A-NOR-DERIVATIVES OF 19β,28-EPOXY-18α-OLEANANE: PREPARATION AND STEREOCHEMISTRY*

Jiří KLINOT, Jiří ROZLN, Eva KLINOTOVÁ and Alois VYSTRČIL

Department of Organic Chemistry, Charles University, 128 40 Prague 2

Received February 26th, 1986

19β,28-Epoxy-A(1)-nor-18α-oleanan-3-one (*IV*) was converted into the A-nor-derivatives *V*—*XII* whose structure and configuration was confirmed by chemical reactions and spectral methods. Proton NMR and IR spectra show that the 2α- and 3β-bonds on the five-membered ring A are pseudoaxial whereas the 2β- and 3α-bonds are pseudoequatorial.

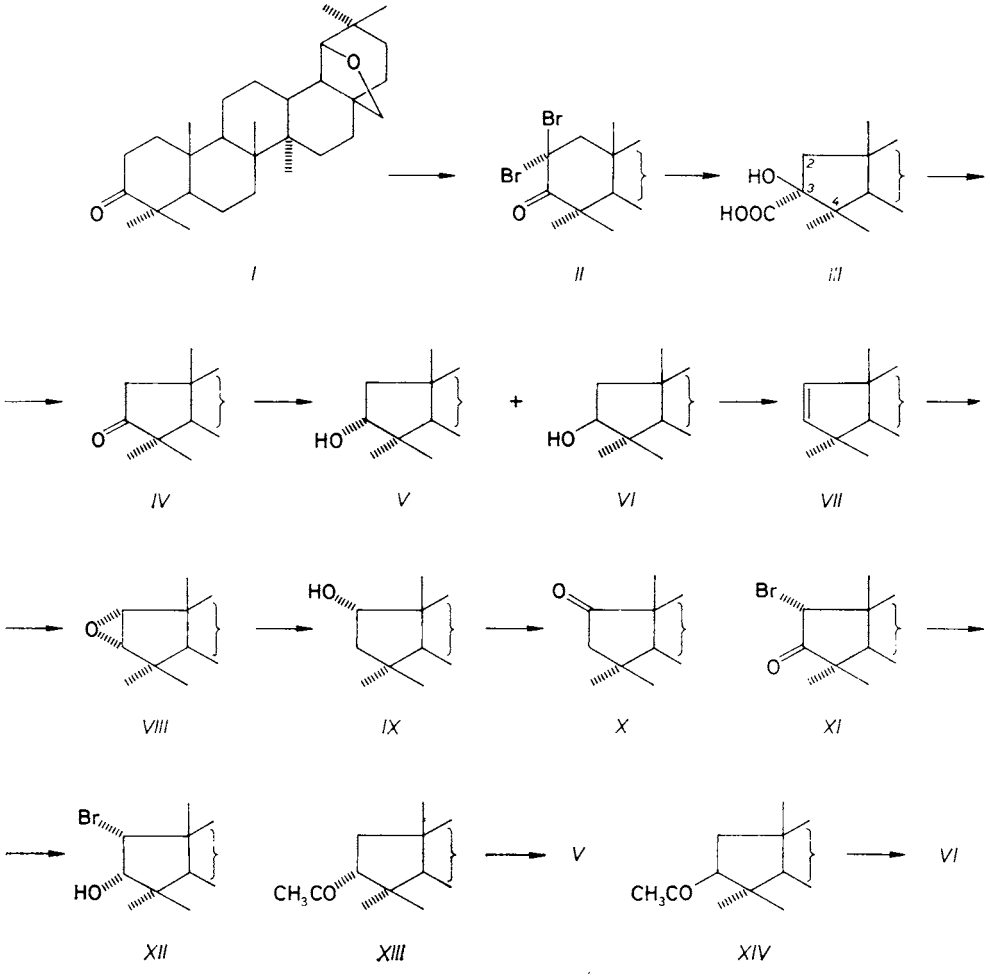
The conformation of the six-membered ring A in triterpenoids and 4,4-dimethyl-5α--steroids with substituents on this ring has been thoroughly studied[1,2]. On the other hand, much less attention has been paid to stereochemistry of the five-membered ring A in A-nortriterpenoids[3], although many of them occur in nature[3-5]. All natural A-nor-triterpenoids contain a double bond or two substituents (usually OH and COOH) in the ring A. This communication concerns the preparation and stereochemistry of some A-nor-derivatives of 19β,28-epoxy-18α-oleanane.

