J_{gem} = 17{\cdot}5$ Hz, CH_2—O—) 4·82 (broad mt, 3α-H). For $C_{26}H_{38}O_5$ (430·6) calculated: 72·52% C, 8·90% H; found: 72·38% C, 8·90% H.

21-Hydroxy-5,7β-cyclo-B-homo-5β-pregnan-3,20-dione (*X*)

The diol *VIII* (1 g) in tert-butanol (150 ml) was treated with water (1·65 ml) and N-bromoacetamide (910 mg) and allowed to stand at room temperature for 21 hours. Butanol was distilled off at room temperature, the residue was diluted with water, and the product was isolated with ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and ether removed. The residue was chromatographed on a silica gel column in ligroin–ether (3 : 1). Fractions with the polar component were combined, evaporated, and the residue was crystallised from acetone to yield 190 mg of the dione *X*, m.p. 194—195°C, $[\alpha]_D^{20}$ +45° (*c* 1·18). IR: 3070 (cyclopropane), 3615 (hydroxyl), 1707 cm^{-1} (carbonyl). NMR: (deuteriochloroform with tetramethylsilane as internal reference): 0·20—0·40 (overlapping mt, two cyclopropane protons), 0·63 (s, 18-H), 1·28 (s, 19-H), 3·00 (broad d, 4-H, one proton, $J = 15$ Hz), 3·23 (broad t, hydroxyl), 4·18 (d, $J_{21,OH} = 3{\cdot}5$ Hz, 21-H). For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·47% C, 9·34% H.

21-Acetoxy-5,7β-cyclo-B-homo-5β-pregnan-3,20-dione (*XI*)

The alcohol *X* (50 mg) in pyridine (2 ml) was acetylated with acetic anhydride (0·6 ml) at room temperature for 18 hours. The reaction mixture was decomposed with ice, the product taken into ether, and the ethereal solution was worked up. The residue was chromatographed on one

plate of silica gel (20 × 20 cm) in ligroin–ether (2 : 1). The zones with the acetate were collected, the product eluted with ether, and the solvent was removed. The residue was crystallised from methanol to yield 35 mg of the acetate *XI*, m.p. 162–164°C, $[\alpha]_D^{20}$ +102° (*c* 1·32). IR: 3070 (cyclopropane), 1718 (carbonyl), 1754, 1728, 1230 cm^{-1} (acetoxy-carbonyl). NMR: (deuteriochloroform with tetramethylsilane as internal reference): 0·35 (mt, cyclopropane protons). 0·64 (s, 18-H), 1·28 (s, 19-H), 2·17 (s, acetate), 3·01 (broad d, one proton, J_{gem} = 15 Hz, 4-H), 4·51 and 4·75 (two d, J_{gem} = 17 Hz, 21 H). For $C_{24}H_{34}O_4$ (386·5) calculated: 74·58% C, 8·87% H, found: 74·62% C, 8·69% H.

3β,21-Dihydroxy-5,7α-cyclo-B-homo-5α-pregnan-20-one (*XII*)

A solution of the diacetate *XIII* (500 mg) in methanol (150 ml) was refluxed with a solution of potassium carbonate (500 mg) in water (4 ml) under nitrogen for 20 minutes. Methanol was removed at room temperature, the residue was diluted with water, and the product taken into chloroform. The extract was washed with water, dried, and the solvent distilled off. The residue was chromarographed over silica gel (50 g) in ligroin–ether (2 : 1). Fractions with the diol were combined, solvents were removed, and the residue was crystallised from methanol–water to yield 290 mg of the diol *XII*, m.p. 148–151°C, $[\alpha]_D^{20}$ +53° (*c* 1·74). IR: 3070 (cyclopropane), 3610, 1075, 1050 (hydroxyl), 1705 cm^{-1} (carbonyl). NMR: −0·05 (dd, J = 4·5 Hz, J' = 8·5 Hz, one cyclopropane proton), 0·30 (t, J = 4·5 Hz, one cyclopropane proton), 0·60 (s, 18-H), 0·88 (s, 19-H), 2·41 (broad t, 17α-H), 3·75 (broad mt, 3α-H), 4·16 (s, 21-H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 75·89% C, 10·11% H.

