PREPARATION OF 2-METHYL-3-OXO TRITERPENOIDS OF 18α-OLEANANE SERIES AND THE CONFORMATION OF RING A*

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2-Methyl-3-hydroxy derivatives *X*, *XIII*, *XV*, *XVI* and 2-methyl-3-oxo derivatives *III*, *VIII* and *IX* of 19β,28-epoxy-18α-oleanane were prepared from ketones *I* and *XVII*. From spectral data it was deduced that compounds *III*, *VIII* and *XV* containing a 2β-methyl group have their A ring in boat conformation. Both isomeric 2-methyl-3-oxo derivatives *VIII* and *IX* are approximately equally stable; 52 ± 4% of the 2β-isomer *VII* were found in their equilibrium mixture.

The conformation of the ring A in 4,4-dimethyl steroids and triterpenoids was studied mainly in 2,3-disubstituted derivatives which have highly polar functional groups (fluorine, chlorine, bromine, hydroxyl, alkoxyl, acetoxyl or carbonyl group) in the positions 2 and 3. In many cases it was found that the ring A exists in boat form (see lit.[1-4] and the references therein). In order to eliminate the effect of polar interactions between the substituents on the conformation of the ring A or on the position of the equilibrium of the chair and boat forms, compounds had to be prepared in which at least one of the substituents in the positions 2 and 3 would be a non-polar group (for example an alkyl group). In this paper we study the preparation and the conformation of the ring A of 2-methyl-3-oxo and 2-methyl-3-hydroxy derivatives of 19β,28-epoxy-18α-oleanane.

For the introduction of the methyl group into position 2 Claisen condensation of 3-oxo derivatives with ethyl formate is usually used in steroid chemistry, followed by hydrogenation of 2-hydroxymethylene-3-ketones in the presence of palladium on charcoal. In this procedure the more stable 2α-methyl ketones are obtained which are formed probably during the chromatographic purification by isomerization of the less stable 2β-isomers formed originally. 2β-Methyl ketones are prepared by hydrogenation of the 1(2)-double bond in 2-methyl-1-en-3-ones (see refs[5-8] and the references therein). These methods were applied to 19β,28-epoxy-18α-oleanan-3-one (*I*).

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On condensation of ketone *I* with ethyl formate in the presence of sodium hydride[9] hydroxymethylene ketone *VII* was obtained[10]. Hydrogenation of compound *VII* on palladium gave 2β-methyl ketone *VIII* as the main product, contaminated with the 2α-isomer *IX* and the unsaturated ketone *VI*. 2β-Methyl ketone *VIII* is also formed as the main product during the hydrogenation in acetic acid on platinum catalyst. In this case the 2α-isomer *IX* and polar substances occur as by-products. Attempts to obtain pure 2β-methyl ketone *VIII* from these mixtures by crystallization or chromatography failed owing to rapid isomerization of this ketone. We succeeded in separating only a small amount of 2α-methyl ketone *IX* from the mixture chromatographically. Isomerization of the crude product of hydrogenation did not afford pure 2α-methyl ketone *IX*, because in contrast to steroid 2-methyl-3-oxo derivatives both isomeric ketones *VIII* and *IX* are approximately equally stable. Further, attempts to obtain ketone *VIII* by hydrogenation of unsaturated ketones *II* and *VI* were made. Ketone *II* was prepared from crude 2β-methyl ketone *VIII* (obtained from hydroxymethylene ketone *VII*) by bromination and subsequent dehydrobromination of the bromo ketone *III* formed. Ketone *VI* was obtained by Mannich reaction of ketone *I* with paraformaldehyde and dimethylamine hydrochloride in boiling dioxane[11]. The ketone *VI* prepared in this manner is usually contaminated with another substance which cannot be separated chromatographically. In pure state ketone *VI* was obtained by oxidation of alcohol *IV*. The *cisoid*-arrangement of the double bond and the carbonyl group in ketone *VI* follows from the low intensity of the absorption in the ultraviolet region (log ε 3·65; see[12]) and from the low ratio of the integrated absorption intensities of the carbonyl group and the double bond bands in the *IR* spectrum ($r^B = B_{(C=O)}/B_{(C=C)} = 2{\cdot}0$; see[13]). On hydrogenation of unsaturated ketones *II* and *VI* in the presence of palladium on charcoal 2β-methyl ketone *VIII* was obtained as the main product, contaminated again by a considerable amount of the 2α-isomer *IX*.

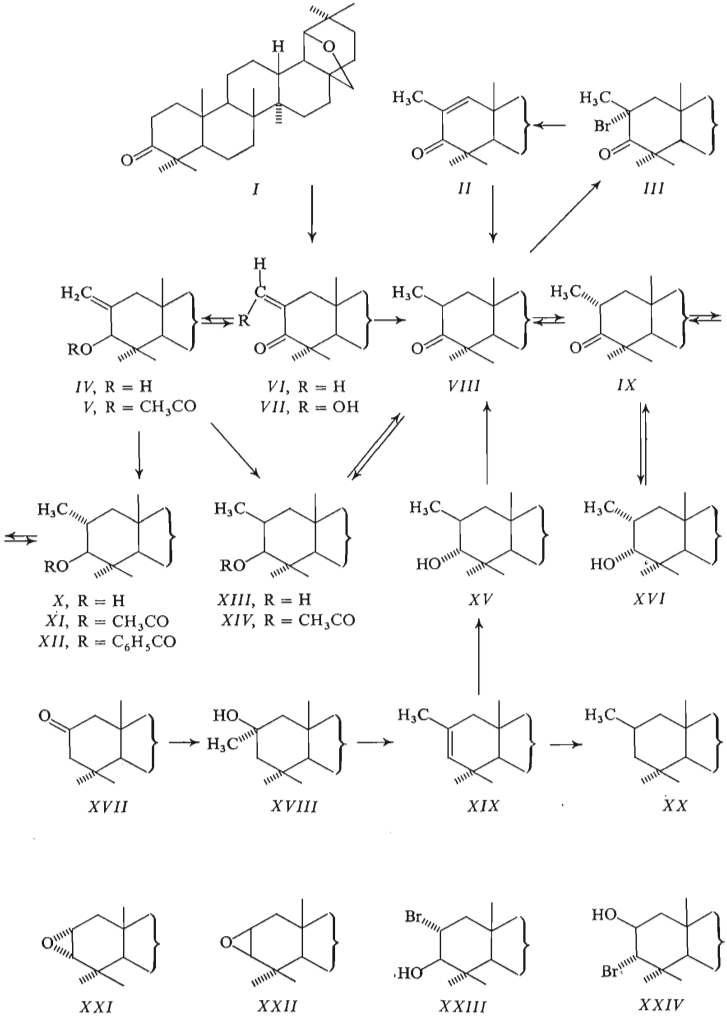
As we were unable to prepare ketones *VIII* and *IX* in pure state by any of these procedures, it was necessary to obtain them on oxidation of corresponding hydroxy derivatives *X*, *XIII*, *XV* and *XVI* under conditions when isomerization does not take place. For the synthesis of these hydroxy derivatives the following three procedures were used:

