4,4-DIMETHYL-A-HOMOCHOLESTANE DERIVATIVES*

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Methylation of A-homo-4a-cholesten-3-one (*I*) with methyl iodide in the presence of potassium tert-butoxide leads to 4,4-dimethyl-4a-cholesten-3-one (*II*) from which the 5,6-unsaturated isomer may be easily obtained by acid-catalyzed double bond shift. Configurations of epimeric 3-hydroxy derivatives of both 4a,5- and 5,6-unsaturated series have been established.

In our earlier paper[1] we reported on the preparation and properties of 3-ketones of the 4,4-dimethyl-A-homoandrostane series. In the extension of this work, we now describe the preparation and stereochemistry of some 4,4-dimethyl-A-homocholestane derivatives bearing an oxygen function at position 3.

We set out from the known[2] A-homo-4a-cholesten-3-one (*I*); its methylation with methyl iodide in the presence of potassium tert-butoxide gave a methylated compound in 79% yield. Its structure as 4,4-dimethyl-A-homo-4a-cholesten-3-one (*II*) is based on spectroscopic data including mass spectrometric determination of the molecular weight, presence of singlets of four methyl groups and a singlet of one olefinic proton in the ^{1}H-NMR spectrum. Similarly to a previous observation[1] in the A-homoandrostane series, the 4a,5-double bond in the ketone *II* is easily shifted into the 5,6-position to give the ketone *III* on treatment with *p*-toluenesulfonic acid in boiling benzene. The structure of the ketone *III* was corroborated by the ^{1}H-NMR spectrum showing a broad doublet of one olefinic proton and four singlets of the tertiary methyls.

Reduction of the ketone *II* with lithium aluminum hydride furnished a mixture of two epimeric alcohols not separable by conventional adsorption chromatographic methods. The separation could be accomplished, after benzoylating the mixture, by column chromatography on silica gel using benzene as eluant. The benzoates *IV* and *V* were obtained in c. 1 : 1 proportion and could be converted to the corresponding hydroxy derivatives by reduction with lithium aluminum hydride; both alcohols *VI* and *VII* were also characterized as acetates *VIII* and *IX*. On oxidation with chromium trioxide–pyridine complex, both *VI* and *VII* gave the ketone *II*. Similarly, hydride reduction of the ketone *III* yielded a mixture of epimeric alcohols

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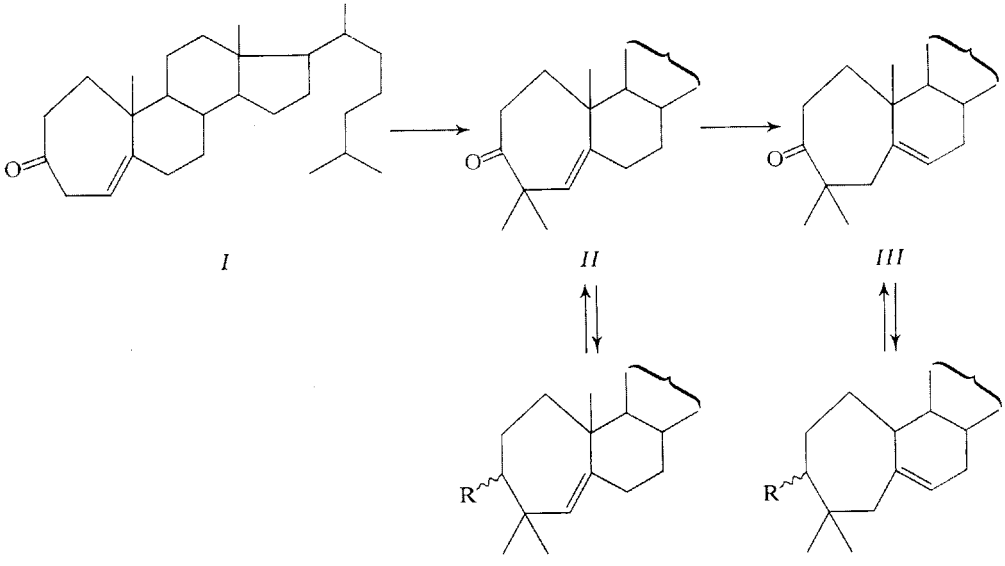
separable as benzoates *X* and *XI* from which individual alcohols *XII* and *XIII* were analogously obtained in the proportion 1 : 2. Again, both *XII* and *XIII* gave the starting ketone *III* on oxidation.



