PARTICIPATION OF 19-SUBSTITUENTS IN ACID CLEAVAGE OF STEROIDAL 3α,4α- AND 4α,5α-EPOXIDES*

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Participation of 19-methoxy and 19-acetoxy groups in 3α,4α- and 4α,5α-epoxides *IIIc*, *IVb,c* on treatment with aqueous perchloric or hydrobromic acid is investigated and compared with acid treatment of structurally similar 19-substituted 6α,7α- and 5α,6α-epoxides *V* and *VI* and with the behavior of analogous 3α,4α- and 4α,5α-bromonium ions. The 3α,4α-epoxides *III* react readily with $5(O)^n$ participation, The reaction is practically quantitative on perchloric acid treatment. Under the same conditions, the 19-methoxy-4α,5α-epoxide *IVb* suffers mainly external attack leading to the diol *XIb*. The neighboring group participation is solely a $5(O)^n$ process giving rise to the cyclic ether *X*. The 19-acetoxy-4α,5α-epoxide *IVc* reacts predominantly with participation of the ambident acetoxy group. This reaction is exclusively a $6(O)^{\pi,n}$ process affording the diol *XVI*. External attack proceeds to a limited extent to give the isomeric diol *XIc*. In this respect the latter compounds react quite analogously to 5α,6α-epoxides *VI* and 4α,5α- and 5α,6α-bromonium ions bearing 19-acetoxyl.

Recently, we investigated[1] the participation of the 19-substituent in the course of hypobromous acid addition to 3,4- and 4,5-unsaturated steroids *Ia–Ic* and *IIa* to *IIc*. Since the bromonium ion shows marked similarity to the protonated epoxide ring on nucleophilic attack[2–5], it appears desirable to investigate the behavior of corresponding epoxides under acidic conditions.

It is the aim of the present paper to investigate 3α,4α- and 4α,5α-epoxides with a 19-methoxy and 19-acetoxy group (*IIIb,c* and *IVb,c*)[6] and to establish the differences due to *a*) the character of the 19-substituent and *b*) the location of the epoxide ring either in 3α,4α- or 4α,5α-positions; in addition, comparison with earlier studies[2–5] on 6α,7α- and 5α,6α-epoxides *Vb,c* and *VIb,c* is now possible.

The 19-methoxy derivative *IIIb* undergoes $5(O)^n$ participation (for notation *cf.* ref.[7]) to give the cyclic ether *VII*. The methoxy group participation accounts for the pronounced instability of the epoxide *IIIb* and attempts at its preparation[6] lead directly to *VII*. The action of aqueous perchloric acid in dioxane on the acetate *IIIc* leads again to *VII* in practically quantitative yield. TLC shows the presence of a trace amount of a polar by-product, presumably diol *VIII*. Treatment of *IIIc*

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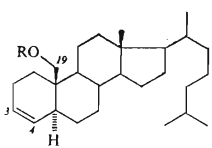
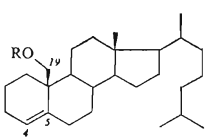
with hydrobromic acid in the same solvent also gives rise to the cyclic ether *VII* which is, however, the minor product while the bromohydrin *IX* predominates. Other products were not observed (Table I). Treatment of the 19-methoxy-4α,5α--epoxide *IVb* with perchloric acid yields four products: The cyclic ether *X*, the diol *XIb*, the allylic alcohol *XIV* and the 4-ketone *XV*. The action of hydrobromic acid proceeds slowly. After prolonged treatment at room temperature the composition of the reaction mixture is the same as after treatment with perchloric acid; in addition, some parent epoxide (*IVb*) is still present after 4 hours (Table I). Treatment of the 19-acetoxy-4α,5α-epoxide *IVc* with perchloric acid gives a mixture of diols *XIc* and *XVI* that can be separated after acetylation to give acetates *XVII* and *XVIII*. The action of hydrobromic acid on *IVc* yields an untractable mixture of products containing no halogen.