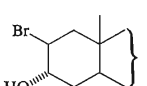
The first of them starts with 2-methylene-3β-hydroxy derivative *IV* which was prepared on reduction of hydroxymethylene ketone *VII* with lithium aluminum hydride or on reduction of methylene ketone *VI* with sodium borohydride. Hydrogenation of the exocyclic double bond of alcohol *IV* on platinum in acetic acid gave rise to a mixture of 2α-methyl-3β-ol *X* and 2β-methyl-3β-ol *XIII* which was separated by chromatography. As a by-product of hydrogenation a mixture of ketones *VIII* and *IX* was isolated in which the 2β-isomer *VIII* prevailed according to optical rotation value. The presence of ketones *VIII* and *IX* in the reaction mixture can be explained by a rearrangement of the unsaturated alcohol *IV*. The rearrangement does not depend on the protic character of the solvent, since it takes place even when hydro-

genation is carried out in dioxane. During hydrogenation on palladium in a mixture of benzene and ethanol an almost quantitative rearrangement takes place. The product is 2β-methyl ketone *VIII* contaminated with 2α-isomer *IX*.In view of the easy isomerization of ketone *VIII* it cannot be decided whether the 2α-isomer *IX* is a direct product of the rearrangement, or whether it is formed from the 2β-isomer *VIII* during hydrogenation or during the working up of the reaction mixture. The rearrangement could be prevented by protecting the hydroxyl group by acetylation. The hydrogenation of acetate *V* (on platinum in acetic acid) led to a mixture of saturated acetates *XI* and *XIV*, which was deacetylated without further separation either by alkaline hydrolysis or by reduction with lithium aluminum hydride. A mixture of alcohols *X* and *XIII* in an approximate 1 : 1 ratio was obtained.

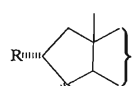
The second method of preparation of hydroxy derivatives is based on hydride reduction of ketones *VIII* and *IX*. 2β-Methyl ketone *VIII* does not react with sodium borohydride under the usual conditions (methanol, room temperature), which is probably due to steric hindrance. On the contrary 2α-methyl ketone *IX* is reduced rapidly and it gives 2α-methyl-3β-ol *X* as the main product in addition to a small amount of 2α-methyl-3α-ol *XVI*. Since 2β-methyl ketone *VIII* is isomerized to an equilibrium mixture of both ketones *VIII* and *IX* in alkaline medium, the reduction of 2β-methyl ketone *VIII* (or its mixture with the 2α-isomer *IX*) with sodium borohydride in the presence of sodium hydroxide leads to alcohols *X* and *XVI* with a 2α-methyl group only. After reduction of the crude ketone *VIII* which was contaminated with 2-methylene ketone *VI*, the unsaturated alcohol *IV* was also isolated from the reaction mixture. On the other hand, 2β-methyl ketone *VIII* is reduced with lithium aluminum hydride, and 2β-methyl-3β-ol *XIII* is formed as the sole product. The synthesis of the last isomer – 2β-methyl-3α-ol *XV* – starts from 2-oxo derivative[14] *XVII*. Its reaction with methyllithium gave rise to the tertiary alcohol *XVIII* which on dehydration gave 2-methyl-2-ene *XIX* (for an analogy see[15]). Substance *XIX* was also obtained by pyrolysis of benzoate *XII*. Hydroboration of the olefin *XIX* gave 2β--methyl-3α-ol *XV* as the main product in addition to a mixture of ketones *VIII* and *IX*. Hydrogenation of the olefin *XIX* gave the saturated derivative *XX*.

The effect of methyllithium on epoxides *XXI* and *XXII* and on *trans*-bromohydrins *XXIII* – *XXV* was studied as another possibility of the preparation of 2-methyl-3--hydroxy derivatives. However, epoxides *XXI* and *XXII* did not react with methyllithium and in the case of bromohydrins either epoxides were formed or the ring A was contracted, depending on their configuration. A similar contraction of the ring A was observed in the reaction of epoxides *XXI* and *XXII* with Grignard's reagent[16]. From bromohydrins *XXIII* and *XXIV* that have bromine in α-configuration A-nor derivative *XXVI* with an α-configuration of the hydroxy ethyl group was formed on reaction with methyllithium; its identification was completed by the oxidation to ketone *XXVII* (see[16]). As a by-product of the reaction with methyllithium 2β,3β-epoxide *XXII* was detected by thin-layer chromatography. Reaction of 2β-bromo-3α-hydroxy

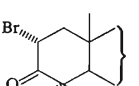

I
II
III
IV, R = H
V, R = CH3CO
VI, R = H
VII, R = OH
VIII
IX
X, R = H
XI, R = CH3CO
XII, R = C6H5CO
XIII, R = H
XIV, R = CH3CO
XV
XVI
XVII
XVIII
XIX
XX
XXI
XXII
XXIII
XXIV



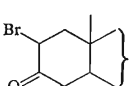
XXV



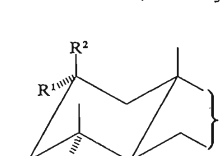
XXVI, R = $CH_3CH(OH)$
XXVII, R = CH_3CO



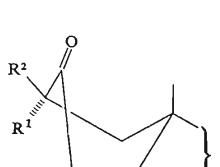
XXVIII



XXIX



C



B

III, R^1 = Br, R^2 = CH_3
VIII, R^1 = H, R^2 = CH_3
IX, R^1 = CH_3, R^2 = H
XXX, R^1 = CH_3, R^2 = Br

derivative *XXV* with methyllithium gave 2α,3α-epoxide *XXI*. It is interesting that the stereochemistry of these reactions is the same as in the case of the reactions of steroid *trans*-2,3-bromohydrins with silver carbonate on Celite[17].