I *II* *III*

Ac: CH_3CO
Bz: C_6H_5CO

IV; R = β-OBz
V; R = α-OBz
VI; R = β-OH
VII; R = α-OH
VIII; R = β-OAc
IX; R = α-OAc

X; R = β-OBz
XI; R = α-OBz
XII; R = β-OH
XIII; R = α-OH

Configurations of the hydroxyl groups in alcohols *VI*, *VII*, *XII* and *XIII* were established by Horeau's method of partial resolution[3]. Based on this method, the hydroxyl groups in alcohols *VI* and *XII* were allotted 3β-configuration whereas 3α-configuration was established for hydroxyl groups in *VII* and *XIII*. This assignment was confirmed by application of the benzoate rule[4,5]. According to this rule, the $\Delta[M]_{D\ ester-alcohol}$ value should be more positive for the 3β than for 3α-derivatives. This was indeed found to be the case (Table I). The same conclusion was drawn from application of the benzoate sector rule[6]. The Dreiding models indicate negative Cotton effect for 3β-benzoyloxy derivatives and positive effect for 3α-epimers. This, again, is in agreement with the values found for both pairs ($\Delta\varepsilon_{240}$ −1·31 and −0·60 for *IV* and *X*, respectively, and $\Delta\varepsilon_{240}$ +0·67 and +2·37 for *V* and *XI*, respectively).

TABLE I

The Differences of Molecular Rotations for 3-Hydroxy Derivatives *VI, VII, XII, XIII* and their Esters *IV, V, VIII, IX, X* and *XI*

Compound	$[M]_{D\ benzoate-alcohol}$[a]	$[M]_{D\ benzoate-acetate}$[a]
VI	+ 85	−12
VII	−120	−68
XII	− 33	—
XIII	− 55	—

[a] Chloroform solution.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, optical rotations were measured in chloroform. The infrared spectra were measured on a Zeiss UR-10 spectrophotometer. The ^{1}H-NMR spectra were measured in deuteriochloroform on Varian HA-100 apparatus using tetramethylsilane as internal standard. The chemical shifts are given in p.p.m. The mass spectra were recorded on the mass spectrometer AEI MS 902. The identity of samples prepared by different routes was checked by mixture melting points and by infrared spectra. The statement "worked up as usual" stands for: The solution was washed with 5% hydrochloric acid, 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*.

4,4-Dimethyl-A-homo-4a-cholesten-3-one (*II*)

a) *From* A-*homo*-4a-*cholesten*-3-*one*[2] (I): The ketone *I* (450 mg) was dissolved in a solution of potassium (0·17 g) in tert-butanol (9 ml) while stirring in nitrogen atmosphere. When all ketone was dissolved methyl iodide (0·6 ml) was added in small portions over a period of 10 minutes, the mixture was then stirred for one hour, poured into water and most of the tert-butanol evaporated *in vacuo*. The product was extracted with ether, the ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. After chromatography on silica gel (50 g) in light petroleum–benzene (9 : 1) the residue (500 mg) afforded the 4,4-dimethyl derivative *II* (380 mg) which was crystallized from methanol, m.p. 77–79°C, $[\alpha]_D^{22}$ +13° (*c* 1·0). Infrared spectrum (tetrachloromethane): 1706, 1670 cm^{-1}. ^{1}H-NMR spectrum: 0·68 (s, 3 H, 18-CH_3); 0·86 (d, 6 H, 26, 27-CH_3, J = 6 Hz); 0·89 (d, 3 H, 21-CH_3, J = 6 Hz); 1·05 (s, 3 H, 19-CH_3 or 4-CH_3); 1·21 (s, 3 H, 19-CH_3 or 4-CH_3); 1·25 (s, 3 H, 19-CH_3 or 4-CH_3); 5·03 (broad s, 1 H, $C_{(4a)}$—H, $J_{4a,6}$ = 1·2 + ca 6 Hz). CD (dioxan): $\Delta\varepsilon_{max}$ = −1·09, λ_{max} = 288 nm. For $C_{30}H_{50}O$ (426·7) calculated: 84·44% C, 11·81% H; found: 84·86% C, 11·72% H.