3β,21-Diacetoxy-5,7α-cyclo-B-homo-5α-pregnan-20-one (*XIII*)

A mixture of the acetate *V* (5·15 g), lead tetraacetate (4·8 g), acetic acid (90 ml), and acetic anhydride (3·5 ml) was heated to 75°C under stirring for 4·5 hours. The reaction mixture was diluted with water, acidified with hydrochloric acid, and the product taken into chloroform. The extract was worked up and the residue after evaporation of the solvent was chromatographed on a silica gel column (500 g) in ligroin–ether (9 : 1). Working up of the fractions with the lipophilic component afforded 3·6 g of the starting material. Continued elution with the same solvent mixture afforded fractions with the polar component. Combination of the coresponding functions and evaporation of the solvent yielded a product (1·67 g) which after crystallisation from methanol gave 1·36 g of the diacetate *XIII*, m.p. 119–121°C, $[\alpha]_D^{20}$ +65° (*c* 1·19). IR: 3072 (cyclopropane), 1735 (carbonyl), 1756, 1735, 1247 cm^{-1} (acetate). NMR: −0·03 (mt, one cyclopropane proton), 0·30 (mt, one cyclopropane proton), 0·61 (s, 18-H), 0·88 (s, 19-H), 2·00 (s, acetate), 2·14 (s, acetate), 2·46 (broad t, 17α-H), 4·47 and 4·70 (two d, J_{gem} = 17 Hz, 21-H), 4·49 (broad mt, 3α-H). For $C_{26}H_{38}O_5$ (430·6) calculated: 72·52% C, 8·90% H; found: 72·68% C, 9·05% H.

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

A mixture of the diol *XII* (1·8 g) and N-bromoacetamide (1·64 g) in tert-butanol (200 ml) and water (3 ml) was allowed to stand at room temperature for 20 hours. Butanol was then removed under reduced pressure, the residue was treated with water, and the product extracted with chloroform. The extract was washed with a sodium hydrogen carbonate solution, water, dried, and the solvent was distilled off. The residue was chromatographed on a silica gel column (220 g) in ligroin–ether (4 : 1). The corresponding fractions were combined, the solvent distilled off, and the product was crystallised from ethyl acetate to yield 340 mg of the dione *XIV*, m.p. 198–201°C, $[\alpha]_D^{20}$ +105° (*c* 1·45). IR: 3070 (cyclopropane), 3610, 1072 (hydroxyl), 1710 cm^{-1} (carbonyl).

NMR: (deuteriochloroform with tetramethylsilane as internal reference): 0·18 (dd, $J = 9$ Hz, $J' = 5$ Hz, one cyclopropane proton), 0·37 (t, $J = 5$ Hz, one cyclopropane proton), 0·64 (s, 18-H), 0·97 (s, 19-H), 1·40 and 2·80 (two d, $J_{gem} = 16$ Hz, two protons, 4-H), 3·22 (t, $J = 5$ Hz, 21-OH), 4·18 (d, $J_{21,OH} = 5$ Hz, 21-H). For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 77·04% C, 9·51% H.

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

The alcohol *XIV* (130 mg) in pyridine (2 ml) was acetylated with acetic anhydride (0·8 ml) at room temperature for 18 hours. The reaction mixture was decomposed with ice, the product taken into ether, and the ethereal solution was worked up. The product after evaporation of the solvent was chromatographed on a silica gel column (10 g) in benzene–ether (9 : 1). The corresponding fractions were combined, solvent was removed, and the residue was crystallised from methanol to yield 95 mg of the acetate *XV*, m.p. 181–182°C, $[\alpha]_D^{20}$ +141° (*c* 1·54). IR: 3075 (cyclopropane), 1728 (carbonyl), 1755,1728, 1230 cm^{-1} (acetoxycarbonyl). NMR: (deuteriochloroform with tetramethylsilane as internal reference): 0·18 (dd, $J = 9$ Hz, $J' = 5$ Hz, one cyclopropane proton), 0·37 (t, $J = 5$ Hz, one cyclopropane proton), 0·65 (s, 18-H), 0·97 (s, 19-H), 1·39 and 2·80 (two d, $J_{gem} = 16$ Hz, 4-H), 2·16 (s, acetate), 4·50 and 4·75 (two d, $J_{gem} = 17$ Hz, 21-H). For $C_{24}H_{34}O_4$ (386·5) calculated: 74·56% C, 8·87% H; found: 74·50% C, 8·88% H.

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