Oxidation of 2α-methyl-3-ols *X* and *XVI* with sodium dichromate in acetic acid and in the presence of sodium acetate gave 2α-methyl ketone *IX*, while a similar oxidation of 2β-methyl-3-ols *XIII* and *XV* gave pure 2β-methyl ketone *VIII*. The most suitable method for the preparation of ketones *VIII* and *IX* is the hydrogenation of methylene ketone *VI* (or hydroxymethylene ketone *VII*) on palladium, then reduction of the crude 2β-methyl ketone *VIII* either with sodium borohydride in alkaline medium, or with lithium aluminum hydride, followed by chromatographic purification of alcohols *X* and *XIII*, and finally their oxidation to ketones. The configuration of the prepared substances follows from the mentioned reaction sequence, from the rule of α-attack (in the case of hydrogenation, addition of diborane and methyllithium and bromination of ketones), from the known course of the reduction of the 3-oxo group with hydrides (formation of 3β-ols) and from the analogies in the steroid field[5-8,15].

We further compared the thermodynamic stability of isomeric 2-methyl-3-oxo derivatives *VIII* and *IX* and analogous derivatives with a polar group in position 2. Isomerization of both 2-methyl ketones *VIII* and *IX* in acid medium (hydrochloric acid in chloroform) gave an equilibrium mixture in which 51 ±3% of the 2β-isomer *VIII* were present according to optical rotation. The base-catalyzed isomerization

TABLE I

Coupling Constants and Chemical Shifts of Ring A Protons

Measured at 100 MHz in deuteriochloroform, unless stated otherwise; tetramethylsilane as internal standard; the three-spin systems were analysed as ABX systems, higher spin systems as first order spectra; accuracy of coupling constants ±0·3 Hz.

Compound	Substituents		Coupling constants, Hz						Chemical shifts, δ, ppm				
	2	3	$-J_{1,1}$	$J_{1\alpha,2}$	$J_{1\beta,2}$	$\sum J_{1,2}$ [a]	$J_{2,3}$	J_{2-H,CH_3}	1α-H	1β-H	2-H	3-H	2-CH_3
IX	α-CH_3	=O	13·1	~13	≦5·7	~19	—	6·3	<1·70	2·06	2·77	—	1·02
IX[b]	α-CH_3	=O	13·2	~13	≦5·8	~19	—	6·3	<1·50	1·82	2·55	—	1·10
XXVIII[c]	α-Br	=O	12·9	13·1	6·2	19·3	—	—	1·79	2·67	5·06	—	—
VIII	β-CH_3	=O	~13	~11	~9	~20	—	6·3	~1·96	[d]	2·83	—	0·99
VIII[b]	β-CH_3	=O	[d]	~11	~9	~20	—	6·3	[d]	[d]	2·49	—	1·05
XXIX[c,e]	β-Br	=O	13·4	11·2	9·4	20·6	—	—	2·48	2·08	5·11	—	—
X	α-CH_3	β-OH	[d]	[d]	[d]	[d]	10·0	~6	[d]	[d]	[d]	2·74	0·99
XXIII	α-Br	β-OH	12·8	12·3	4·4	16·7	10·4	—	~1·53	2·41	4·38	3·23	—
XVI	α-CH_3	α-OH	[d]	[d]	[d]	[d]	2·0	~6	[d]	[d]	[d]	3·13	~0·95
XIII	β-CH_3	β-OH	[d]	[d]	[d]	[d]	2·3	~6·5	[d]	[d]	[d]	3·30	0·98
XV	β-CH_3	α-OH	[d]	[d]	[d]	[d]	~11·5[f]	~6	[d]	[d]	[d]	3·46	~0·94
XXV[g]	β-Br	α-OH	[d]	[d]	[d]	18·3	11·9	—	~2·14	~2·14	4·34	3·88	—

[a] $\sum J_{1,2} = J_{1\alpha,2} + J_{1\beta,2}$; [b] in C_6D_6; [b] practically identical values were obtained in corresponding 2-bromo derivative of 20β,28-epoxy-18α, 19βH-ursan-3-one; [d] undeterminable value; [e] lit.[19]; [f] in a mixture of $CDCl_3$ and C_6H_6 (2 : 1) 11·3 Hz were found; [g] lit.[4].

(potassium hydroxide in a mixture of methanol and benzene) led to a value 53 ± 3%. In corresponding 2-chloro, bromo and methoxy ketones about 42% of the 2β-isomer[3,18] were found in equilibrium mixtures. Hence, the substitution of the methyl group by a polar substituent (Cl, Br, OR) has little effect on the difference of Gibbs energy between 2α- and 2β-substituted 3-oxo derivatives (1·0 ± 0·7 kJ . mol^{-1} in favour of the α-isomer).

The spectral data of the prepared 2-methyl derivatives are surveyed in Tables I and II. In Table I the parameters of the ^{1}H-NMR spectra of analogous bromo derivatives (bromo ketones *XXVIII* and *XXIX* and bromohydrins *XXIII* and *XXV*) in which the conformation of the ring A is already known[1,4,19] are also given for comparison. For the conformation of the ring A in 3-oxo derivatives substituted in position 2 the values of vicinal coupling constants $J_{1\alpha,2}$, $J_{1\beta,2}$ and their sum $(\sum J_{1,2})$ (ref.[1-3]) are characteristic. From Table I it is evident that in 2β-methyl ketone *VIII* these values are practically identical with the values found in 2β-bromo ketone *XXIX*; it is similar in the case of 2α-isomers *IX* and *XXVIII*. Hence, the geometry of the ring A in corresponding 2-methyl and 2-bromo ketones is similar. The coupling constants of 2-methyl ketone *IX* are in agreement with the chair form *IXC*. In the 2β-isomer *VIII* the high values $J_{1\alpha,2}$ and $J_{1\beta,2}$ and especially the high value of $\sum J_{1,2}$ do not correspond to the chair form *VIIIC*, and indicate that the boat form *VIIIB** predominates highly at conformation equilibrium. In agreement with this is the strongly positive Cotton effect of the ketone *VIII* (Table II), characteristic of the boat form of similar