The structure of the bromohydrin *IX* was established by ^{1}H-NMR spectral evidence showing the presence of axial hydroxy and bromine groups (Table II). The



Ia, R = H
Ib, R = CH_3
Ic, R = Ac



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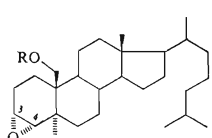
IIc, R = Ac



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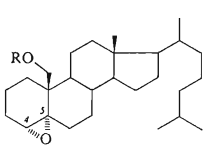
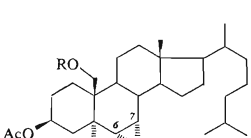
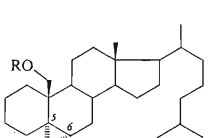


IVb, R = CH_3
IVc, R = Ac



Vb, R = CH_3
Vc, R = Ac



VIb, R = CH_3
VIc, R = Ac

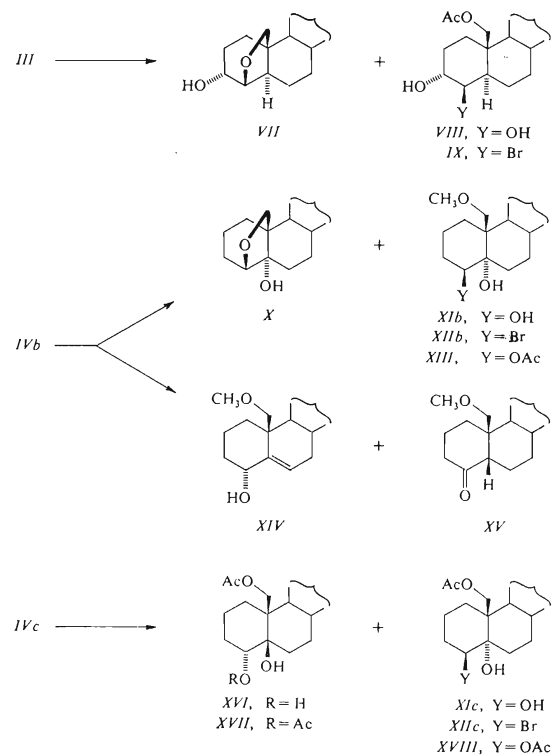
TABLE I

Yields and Ratios of Epoxides *III*—*VI* Cleavage Products

Starting compound	Neighboring group	Reagent	Mode of reaction, % of the total yield				Total yield %	Ref.
			5(O)^n	6(O)$^{n-1}$	ext.[a]	other		
IIIb	OCH_3	$HClO_4$	100 (*VII*)[b]	—	—	—	95[b]	—
IIIc	OAc	$HClO_4$	98 (*VII*)	—	2 (*VIII*)[c]	—	93	—
IIIc	OAc	HBr	33 (*VII*)	—	67 (*IX*)	—	89	—
IVb	OCH_3	$HClO_4$	20 (*X*)	—	60 (*XIb*)	14 (*XIV*), 6 (*XV*)	95	—
IVb	OCH_3	HBr	37 (*X*)	—	25 (*XIb*)	24 (*IVb*), 14 (*XV*)	81	—
IVc	OAc	$HClO_4$	—	66 (*XVI*)[d]	34 (*XIc*)[e]	—	90	—
Vb	OCH_3	$HClO_4$	95	—	5	—	92	4
Vc	OAc	$HClO_4$	74	—	26	—	93	4
Vc	OAc	HBr	8	—	92	—	88	4
VIb	OCH_3	$HClO_4$	18	—	63	19	98	5
VIb	OCH_3	HBr	—	—	100	—	95	5
VIc	OAc	$HClO_4$	—	96	4	—	87	5
VIc	OAc	HBr	—	49	51	—	98	5

[a] Products of external nucleophile attack; [b] estimated (see the text); [c] structure not proved; [d] isolated as *XI*; [e] isolated as *XIV*.