b) *From* 4,4-*dimethyl*-A-*homo*-4a-*cholesten*-3β-*ol* (VI): A solution of the alcohol *VI* (100 mg in pyridine (3 ml) was added to a chromium trioxide (70 mg)–pyridine (1 ml) complex and allowed to stand at room temperature overnight. The usual workup gave the ketone *II* (90 mg) which was crystallized from methanol, m.p. 77–79°C.

c) *From* 4,4-*dimethyl*-A-*homo*-4a-*cholesten*-3α-*ol* (VII): The alcohol *VII* (100 mg) was oxidized with chromium trioxide (70 mg)–pyridine (1 ml) complex in the same manner as in case *b*). The crude product (95 mg) was crystallized from methanol to yield the ketone *II* (53 mg), m.p. 77—79°C.

4,4-Dimethyl-A-homo-5-cholesten-3-one (*III*)

a) *From* 4,4-*dimethyl*-A-*homo*-4-*cholesten*-3-*one* (II): *p*-Toluenesulfonic acid (180 mg) was added to a solution of the ketone *II* (500 mg) in benzene (30 ml) and the mixture was refluxed for 10 h. The mixture was poured into water and the product was extracted with benzene. The extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. After chromatography on silica gel (60 g) in light petroleum the residue (500 mg) gave the ketone *III* (400 mg), which was crystallized from methanol, m.p. 152—154°C, $[\alpha]_D^{22}$ −3° (*c* 1·0). Infrared spectrum (tetrachloromethane): 1703, 1663 cm^{-1}. ^{1}H-NMR spectrum: 0·69 (s, 3 H, 18-CH_3); 0·86 (d, 6 H, 26 + 27-CH_3, J = 6 Hz); 0·91 (d, 3 H, 21-CH_3, J = 6 Hz); 0·99 (s, 3 H, 19-CH_3 or 4-CH_3); 1·055 (s, 3 H, 19-CH_3 or 4-CH_3); 1·11 (s, 3 H, 19-CH_3 or 4-CH_3); 5·48 (broad doublet, 1 olefinic H, $C_{(6)}$—H, $J_{6,7}$ = 4·5 + 2 Hz). CD spectrum (dioxan): $\Delta\varepsilon_{max_1}$ = −0·83, λ_{max_1} = 291·5 nm, $\Delta\varepsilon_{max_2}$ = −0·81, λ_{max_2} = 300 nm. For $C_{30}H_{50}O$ (426·7) calculated: 84·44% C, 11·81% H; found: 84·04% C, 11·71% H .

b) *From* 4,4-*dimethyl*-A-*homo*-5-*cholesten*-3β-*ol* (XII): The alcohol *XII* (40 mg) was oxidized with chromium trioxide (20 mg)–pyridine (0·5 ml) complex in the same manner as in the cases mentioned above. The crude product (36 mg) was crystallized from methanol to yield the ketone *III* (28 mg), m.p. 152—154°C, $[\alpha]_D^{22}$ −3° (*c* 1·0).

c) *From* 4,4-*dimethyl*-A-*homo*-5-*cholesten*-3α-*ol* (XIII): The alcohol *XIII* (40 mg) was oxidized with chromium trioxide (20 mg)–pyridine (0·5 ml) complex in the same manner as in case *b*). The crude product (35 mg) was crystallized from methanol to yield the ketone *III* (24 mg), m.p. 152—154°C, $[\alpha]_D^{22}$ −3° (*c* 1·0).

4,4-Dimethyl-A-homo-4a-cholesten-3β-yl 3-Benzaote (*IV*)

a) *From* 4,4-*dimethyl*-A-*homo*-4a-*cholesten*-3-*one* (II): Lithium aluminum hydride (130 mg) was added to a solution of the ketone *II* (260 mg) in ether (20 ml) and the mixture was refluxed for two hours. The excess hydride was destroyed with saturated aqueous solution of sodium sulfate and the mixture was then passed through a small column of sodium sulfate. After concentration *in vacuo* the filtrate afforded the crude product (250 mg) which was benzoylated with benzoyl chloride (0·9 ml) in pyridine (3 ml) overnight. The excess benzoyl chloride was destroyed with a piece of ice and the product was extracted with ether. After the usual workup the ethereal extract afforded the crude product (300 mg) which was chromatographed on silica gel (100 g) in light petroleum. After crystallization from methanol the first less polar fraction (125 mg) afforded the benzoyloxy derivative *IV* (96 mg), m.p. 113 to 114°C, $[\alpha]_D^{22}$ +52° (*c* 1·0). Infrared spectrum (tetrachloromethane): 1718, 1274 cm^{-1}. For $C_{37}H_{56}O_2$ (532·8) calculated: 83·41% C, 10·59% H; found: 83·88% C, 10·61% H.