TABLE II

Characteristic Spectral Parameters of 3-Oxo Derivatives

Compound	Substituents in the position 2	IR[a]	UV[b]		CD[c]		
		ν(CO) cm^{-1}	λ nm	ε l.mol^{-1}.cm^{-1}	λ nm	Δε	Γ nm
IX	α-CH_3	1 706	296[d]	29	293[d]	−0·60	39
VIII	β-CH_3	1 713	294[d]	35	293[d]	+3·65	37
III	α-Br, β-CH_3	1 704	320	142	326	−1·64	38
					285	+0·40	25

[a] Measured in approximately 0·5% solutions in tetrachloromethane on a UR-20 spectrophotometer, calibrated in the carbonyl region using atmospheric water vapour; cell thickness 1 mm, accuracy ±1 cm^{-1}; [b] measured in cyclohexane on a Unicam SP 700; [c] measured in dioxane on a Roussel-Jouan 185 dichrograph; [d] the band has a vibronic structure.

* For the sake of simplicity one of the possible classical boat forms is shown in the conformational formula *B*, without regard to the true geometry of the boat form of the ring A.

derivatives[3]. These results and the results given in papers[1-3,19] can now be generalized in the following manner: in 3-oxo derivatives which have two axial methyl groups (4β, 10β) and a further substituent in the position 2β (alkyl, halogen, OR) in the ring A, the ring A exists in the boat form practically exclusively.

From spectral data of bromo ketone *III* (Table II) the conformation of the ring A and the configuration of bromine in position 2 can be derived simultaneously, similarly as in the analogous steroid 2-methyl-2-bromo ketone[5]. The small change of the carbonyl stretching frequency, the high bathochromic shift and the increase in intensity of the $n \rightarrow \pi^*$ transition of bromo ketone in comparison with ketones *VIII* and *IX* clearly indicate the presence of an axial bromine atom. Of the four possibilities (*IIIC*, *IIIB*, *XXXC*, *XXXB*) the forms *IIIC* and *XXXB* can be thus eliminated. Between the remaining two forms the decision can be made on the basis of the sign of the Cotton effect; the strongly negative Cotton effect at 326 nm is compatible with the form *IIIB* only, so that the mentioned bromo ketone is the 2α-bromo-2β-methyl derivative with the ring A in boat form. The difference of the $\Delta\varepsilon$ values (−5·3) between the bromo ketone *III* and 2β-methyl ketone *VIII* (conformation *VIIIB*) corresponds to the introduction of an axial bromine into the negative octant. The CD curve of bromo ketone *III* also shows a weak positive maximum at 285 nm. It is possible that it is due to the chair form *IIIC*, but its content must be negligible because in the carbonyl region of the IR spectrum no band could be detected that would correspond to the presence of an equatorial bromo ketone.

From the 1H-NMR spectra of 2-methyl-3-ols *X*, *XIII*, *XV* and *XVI* only the vicinal coupling constant $J_{2,3}$ could be obtained. The observed $J_{2,3}$ values correspond to *cis*-configuration of the methyl and the hydroxyl group in compounds *XIII* and *XVI* and to *trans*-configuration in compounds *X* and *XV*. These values are in 2α-methyl-3β-ol *X* and 2β-methyl-3α-ol *XV* almost identical as in analogous 2-bromo-3-ols *XXIII* and *XXV*, respectively. In addition to this from the high $J_{2,3}$ value of 2β-methyl-3α-ol *XV* it is evident that the ring A exists practically in boat form only. In papers[3,4] it was found that in similar triterpenoid derivatives, containing bromine or chlorine in the position 2β the boat form prevails strongly, while if an OR group is in this position, the chair and the boat forms occur in a 1 : 1 ratio (unless the boat form is further stabilized by an intramolecular hydrogen bond). From this comparison it follows that the methyl group in the position 2β destabilizes the chair form approximately equally as bromine or chlorine, but much more strongly than an oxygen containing functional group.

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotations were measured in chloroform (*c* 0·5—1·5) on an automatic polarimeter, Bendix–Ericsson, with a ±1—2° accuracy. The infrared spectra were measured in chloroform on a UR-10 spectrophotometer (Zeiss, Jena),

and the ultraviolet spectra in cyclohexane on a Unicam SP 700 spectrophotometer. The ^{1}H-NMR spectra were measured in deuteriochloroform at 100 MHz on a Varian HA-100 instrument, with tetramethylsilane as internal reference. The chemical shifts are given in ppm in δ-scale. In Table I and in the text only the signals of characteristic groups in ring A are given. Further the singlets of seven skeletal methyl groups were found in the spectra of all measured compounds, in the 0·70—1·60 ppm region, the singlet of 19αH (3·52—3·55 ppm) and the AB system of the $C_{(28)}H_2$ group (3·43—3·45 d and 3·77—3·78 d, $J \sim 8$ Hz). For column chromatography neutral alumina was used (Reanal, activity II) and silica gel (Silpearl, Kavalier, Votice). The course of the reactions was followed and the purity of the samples checked by thin-layer chromatography on alumina, silica gel G (Type 60, Merck) and silica gel with 10% of silver nitrate. The chromatograms were run in heptane–ether (7 : 3) or benzene–ether (19 : 1). The identity of the substances was confirmed by mixture melting points, infrared spectra and thin-layer chromatography. Under the "conventional work -up" the following is meant: washing of the organic extract with water, saturated sodium hydrogen carbonate solution, water and drying over sodium sulfate. The solvents were distilled off under reduced pressure. Samples for analysis were dried at 100°C and 20—200 Pa over phosphorus pentoxide for 8—12 h.

19β,28-Epoxy-2-methyl-18α-olean-1-en-3-one (*II*)

A mixture of bromo ketone *III* (0·80 g), anhydrous lithium chloride (0·80 g), lithium carbonate (1 g) and dimethylformamide (25 ml) was refluxed for 9 h, then diluted with water and extracted with ether. The extract was washed with dilute hydrochloric acid, sodium carbonate solution and water and filtered through a layer of alumina. Ether was distilled off, the residue dissolved in benzene and chromatographed on alumina. Ketone *II* was eluted with benzene, yield 0·50 g, m.p. 248—250°C (benzene–heptane), $[\alpha]_D$ +110°. IR spectrum: 1 660 (CO), 1 037 cm^{-1} (COC). UV spectrum: 235 nm (log ε 4·06), 333 nm (log ε 1·88). ^{1}H-NMR spectrum: 1·76 d; $J_{1,r.} = 1·3$ Hz (2-CH_3); 6·88 bs (1-H). For $C_{31}H_{48}O_2$ (452·7) calculated: 82·24% C, 10·69% H; found: 82·50% C, 10·67% H.