structure of the cyclic ether *X* follows essentially from spectral evidence. In the ^{1}H-NMR spectrum the signal of the methoxy group is absent while the narrow multiplet due to $C_{(4)}$—H establishes the axial conformation of the $C_{(4)}$-oxygen atom. The IR spectrum shows the presence of a free tertiary hydroxy group. The structure *X* is also substantiated by mass determination and elemental analysis. The signal for the methoxy group appears in the ^{1}H-NMR spectrum of the diol *XIb* and the axial nature of one hydroxyl follows from the width of the narrow multiplet of the $C_{(4)}$—H. Acetylation of the secondary hydroxyl yielded a monoacetate *XIII* possessing no intramolecular hydrogen bonding. This fact proves that the hydroxy group



at $C_{(4)}$ has the β-configuration and excludes the alternative 4α-OH-5β-OH structure. The structure of the allylic alcohol *XIV* was derived from its chemical and spectral properties. Oxidation of *XIV* gives rise to the α,β-unsaturated ketone *XIX* which was also obtained from the diol *XIb* by oxidation with pyridinium chlorochromate[8] followed by dehydration with thionyl chloride in pyridine. The α-configuration of the hydroxyl at $C_{(4)}$ in *XIV* is evident from the absence of an intramolecular hydrogen bonding (IR) and from the coupling of the $C_{(4)}$—H in the ^{1}H-NMR spectrum (Table II). The ketone *XV* is identical with the known compound[6]. The diacetate *XVII* differs from its isomer *XVIII* by the presence of an intramolecular hydrogen bridge (IR); the ^{1}H-NMR spectrum reveals the axial nature of the acetoxy groups at $C_{(4)}$ both in *XVII* and *XVIII*.

The ease of 5(O)^n participation in 3α,4α-epoxide *IIIb,c* is apparent from the instability of the 19-methoxy derivative *IIIb* which could not be isolated due to spontaneous conversion to the product of intramolecular cyclization[6] *VII*. Approximately the same behavior is observed with the 19-acetate *IIIc* on hydrolysis with aqueous perchloric acid. These results are in line with the behavior of the analogous 3α,4α-bromonium ion[1]. The important role of external attack in the action of hydrobromic acid on the 19-acetoxy derivative *IIIc* is expected from analogy with the behavior of earlier investigated steroidal epoxides towards this strong nucleophile[2-5]. There is no substantial difference in the behavior of 19-acetoxy-3α,4α- and 6α,7α-epoxides *IIIc* and *Vc* (Table I). The reactivity toward hydrobromic acid is virtually the same; on treatment with perchloric acid the 3α,4α-epoxide *IIIc* shows a more pronounced tendency towards neighboring group participation.

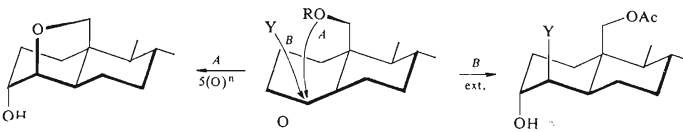
TABLE II

^{1}H-NMR Data of Epoxide Cleavage Products

Compound	18-H	19-H[a]	3-H (*W* in Hz)	4-H (*W* in Hz)
VII	0·65	3·74	3·90 m[b]	3·90 m[b]
IX	0·64	4·67	4·07 m (12)	4·27 m (12)
X	0·63	3·87	—	3·64 m (10)
XIb	0·63	3·74	—	3·40 m[b]
XIV	0·68	3·36	—	4·28 m (25)
XV	0·61	3·44	—	—

[a] Center of AB system; [b] overlapped by other signals.

When comparing the reactions of 4α,5α-epoxides *IV* with their 3α,4α-counterparts *III*, one difference should be pointed out. While in 3α,4α-epoxides both 19-methoxy and 19-acetoxy groups participate by an $5(O)^n$ process, in 4α,5α-epoxides the participating 19-groups react differently: $5(O)^n$ participation is characteristic of the 19-methoxy group while the ambident 19-acetoxy group prefers the $6(O)^{n,n}$ process to the alternative $5(O)^n$ reaction.