b) *From* 4,4-*dimethyl*-A-*homo*-4a-*cholesten*-3β-*ol* (VI): The alcohol *VI* (50 mg) was benzoylated with benzoyl chloride (0·1 ml) in pyridine (1 ml overnight. The usual workup gave the crude product (55 mg) which was crystallized from methanol to yield 34 mg of the benzoyloxy derivative *IV*, m.p. 113—114°C, $[\alpha]_D^{22}$ +52° (*c* 1·0).

4,4-Dimethyl-A-homo-4a-cholesten-3α-yl 3-Benzoate (*V*)

a) Elution of the chromatography after isolation of the 3β-epimer *IV* (see *a*) in the preceding procedure) with light petroleum–ether (99 : 1) and working up the corresponding fractions left a product (140 mg) which was crystallized from ethanol to give the benzoyloxy derivative *V* (110 mg), m.p. 136–137·5°C, $[\alpha]_D^{22}$ +11° (*c* 1·0). Infrared spectrum (tetrachloromethane): 1717, 1674, 1604, 1585, 1284 cm^{-1}. For $C_{37}H_{56}O_2$ (532·8) calculated: 83·41% C, 10·59% H; found: 83·59% C, 10·62% H.

b) The alcohol *VII* (50 mg) was benzoylated with benzoyl chloride (0·1 ml) in pyridine (1 ml) overnight. The usual workup gave the crude product (53 mg) which was crystallized from ethanol to yield 36 mg of the benzoyloxy derivative *V*, m.p. 136–137·5°C, $[\alpha]_D^{22}$ +11° (*c* 1·0).

4,4-Dimethyl-A-homo-4a-cholesten-3β-ol (*VI*)

Lithium aluminium hydride (100 mg) was added to a solution of the benzoyloxy derivative *IV* (170 mg) in ether (8 ml) and the mixture was allowed to stand at room temperature for one hour. The excess hydride was destroyed with saturated aqueous solution of sodium sulfate and the reaction mixture was passed through a small column of sodium sulfate. After evaporation of the solvent *in vacuo* the filtrate afforded 165 mg of the crude product which was separated on two plates of silica gel (20 × 20 cm) in light petroleum–ether (8 : 2). The corresponding zones were collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (130 mg) was crystallized from ligroin to yield the alcohol *VI* (101 mg), m.p. 110–111°C, $[\alpha]_D^{22}$ +45° (*c* 1·0). Infrared spectrum (chloroform): 3635, 1038, 1020 cm^{-1}. ^{1}H-NMR spectrum: 0·68 (s, 3 H, 18-CH_3); 0·87 (d, 6 H, 26 + 27-CH_3, J = 6 Hz); 0·905 (d, 3 H, 21-CH_3, J = 6 Hz); 1·03 (s, 3 H, 19-CH_3 or 4-CH_3); 1·13 (s, 3 H, 19-CH_3 or 4-CH_3); 3·51 (broad triplet, 1 H, C_3–H, J = 12 Hz); 4·97 (broad s, 1 H, $C_{(4a)}$–H). For $C_{30}H_{52}O$ (428·7) calculated: 84·04% C, 12·23% H; found: 84·07% C, 12·37% H.