2α-Bromo-19β,28-epoxy-2β-methyl-18α-oleanan-3-one (*III*)

A solution of bromine (367 mg) in acetic acid (4·2 ml) was added dropwise over 30 min to a solution of crude ketone *VIII* (1 g) in a mixture of chloroform (12 ml) and acetic acid (12 ml) and the mixture was allowed to stand in darkness for 1·5 h. After dilution with water and chloroform it was submitted to the conventional work-up. On crystallization from a mixture of chloroform and methanol bromo ketone *III* (0·80 g) was obtained, m.p. 234—235°C, $[\alpha]_D$ +18°. IR spectrum: 1 698 (CO), 1 037 cm^{-1} (COC). ^{1}H-NMR spectrum: 1·845 s (2β-CH_3); 2·59 d (1α-H; broadening caused by long-range coupling); 2·44 d (1β-H); $J_{1,1} = 15·5$ Hz. For $C_{31}H_{49}BrO_2$ (533·6) calculated: 69·40% C, 9·25% H, 14·94% Br; found: 68·95% C, 9·48% H, 14·89% Br.

19β,28-Epoxy-2-methylene-18α-oleanan-3β-ol (*IV*)

A) A solution of sodium borohydride (300 mg) in methanol (50 ml) was added under stirring to a solution of ketone *VI* (300 mg) in benzene (100 ml) and the mixture was allowed to stand at room temperature overnight, then decomposed with a saturated ammonium chloride solution and worked up in the conventional manner. After crystallization from chloroform–benzene hydroxy derivative *IV* was obtained (230 mg), m.p. 299—301°C, $[\alpha]_D$ +35°. IR spectrum: 3 600 (OH), 3 090, 1 653, 900 (C=CH_2), 1 030 cm^{-1} (COC). For $C_{31}H_{50}O_2$ (454·7) calculated: 81·88% C, 11·08% H; found: 81·71% C, 11·10% H.

B) A suspension of lithium aluminum hydride (3 g) in ether (100 ml) was added to a solution of ketone *VII* (2 g) in 150 ml of a benzene–ether mixture (1 : 1) and the mixture was allowed to stand at room temperature for 8 h. After decomposition with methanol and saturated sodium sulfate solution the organic layer was separated and worked up in the conventional manner. After crystallization from a mixture of chloroform and benzene compound *IV* was obtained (1·9 g), identical with the preparation described under *A*). M.p. 295—297°C, $[\alpha]_D$ +37°.

C) A mixture of acetate *V* (50 mg), potassium hydroxide (200 mg), ethanol (4 ml) and benzene (4 ml) was refluxed for 3 h, diluted with water, extracted with ether and submitted to the conventional work-up. After crystallization from benzene compound *IV* was obtained (40 mg), identical with the sample mentioned under *A*. M.p. 298—300°C, $[\alpha]_D$ +36°.

3β-Acetoxy-19β,28-epoxy-2-methylene-18α-oleanane (*V*)

A mixture of hydroxy derivative *IV* (790 mg), pyridine (75 ml) and acetic anhydride (25 ml) was heated at 100°C for 6 h and then allowed to stand at room temperature for 2 days. After pouring onto ice the formed precipitate was filtered off under suction, washed with water and crystallized from a mixture of chloroform and methanol. Yield 720 mg of acetate *V*, m.p. 290 to 291°C, $[\alpha]_D$ +39°. IR spectrum: 3090, 1655, 900 (C=CH_2), 1729, 1380, 1255 (CH_3COO), 1033 cm^{-1} (COC). For $C_{33}H_{52}O_3$ (496·8) calculated: 79·78% C, 10·55% H; found: 79·76% C, 10·58% H.

19β,28-Epoxy-2-methylene-18α-oleanan-3-one (*VI*)

A) A mixture of hydroxy derivative *IV* (100 mg), anhydrous sodium acetate (150 mg), sodium dichromate dihydrate (150 mg) and acetic acid (25 ml) was stirred for 4 h. During this time all hydroxy derivative *IV* dissolved. The mixture was diluted with water, extracted with ether and the ethereal extract worked up in the conventional manner. After crystallization of the crude product *VI* (97 mg) from a mixture of chloroform and methanol 71 mg of ketone *VI* were obtained, m.p. 231—233°C, $[\alpha]_D$ +90°. IR spectrum: 3090, 1684, 1607 (CO—C=CH_2), 1032 cm^{-1} (COC). UV spectrum: 230 nm (log ε 3·65). For $C_{31}H_{48}O_2$ (452·7) calculated: 82·24% C, 10·69% H; found: 82·18% C, 10·73% H.

B) Paraformaldehyde (400 mg) and dimethylamine hydrochloride (1 g) were added to a solution of ketone *I* (2 g) in dioxane (150 ml) and the mixture was refluxed for 10 h. After dilution with water to triple its volume it was extracted with chloroform. The extract was washed with dilute hydrochloric acid and worked up in the conventional manner. Yield 1·9 g of ketone *VI*, m.p. 228—231°C (chloroform–methanol), $[\alpha]_D$ +88°. The preparations prepared in this manner contain chromatographically inseparable impurity of unknown structure. After reduction of the crude product *VI* to hydroxy derivative *IV* and after purification of derivative *IV* the pure ketone *VI* can be prepared as under *A*).