VII *IIIb*, R = CH_3; *IIIc*, R = Ac *VIII*, Y = OH; *IX*, Y = Br

SCHEME 1

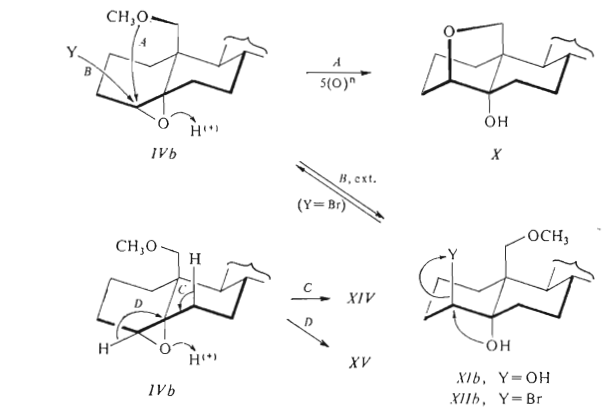
Treatment of the 4α,5α-epoxide *IVb* with perchloric acid gives the product of $5(O)^n$ participation (*X*) in only 20% yield, the product of external attack (*XIb*) being predominant. Both compounds are accompanied by products of 6β—H elimination (*XIV*) and 4β-hydride shift (*XV*) (Table I). A larger propensity to external attack in the 4α,5α- than in the 5α,6α-epoxides[5] *VIb* parallels the same tendency in the

TABLE III

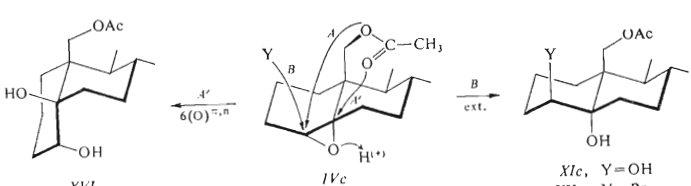
Analytical and Physical Data of Epoxide Cleavage Products

Compound	Formula (m.w.)	Calculated/Found			M.p., °C $[\alpha]_D^{20}$
		% C	% H	% Br	
VII	$C_{27}H_{46}O_2$	80·54	11·51	—	175—176
	(402·7)	80·31	11·49	—	+42°
IX	$C_{29}H_{49}BrO_3$	67·03	9·50	15·38	oil
	(519·6)	66·91	9·57	15·52	+22°
X	$C_{27}H_{46}O_2$	80·54	11·51	—	171—172
	(402·7)	80·36	11·64	—	+17°
XIV	$C_{28}H_{48}O_2$	80·71	11·61	—	oil
	(416·7)	80·62	11·74	—	—51°

4α,5α- and 5α,6α-bromonium ions[1,7,9]. It may be explained in the same manner: the capability of the A-ring to adopt not only the conformation A_1 favorable for $5(O)^n$ participation, but also the conformation A_2 (Fig. 1) (ref.[1,10]) with a greater distance of the 19-oxygen from the reaction center at $C_{(4)}$ (Fig. 1). The rigid B-ring has not this unfavorable choice[1].



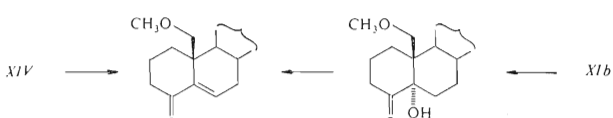
SCHEME 2



SCHEME 3

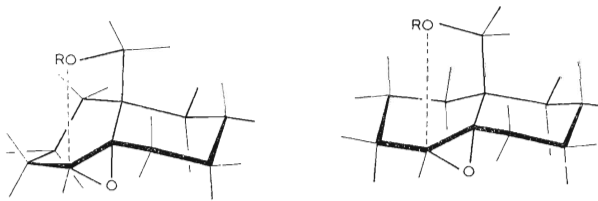
Treatment of the 4α,5α-epoxide *IVb* with hydrobromic acid leaves (even after 4 h) some starting compound unaffected. Apart from this difference, the reaction mixture is qualitatively identical and quantitatively closely similar to that obtained on the action of perchloric acid. A striking fact is that no bromohydrin was obtained. The expected bromohydrin should possess the structure *XIIb*. In an earlier work[1] an attempt was made to prepare this compound by the addition of hypobromous

acid to the 4,5-unsaturated derivative *IIb*. However, isolation failed due to the great ease with which this compound cyclizes to the epoxide *IVb*. This indicates that in cleavage of the epoxide *IVb* by aqueous hydrobromic acid the equilibrium between the epoxide and bromohydrin is set up comparatively rapidly, the epoxide being slowly consumed by reactions leading irreversibly to *X*, *XIb*, *XIV* and *XV*. The failure to isolate the bromohydrin even from the reaction mixture from which the epoxide *IVb* can still be obtained may be attributed to the easy conversion of the bromohydrin *XIIb* to the epoxide under the conditions of the isolation procedure[1].