4,4-Dimethyl-A-homo-4a-cholesten-3α-ol (*VII*)

Lithium aluminum hydride (60 mg) was added to a solution of the benzoyloxy derivative *V* (100 mg) in ether (4 ml) and the mixture was allowed to stand at room temperature for two hours. The same workup as in the preparation of the alcohol *VI* gave 90 mg of the crude product which was preparatively chromatographed on two plates of silica gel (20 × 20 cm) in light petroleum–ether (8 : 2). The corresponding zones were collected, eluted with ether and the solvent evaporated *in vacuo*. After crystallization from ligroin the residue (75 mg) afforded the alcohol *VII* (53 mg), m.p. 125–126°C, $[\alpha]_D^{22}$ +42° (*c* 1·0). Infrared spectrum (chloroform): 3635, 3630 (inflex) cm^{-1}. ^{1}H-NMR spectrum: 0·68 (s, 3 H, 18-CH_3); 0·865 (d, 6 H, 26 + 27-CH_3, J = 6 Hz); 0·90 (d, 3 H, 21-CH_3, J = 6 Hz); 1·035 (s, 3 H, 19-CH_3 or 4-CH_3); 1·07 (s, 19-CH_3 or 4-CH_3); 1·09 (s, 3 H, 19-CH_3 or 4-CH_3); 3·65 (mt, 1 H, C_3–H); 5·01 (broad s, 1 H, C_{4a}–H). Mol. weight (mass spectrometry): 428; for $C_{30}H_{52}O$ calculated: 428·7.

4,4-Dimethyl-A-homo-4a-cholesten-3β-yl 3-Acetate (*VIII*)

The alcohol *VI* (70 mg) was acetylated with acetic anhydride (0·4 ml) in pyridine (3 ml) overnight. The usual workup gave the crude product (67 mg) which was crystallized from methanol to yield the acetate *VIII* (47 mg), m.p. 84–85°C, $[\alpha]_D^{22}$ +62° (*c* 0·5). Infrared spectrum (tetrachloromethane): 3050, 1738, 1247, 1020 cm^{-1}. Mol. weight (mass spectrometry): 470; for $C_{32}H_{54}O_2$ calculated: 470·7.

4,4-Dimethyl-A-homo-4a-cholesten-3α-yl 3-Acetate (*IX*)

The alcohol *VII* (50 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (3 ml) overnight. The usual workup gave the crude product (50 mg) which was crystallized from methanol to yield the acetate *IX* (30 mg), m.p. 101–102°C, $[\alpha]_D^{22}$ +27° (*c* 0·5). Infrared spectrum (tetrachloromethane): 1738, 1248, 1019 cm^{-1}. Mol. weight (mass spectrometry): 470; for $C_{32}H_{54}O_2$ calculated: 470·7.

4,4-Dimethyl-A-homo-5-cholesten-3β-yl 3-Benzoate (*X*)

a) *From* 4,4-*dimethyl*-A-*homo*-5-*cholesten*-3-*one* (III): Lithium aluminum hydride (100 mg) was added to a solution of the ketone *III* (150 mg) in ether (10 ml) and the mixture was allowed to stand at room temperature for 1 hour. The excess of hydride was destroyed with saturated aqueous solution of sodium sulfate and the mixture was then passed through a small column of sodium sulfate. After concentration *in vacuo* the filtrate afforded the crude product (150 mg) which was treated with benzoyl chloride (0·6 ml) in pyridine (2 ml) overnight. The usual workup gave the crude product (180 mg) which was preparatively chromatographed on five plates of silica gel (20 × 20 cm) in light petroleum–ether (9·5 : 0·5) with threefold elution. The corresponding less polar zones were collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (35 mg) was crystallized from methanol to yield the benzoyloxy derivative *X* (22 mg), m.p. 125–127°C, $[\alpha]_D^{22}$ +9° (*c* 0·5). Infrared spectrum (tetrachloromethane): 1721, 1714 (inflex), 1278 cm^{-1}. For $C_{37}H_{56}O_2$ (532·8) calculated: 83·41% C, 10·59% H; found: 83·02% C, 10·60% H.

b) *From* 4,4-*dimethyl*-A-*homo*-5-*cholesten*-3β-*ol* (XII): The alcohol *XII* (40 mg) was treated with benzoyl chloride (0·1 ml) in pyridine (1 ml) overnight. The usual workup gave the crude product (35 mg) which was crystallized from methanol to yield the benzoyloxy derivative *X* (22·5 mg), m.p. 125–127°C, $[\alpha]_D^{22}$ +8° (*c* 1·0).