19β,28-Epoxy-2-hydroxymethylene-18α-oleanan-3-one (*VII*)

Ethyl formate (1·6 ml) and a solution of 19β,28-epoxy-18α-oleanan-3-one[20] (*I*, 4 g) in benzene (160 ml) were added under nitrogen and under stirring to a suspension of sodium hydride (4 g) in benzene (50 ml) and the mixture was stirred for 24 h. Methanol was added (16 ml) and the solution was acidified with 2M hydrochloric acid and extracted with benzene. The extract was washed with water and dried over sodium sulfate. After evaporation of benzene and crystallization from benzene–ethanol crude derivative *VII* (3·28 g) was obtained, m.p. 248—252°C. This

preparation was used for further reactions. The analytical sample obtained by chromatography on silica gel (elution with benzene) and repeated crystallization from benzene–ethanol had m.p. 253–257°C, $[\alpha]_D$ +76°. Lit.[10] gives m.p. 258–259°C. IR spectrum: 1 634, 1 584 (CO—C=C). 1 037 cm^{-1} (COC). UV spectrum in methanol: 295 nm (log ε 3·88); in methanolic 10^{-2}M-NaOH: 315 nm (log ε 4·22). For $C_{31}H_{48}O_3$ (468·7) calculated: 79·43% C, 10·32% H; found: 79·31% C, 10·58% H.

19β,28-Epoxy-2β-methyl-18α-oleanan-3-one (*VIII*)

A) A mixture of hydroxy derivative *XIII* (700 mg), anhydrous sodium acetate (700 mg), sodium dichromate dihydrate (1 g) and acetic acid (100 ml) was stirred at room temperature for 3 h. Derivative *XIII* dissolved within 20–30 min. The excess of the reagent was decomposed with methanol, the mixture was diluted with water, extracted with ether and further worked up in the conventional manner. After concentration of the ethereal solution ketone *VIII* (680 mg) crystallized out, m.p. 237–239°C, $[\alpha]_D$ +156·5°. Crystallization from a benzene–light petroleum mixture gave ketone *VIII* (439 mg) of m.p. 237–239°C (according to thin-layer chromatography on silica gel a partial isomerization to α-isomer *IX* takes place during the heating to the melting point), $[\alpha]_D$ +157·5°. IR spectrum: 1707 (CO), 1037 cm^{-1} (COC). For $C_{31}H_{50}O_2$ (454·7) calculated: 81·88% C, 11·08% H; found: 81·74% C, 11·27% H. During the repetitions of this oxidation the crude products and the samples after crystallizations from benzene–light petroleum or chloroform–methanol had $[\alpha]_D$ within the +157 ± 2° limits.

B) Hydroxy derivative *XV* (51 mg) was oxidized in the same manner as under *A*. Ketone *VIII* (40 mg) was obtained which was identical with the sample described under *A*. M.p. 233–237°C (chloroform–methanol), $[\alpha]_D$ +155°.

C) Crude hydroxymethylene ketone *VII* (500 mg) was dissolved in a mixture of benzene (50 ml) and ethanol (50 ml). Palladium (10%) on charcoal (200 mg) was added and the mixture shaken under hydrogen for 30 h (until the reaction with iron trichloride was negative). The catalyst was filtered off, the solvents were distilled off under reduced pressure. Crude ketone *VIII* (330 mg) contaminated with the isomer *IX* and ketone *VI* was obtained, m.p. 210–214°C (chloroform–methanol), $[\alpha]_D$ +137°. Attempts at purification by repeated crystallization did not afford pure ketone *VIII*. During attempts at chromatographic separation partial isomerization to the α-isomer *IX* took place.

D) A solution of hydroxymethylene ketone *VII* (400 mg) in acetic acid (60 ml) was hydrogenated on Adams catalyst (30 mg) for 6 h. The catalyst was filtered off and water was added to the solution. The separated product was filtered off under suction, washed with water and crystallized from chloroform–methanol. Crude ketone *VIII* (350 mg) was obtained, contaminated with the isomer *IX* and traces of polar substances. M.p. 205–215°C, $[\alpha]_D$ +125°. Repeated crystallization from chloroform–methanol and from ethyl acetate gave a preparation melting at 231–233°C, $[\alpha]_D$ +139°.

E) A mixture of ketone *II* (200 mg), 5% palladium on charcoal (100 mg), benzene (25 ml) and ethanol (20 ml) was shaken under hydrogen for 2 h. The catalyst was filtered off and the solvents were distilled off under reduced pressure. Crystallization from chloroform–methanol gave ketone *VIII*, contaminated with the isomer *IX*. M.p. 221–228°C, $[\alpha]_D$ +142°.

F) A mixture of ketone *VI* (200 mg), 10% of palladium on charcoal (50 mg), benzene (50 ml) and ethanol (50 ml) was hydrogenated for 2 h. After working up as under *E* a mixture of ketones *VIII* and *IX* (190 mg) was obtained, $[\alpha]_D$ +113°.

G) Hydroxy derivative *IV* (500 mg) was hydrogenated in a mixture of benzene (50 ml) and ethanol (50 ml) on 10% palladium on charcoal (50 mg) as under *E*. A mixture of ketones *VIII* and *IX* was obtained (420 mg), m.p. 213–217°C, $[\alpha]_D$ +129°.

19β,28-Epoxy-2α-methyl-18α-oleanan-3-one (*IX*)

A) Hydroxy derivative *X* (850 mg) was oxidized in the same manner as in the preparation of ketone *VIII* under *A*. Concentration of the ethereal extract induced the crystallization of ketone *IX* (820 mg), m.p. 245–250°C, $[\alpha]_D$ +32·7°. Crystallization from a benzene–light petroleum mixture gave 568 mg of ketone *IX*, m.p. 253–254°C, $[\alpha]_D$ +32·5°. IR spectrum: 1700 (CO), 1037 cm^{-1} (COC). For $C_{31}H_{50}O_2$ (454·7) calculated: 81·88% C, 11·08% H; found: 81·95% C, 11·14% H. When this oxidation was reproduced the crude samples and the crystallized samples had $[\alpha]_D$ within the +32·5° ± 0·5° limit.

B) Applying the same procedure as under *A* hydroxy derivative *XVI* (50 mg) was converted to ketone *IX* (35 mg), m.p. 250–251°C (chloroform–methanol), $[\alpha]_D$ +33°.

C) Crude ketone *VIII* (350 mg; see preparation of compound *VIII* under *C*) was chromatographed on alumina (50 g). Benzene–light petroleum (1 : 1) eluted ketone *IX* (80 mg), m.p. 251–252°C (chloroform–methanol), $[\alpha]_D$ +34°. Further elution with benzene–light petroleum and benzene alone gave a mixture of ketones *VIII*, *IX* and *VI*.