XIX *XX*

In the cleavage of the 19-acetoxy-4α,5α-epoxide *IVc* with aqueous perchloric acid the product of participation (*XVI*) is solely due to the $6(O)^{\pi,n}$ process. No product of $5(O)^{n}$ participation was obtained though this process could also be conceivable. This is completely in line with the behavior of the analogous 4α,5α-bromonium ion[1] and also with the reactions of both the 5α,6α-epoxide[3,5,11–13] and bromonium ion[7,9–18]. Formation of the diol *XIc* is due to external attack by water and parallels analogous cleavage of the 5α,6α-epoxide[5].



A_1 A_2

FIG. 1

Conformations of the 4α,5α-Epoxide *IV*

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa (0·2 Torr). Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane unless

otherwise stated. The ^{1}H-NMR spectra were recorded on a Tesla BS 476 instrument (60 MHz) in deuteriochloroform at 30°C with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants were obtained from the first order analysis. The CD spectra were recorded on a Dichrographe II (Jouan–Roussel) in dioxane. The mass spectra were recorded on a Jeol JMS D—100 spectrometer operating at 14—75 eV. The samples were introduced using a direct inlet at lowest temperature enabling evaporation. The elemental compositions of ions were determined by accurate mass measurements. The identity of the 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. Usual work up of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid, water, a 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

Cleavage of Epoxides *IIIb*, *IIIc*, *IVb*, *IVc*

The epoxide (200 mg) was dissolved in dioxane (6—8 ml), water (0·5 ml) was added and the mixture was treated with acid, *i.e.* 72% aqueous perchloric acid (0·3 ml) or 48% aqueous hydrobromic acid (0·5 ml) ar room temperature for 20 min. The mixture was diluted with ether and water, the organic layer was washed ten times with water, dried with sodium sulfate and the solvent was removed *in vacuo*. The residue was chromatographed on four preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (85 : 10 : 5) for development. Corresponding fractions were collected, eluted with ether, the solvent was evaporated *in vacuo* and the residue was dried in vacuum desiccator overnight. The yields of products are given in Table I. The compounds were crystallized from a mixture of acetone, methanol and water. The ^{1}H-NMR data of the products are given in Table II and the analytical and physical data in the Table III.

19-Methoxy-5α-cholestanc-4β,5-diol 4-Monoacetate (*XIII*)·

The diol *XIb* (37 mg) was dissolved in pyridine (1 ml) and treated with acetic anhydride (0·5 ml) at room temperature for 2 days. The mixture was decomposed with ice and water, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water to yield the acetate *XIII* (19 mg), m.p. 95—97°C, $[\alpha]_D^{20}$ +23° (*c* 3·8). ^{1}H-NMR spectrum: 0·68 (3 H, s, 18-H), 2·07 (3 H, s, CH_3CO_2), 3·32 (3 H, s, CH_3O), 3·68 (1 H, d, J = 10 Hz, 19-H), 3·90 (1 H, d, J = 10 Hz, 19-H), 4·72 (1 H, m, W = 11 Hz, 4α-H). For $C_{30}H_{52}O_4$ (476·7) calculated: 75·58% C, 10·99% H; found: 75·44% C, 11·02% H.