4,4-Dimethyl-A-homo-5-cholesten-3α-yl 3-Benzoate (*XI*)

a) Elution of the more polar corresponding zones after isolation of 3β-isomer *X* with ether and evaporation of the solvent *in vacuo* left the oily benzoyloxy derivative *XI* (70 mg) which was crystallized from methanol, m.p. 42–45°C, $[\alpha]_D^{22}$ +4° (*c* 1·0). Infrared spectrum (tetrachloromethane): 1720, 1114 (inflex), 1275 cm^{-1}. Mol. weight (mass spectrometry): 532; for $C_{37}H_{56}O_2$ calculated: 532·8. For $C_{37}H_{56}O_2$ (532·8) calculated: 83·41% C, 10·59% H; found: 83·02% C, 10·60% H.

b) The alcohol *XIII* (10 mg) was treated with one drop of the benzoyl chloride in pyridine (0·5 ml) overnight. The usual workup gave the product (15 mg) which was preparatively chromatographed on one plate of silica gel (10 × 7·5 cm) in light petroleum–ether (9·5 : 0·5). The corresponding zone was eluted with ether and the solvent evaporated *in vacuo*. The residual oil (7·5 mg) was crystallized from methanol to yield the benzoyloxy derivative *XI* (5 mg), m.p. 42–45°C, $[\alpha]_D^{22}$ +4° (*c* 1·0).

4,4-Dimethyl-A-homo-5-cholesten-3β-ol (*XII*)

Lithium aluminum hydride (150 mg) was added to a solution of the benzoyloxy derivative *X* (300 mg) in ether (10 ml) and the mixture was allowed to stand at room temperature for 1 hour. The usual workup gave the crude product (300 mg) which was chromatographed on 6 plates of silica gel (20 × 20 cm) in light petroleum–ether (9 : 1) with threefold elution. The corres-

ponding zones were collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (257 mg) was crystallized from heptane to yield the alcohol *XII* (186 mg), m.p. 85–87°C, $[\alpha]_D^{22}$ +18° (*c* 1·0). Infrared spectrum (chloroform): 3635, 1045, 1660 cm^{-1}. For $C_{30}H_{52}O$ (428·7) calculated: 84·04% C, 12·23% H; found: 83·83% C, 12·38% H.

4,4-Dimethyl-A-homo-5-cholesten-3α-ol (*XIII*)

Lithium aluminum hydride (30 mg) was added to a solution of the benzoyloxy derivative *XI* (60 mg) in ether (2 ml) and the mixture was allowed to stand at room temperature for 1 hour. The usual work up gave the crude product (60 mg) which was chromatographed on one plate of silica gel (20 × 20 cm) in light petroleum–ether (9 : 1) with twofold elution. The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (55 mg) is an oil which is homogenous by TLC, but resisted all attempts at crystallization; $[\alpha]_D^{22}$ +18° (*c* 0·5). Infrared spectrum (chloroform): 3623, 1033, 1662, 1670, 3098 cm^{-1}. Mol. weight (mass spectrometry): 428; for $C_{30}H_{52}O$ calculated: 428·7.

Determination of the Configuration of Hydroxy Derivatives *VI*, *VII*, *XII* and *XIII* according to Horeau's Method

The hydroxy derivative *VI*, resp. *XII* (11 mg) was treated with (±) α-phenylbutyric acid anhydride (25 mg) in pyridine (0·1 ml) at room temperature for 18 h. A drop of water was added and the mixture set aside for 30 minutes, then rinsed with water into a flask containing a small volume of benzene. The content of the flask was then neutralized with 0·1M sodium hydroxide using phenolphthalein as indicator and then extracted four times with benzene. The aqueous layer was acidified with one drop of 5% hydrochloric acid and extracted with benzene. The extract was washed with water, dried over sodium sulfate and concentrated to a small volume *in vacuo*. Measuring a part of this solution (0·78 ml) in a 5 cm tube gave values of α −0·035° and −0·034° respectively.

The same procedure was applied to the hydroxy derivatives *VII* and *XIII* to give the values, of α +0·015° and +0·077°, respectively.

The analyses were carried out in the analytical laboratories of the Institute by Mr V. Štěrba, Mrs V. Rusová and Mrs E. Sýkorová (direction Dr J. Horáček). The IR spectra were recorded by Mr P. Formánek (direction Dr J. Smolíková), the mass spectra by Dr A. Trka and the ^{1}H-NMR *spectra by Dr M. Buděšínský.*

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