Isomerization of Ketones *VIII* and *IX*

A) Hydrochloric acid (36%; 0·14 ml) was added to a solution of ketone *VIII* or *IX* (50–60 mg) in chloroform (5 ml) and the mixture was shaken and allowed to stand at room temperature for 41 h. After dilution with chloroform and working up in the conventional manner the residue was induced to crystallize by addition of a few drops of methanol and then dried at 100°C for 3 h. Infrared spectrophotometry and thin-layer chromatography confirmed that no side-reactions took place. The equilibrium mixture obtained in this manner (compounds *VIII* and *IX*) had $[\alpha]_D$ +96° ± 3° (average of 10 independent measurements).

B) A solution of potassium hydroxide (250 mg) in methanol (5 ml) was added to a solution of ketone *VIII* or *IX* (50–60 mg) in benzene (5 ml) and the mixture was allowed to stand at room temperature for 65 h. After dilution with water, extraction with ether and working up as under *A*, the obtained equilibrium mixture had $[\alpha]_D$ +98·5° ± 2° (average of 10 independent measurements).

19β,28-Epoxy-2α-methyl-18α-oleanan-3β-ol (*X*) and
19β,28-Epoxy-2α-methyl-18α-oleanan-3α-ol (*XVI*)

Crude ketone *VIII* (2 g), contaminated with ketones *VI* and *IX*, (see the preparation of compound *VIII* under *C*), was dissolved in benzene (100 ml) and a solution of sodium borohydride (2 g) in methanol (60 ml) and sodium hydroxide (500 mg) was added in parts to it; the mixture was allowed to stand at room temperature for 10 h and then decomposed with a saturated ammonium chloride solution. Benzene (100 ml) was added and the organic layer was separated and worked up in the conventional manner. The crude product (2 g) was dissolved in benzene and chromatographed on silica gel (250 g). Benzene–ether mixture (19 : 1) eluted gradually: 100 mg of a mixture of non-polar substances which were not identified; 180 mg of hydroxy derivative *XVI* which was rechromatographed on alumina with benzene and crystallized from chloroform–heptane to give 70 mg of a product with m.p. 244·5–246°C, $[\alpha]_D$ +35°. IR spectrum:

3630 (OH), 1034 cm^{-1} (COC). For $C_{31}H_{52}O_2$ (456·7) calculated: 81·52% C, 11·48% H; found: 81·28% C, 11·51% H. The same solvent mixture eluted further 90 mg of a mixture of substances *XVI* and *IV* and 250 mg of derivative *IV*, identical with the sample described above. M.p. 300 to 301°C (chloroform–heptane), $[\alpha]_D$ +36°.

A mixture of compounds *IV* and *X* (400 mg) was then eluted. Benzene–ether mixture (9 : 1) eluted 950 mg of hydroxy derivative *X*. M.p. 253—255°C (chloroform–heptane), $[\alpha]_D$ +35°. IR spectrum: 3635, 3615 (OH), 1030 cm^{-1} (COC). For $C_{31}H_{52}O_2$ (456·7) calulated: 81·52% C, 11·48% H; found: 81·31% C, 11·44% H.

3β-Benzoyloxy-19β,28-epoxy-2α-methyl-18α-oleanane (*XII*)

A solution of hydroxy derivative *X* (100 mg) and benzoyl chloride (2 ml) in pyridine (20 ml) was allowed to stand at room temperature for 15 h and then diluted with water and extracted with ether. The extract was washed with dilute hydrochloric acid and worked up in the conventional manner. The residue was dissolved in benzene and the solution filtered through silica gel (5 g). Benzoate *XII* (80 mg) was obtained, m.p. 241—243°C (chloroform–methanol), $[\alpha]_D$ +39°. IR spectrum: 1707, 1600, 1582, 1276, 1113 cm^{-1} (C_6H_5COO). For $C_{38}H_{56}O_3$ (560·8) calculated: 81·38% C, 10·07% H; found: 81·26% C, 10·12% H.

19β,28-Epoxy-2β-methyl-18α-oleanan-3β-ol (*XIII*) and
19β,28-epoxy-2α-methyl-18α-oleanan-3β-ol (*X*)

A) A solution of acetate *V* (800 mg) in acetic acid (150 ml) was hydrogenated under shaking on Adams catalyst (100 mg) for 2·5 h. The catalyst was filtered off, the filtrate diluted with water and the separated precipitate filtered off under suction, washed with water and dried. Yield 780 mg of a mixture of acetates *XI* and *XIV*. This mixture was dissolved in benzene (30 ml), a solution of 2·5 g of potassium hydroxide in ethanol (30 ml) was added and the mixture was refluxed for 12 h. After dilution with water it was extracted with ether. The ethereal extract was washed with dilute hydrochloric acid and worked up in the conventional manner. The obtained mixture of hydroxy derivatives *X* and *XIII* (770 mg) was dissolved in benzene and chromatographed on silica gel (100 g). Using light petroleum–ether mixture (9 : 1) hydroxy derivative *XIII* (400 mg) was eluted, m.p. 266—268°C (chloroform–heptane), $[\alpha]_D$ +93°. IR spectrum: 3630 (OH), 1030 cm^{-1} (COC). For $C_{31}H_{52}O_2$ (456·7) calculated: 81·52% C, 11·48% H; found: 81·48% C, 11·54% H. Elution with light petroleum–ether (4 : 1) gave 360 mg of hydroxy derivative *X*, identical with the sample described above. M.p. 254—255°C (chloroform–heptane), $[\alpha]_D$ +35°. The same results were obtained if the deacetylation of the crude mixture of acetates *XI* and *XIV* was carried out with lithium aluminum hydride in ether at room temperature.

B) A solution of hydroxy derivative *IV* (500 mg) in acetic acid (150 ml) was hydrogenated under shaking on platinum oxide (Adams; 100 mg) catalyst for 2 h. The catalyst was filtered off, the filtrate diluted with water, extracted with ether and worked up in the conventional manner. Chromatography as under *A* gave a mixture of ketones *VIII* and *IX* (130 mg), m.p. 205—213°C, $[\alpha]_D$ +119°. Further hydroxy derivative *XIII* (140 mg) was obtained, melting at 266·5—267·5°C (chloroform–heptane), $[\alpha]_D$ +93°, and hydroxy derivative *X* (100 mg), 252—254°C (ether–heptane), $[\alpha]_D$ +35°. Both hydroxy derivatives were identical with the samples described under *A*. The formation of ketone *VIII* was also observed when hydrogenation was carried out in dioxane.