5β-Cholestane-4α,5,19-triol 4,19-Diacetate (*XVII*)

The crude mixture of the diols *XIc* and *XVI* (110 mg) was dissolved in pyridine (1 ml) and treated with acetic anhydride (0·2 ml) at room temperature for 2 days. The mixture was decomposed with ice and water, the product extracted with ether and the ethereal solution worked up as usual. The residue was chromatographed on two preparative plates of silica gel (20 × 20 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) for development. The polar zones were collected, eluted with ether and evaporated to yield the acetate *XVII* (81 mg). This product was crystallized from a mixture of acetone, methanol and water to afford *XVII* (52 mg), m.p. 122—124°C, $[\alpha]_D^{20}$ −8° (*c* 3·7). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·03 (3 H, s, CH_3CO_2), 2·05 (3 H, s, CH_3CO_2), 4·36 (2 H, brd s, 19-H), 4·82 (1 H, m, W = 11 Hz, 4β-H). IR

spectrum: 1240, 1738, 3510, 3602 cm^{-1}. For $C_{31}H_{52}O_5$ (504·8) calculated: 73·77% C, 10·38% H; found: 73·58% C, 10·51% H.

5α-Cholestane-4β,5,19-triol 4,19-Diacetate (*XVIII*)

The corresponding lipophilic zones after the chromatography of the acetylation products of the diols *XIc* and *XVI* were collected and eluted with ether. The eluate was evaporated and the residue was dried in vacuum desiccator overnight to yield the diacetate *XVIII* (33 mg). The product was crystallized from a mixture of acetone, methanol and water to afford *XVIII* (18 mg), m.p. 114—116°C, $[\alpha]_D^{20}$ +23° (*c* 2·4). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 4·39 (1 H, d, J = 12 Hz, 19-H), 4·80 (1 H, d, J = 12 Hz, 19-H), 4·65 (1 H, m, W = 10 Hz, 4α-H). IR spectrum: 1240, 1725 sh, 1739, 3605 cm^{-1}. For $C_{31}H_{52}O_5$ (504·8) calculated: 73·77% C, 10·38% H; found: 73·62% C, 10·49% H.

19-Methoxy-5-cholesten-4-one (*XIX*)

a) The alcohol *XIV* (20 mg) was dissolved in dichloromethane (2 ml) and stirred with pyridinium chlorochromate (40 mg) in the presence of sodium acetate (20 mg) and sodium sulfate (50 mg) at room temperature for 2 h. The mixture was filtered through a column of aluminum oxide (2 g). The eluent was evaporated to afford the oily ketone *XIX* (17 mg), $[\alpha]_D^{20}$ —46° (*c* 2·0). IR spectrum: 1633, 1692, 2818 cm^{-1}. For $C_{28}H_{46}O_2$ (414·7) calculated: 81·10% C, 11·18% H; found: 80·98% C, 11·27% H.

b) The hydroxy ketone *XX* (35 mg) was dissolved in pyridine (1 ml) and treated with thionyl chloride (0·1 ml) at 0°C for 10 min. The mixture was decomposed with ice and water, the product taken up in ether and the ethereal phase was worked up as usual to yield the oily *XIX* (26 mg), $[\alpha]_D^{20}$ —48° (*c* 0·9), identical with the compound prepared in the previous experiment.

5-Hydroxy-19-methoxy-5α-cholestan-4-one (*XX*)

The diol *XIb* (40 mg) was dissolved in dichloromethane (3 ml) and stirred with pyridinium chlorochromate (70 mg), sodium acetate (40 mg) and sodium sulfate (70 mg) at room temperature for 1 h. The solution was filtered through a column of aluminum oxide (3 g) and the filtrate was evaporated to yield the oily hydroxy ketone *XX* (32 mg), $[\alpha]_D^{20}$ +63° (*c* 2·6). ^{1}H-NMR spectrum: 0·66 (3 H, s, 18-H), 3·21 (3 H, s, CH_3O), 3·23 (1 H, d, J = 10 Hz, 19-H), 3·46 (1 H, d, J = 10 Hz, 19-H). IR spectrum: 1705, 1717, 2812, 3601 cm^{-1}. For $C_{28}H_{48}O_3$ (432·7) calculated: 77·73% C, 11·18% H; found: 77·64% C, 11·25% H.

The analyses were carried out in the Analytical Laboratory of this Institute (head Dr J. Horáček). The IR *spectra were recorded by Mrs K. Matoušková and interpreted by Dr S. Vašíčková. The* ^{1}H-NMR *spectra were recorded by Dr D. Šaman, Mrs J. Jelínková and M. Snopková. The mass spectra were recorded and interpreted by Dr F. Tureček.*

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