C) Ketone *VIII* (65 mg) was extracted in a Soxhlet extractor with boiling ether into a mixture of ether (50 ml) and lithium aluminum hydride (150 mg). The solution was refluxed for 6 h, the ethyl acetate was added, followed by water, the mixture was acidified with dilute hydrochloric

acid, extracted with ether and submitted to the conventional work-up. Hydroxy derivative *XIII* (50 mg) was obtained, with m.p. 268–270°C (chloroform–heptane), $[\alpha]_D$ +90°. The isomer *XV* could not be detected in the reaction mixture. Derivative *XIII* was prepared in the same manner, starting with crude ketone *VIII* (see the preparation of *VIII* under *C*, *D* or *F*). In these cases it was necessary to separate the derivative *XIII* from the impurities (compounds *X*, *IV* and further unidentified compounds) by chromatography on silica gel. Attempts at reduction of ketone *VIII* with sodium borohydride in benzene–methanol and at room temperature for up to 7 days were unsuccessful. Only the unreacted ketone *VIII* was obtained.

19β,28-Epoxy-2β-methyl-18α-oleanan-3α-ol (*XV*)

Gaseous diborane was introduced into a solution of derivative *XIX* (500 mg) in tetrahydrofuran (50 ml) at 0°C for 30 min. 4M-NaOH solution (25 ml) and 30% hydrogen peroxide (25 ml) were then added and the mixture stirred for 3 h. The organic layer was separated, diluted with ether, washed with dilute hydrochloric acid and worked up in the conventional manner. The amorphous product obtained (500 mg) was dissolved in benzene and chromatographed on silica gel (100 g). Light petroleum–ether mixture (9 : 1) eluted consecutively derivative *XIX* (20 mg), a mixture of ketones *VIII* and *IX* (130 mg) and hydroxy derivative *XV* (210 mg) with m.p. 232–233°C (chloroform–heptane), $[\alpha]_D$ +92°. IR spectrum: 3620 (OH), 1032 cm^{-1} (COC). For $C_{31}H_{52}O_2$ (456·7) calculated: 81·52% C, 11·48% H; found: 81·61% C, 11·42% H. Further, more polar, components were not identified.

19β,28-Epoxy-2α-methyl-18α-oleanan-2β-ol (*XVIII*)

A 0·8M solution of methyllithium in ether (15 ml) was added to a solution of ketone *XVII* (250 mg; prepared according to ref.[14]) in ether (30 ml) and the mixture was allowed to stand at room temperature for 24 h. The excess of the reagent was decomposed with water, the ethereal layer was washed with dilute hydrochloric acid and worked up in the conventional manner. Yield, 230 mg of derivative *XVIII*, m.p. 230–232°C (ether–light petroleum), $[\alpha]_D$ +53°. IR spectrum: 3605 (OH), 1030 (COC) cm^{-1}. For $C_{31}H_{52}O_2$ (456·7) calculated: 81·52% C, 11·48% H; found: 81·38% C, 11·60% H.

19β,28-Epoxy-2-methyl-18α-olean-2-ene (*XIX*)

A) A mixture of alcohol *XVIII* (200 mg), acetic acid (15 ml), and 70% perchloric acid (one drop) was heated at 80°C for 1 h. After dilution with water (30 ml) the formed precipitate was filtered off under suction and washed with water. Crystallization of the product from chloroform–methanol gave derivative *XIX* (180 mg), m.p. 225–226°C, $[\alpha]_D$ +75°. IR spectrum: 1031 cm^{-1} (COC). ^{1}H-NMR spectrum: 1·595 d; J = 1·2 Hz (2-CH_3); 5·07 bs (3-H); 1·82 d; J = 16·5 Hz (1ξ-H). For $C_{31}H_{50}O$ (438·7) calculated: 84·86% C, 11·49% H; found: 84·89% C, 11·34% H.

B) Benzoate *XII* (40 mg) was heated at 330–340°C for 20 min. The product was dissolved in benzene and chromatographed on alumina (5 g). Elution with benzene gave derivative *XIX* (20 mg), identical with the sample described under *A*. M.p. 225–226°C (chloroform–methanol), $[\alpha]_D$ +73°.

19β,28-Epoxy-2β-methyl-18α-oleanane (*XX*)

A solution of derivative *XIX* (150 mg) in acetic acid (50 ml) was shaken under hydrogen in the presence of platinum oxide according to Adams (50 mg) for 10 h. The catalyst was filtered off,

the filtrate diluted with water and extracted with ether, and the extract worked up in the conventional manner. Yield 140 mg of derivative *XX*, m.p. 180–181°C (benzene–methanol). An analytical sample, obtained by repeated crystallization from ethanol had m.p. 187–188°C, $[\alpha]_D$ +89°. IR spectrum: 1030 cm^{-1} (COC). ^{1}H-NMR spectrum: 0·83 d; $J \sim 6{\cdot}4$ Hz (2β-CH_3). For $C_{31}H_{52}O$ (440·7) calculated: 84·48% C, 11·48% H; found: 84·41% C, 11·52% H.

Reaction of Bromohydrins *XXIII*, *XXIV* and *XXV* with Methyllithium

A 0·8M solution of methyllithium in ether (10 ml) was added to bromohydrin[20] *XXV* (50 mg) under nitrogen and the mixture was allowed to stand at room temperature for 48 h. After dilution with water it was worked up in the conventional manner. This yielded 2α,3α; 19β,28-diepoxy-18α-oleanane (*XXI*, 45 mg) which was identical with an authentic sample[20]; m.p. 254–257°C, $[\alpha]_D$ +42°.

Applying the same procedure (reaction time 2 h) 2α-(1ξ-hydroxyethyl)-19β,28-epoxy-A(3)-nor-18α-oleanane (*XXVI*, 45 mg) identical with an authentic specimen[16] was obtained from bromohydrin *XXIII* or *XXIV* (50 mg; see[14,20]). M.p. 263–267°C (chloroform–ethyl acetate), $[\alpha]_D$ +44°. Lit.[16] gives m.p. 261–265°C, $[\alpha]_D$ +44°. Oxidation of compound *XXVI* according to ref.[16] gave ketone *XXVII*, identical with the described sample[16]. Traces of epoxide[14] *XXII* could be detected in the crude product after the reaction with methyllithium by thin-layer chromatography.

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