The starting 19β,28-epoxy-A(1)-nor-18α-oleanan-3-one (*IV*) was prepared from 19β,28-epoxy-18α-oleanan-3-one (*I*) by the known procedure[6-8] *via* dibromo ketone *II* and hydroxy acid *III*. A slight modification of the described conversion of *II* to *III* in an alkaline medium, followed by oxidation of *III* with lead tetraacetate, gave the A-nor-ketone *IV* in a total yield of 50%. In the next step the ketone *IV* was reduced. The literature data on the reduction of similar A(1)-nor-3-ketones with sodium borohydride or lithium aluminium hydride are somewhat confused: some authors report the exclusive formation of 3β-hydroxy derivatives[9,10], other describe reduction to mixtures of both epimeric alcohols[8,11-15] with β-isomers[8,11] or α-isomers (80%) (ref.[15]) predominating. Reduction of the ketone *IV* with lithium aluminium hydride is reported[8] to afford a mixture of the β-isomer *VI* (60%) and the α-isomer *V* (40%). In neither of the cited cases the configuration of the alcohols has been proven. In our hands, reduction of *IV* with sodium borohydride afforded predominantly the 3β-hydroxy derivative *VI* together with minor amount of the 3α-epimer *V*. Configuration of the alcohols *V* and *VI* has been confirmed by correlation with the epimeric 3-acetyl-A(1)-nor-derivatives *XIII* and *XIV* of known[8,16] configuration at $C_{(3)}$.

* Part LXXXII in the series Triterpenes; Part LXXXI: This Journal *52*, 501 (1987).

Baeyer–Villiger oxidation of ketones *XIII* and *XIV* with 3-chloroperoxybenzoic acid proceeded only slowly even at high concentration of the acid. After standing at 20°C for 14 days the reaction mixtures afforded the corresponding 3-acetoxy derivatives which, without characterization, were hydrolysed to the respective alcohols *V* and *VI*.

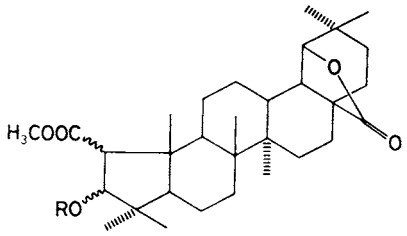
Dehydration of the 3β-hydroxy derivative *VI* (or the crude mixture of *V* and *VI* obtained by reduction of *IV*) with phosphorus oxychloride in pyridine gave the olefin *VII*. Huneck[8] claimed to obtain this olefin on heating the hydroxy acid *III* with copper powder to 360°C; however, our attempts to reproduce this reaction were unsuccessful. The olefin *VII* reacted with 3-chloroperoxybenzoic acid to give the epoxide *VIII*; its α-configuration follows from the α-attack rule[8,16,17]. Reduction of *VIII* with lithium aluminium hydride afforded the 2α-hydroxy derivative *IX* which was oxidized to a ketone identical with the 2-oxo derivative *X* described by us earlier[17].



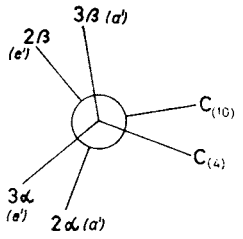
The 3-oxo derivative *IV* was brominated only sluggishly, requiring an excess of bromine (3 mol) and a reaction time of 5 days and giving the monobromo ketone *XI* as the sole product. Reduction of *XI* with sodium borohydride in the presence of boric acid (to suppress isomerization of the bromo ketone during the reduction; see *e.g.* refs[17,18]) led to the bromohydrin *XII* which on oxidation with sodium dichromate afforded back the bromo ketone *XI*. The *cis*-configuration of *XII* follows from the presence of a strong intramolecularly bonded hydroxyl band in the infrared spectrum (3 558 cm^{-1} in CCl_4) and from the formation of *IV* on treatment of *XII* with an alkali metal hydroxide. The configuration of the hydroxy group was confirmed by hydrogenation of *XII* over palladium leading to the 3α-hydroxy derivative *V*. The products of reduction of the ketone *IV* and the bromo ketone *XI* with sodium borohydride show clearly that the 2α-bromine atom changes the reaction stereochemistry in favour of the *cis*-bromohydrin. A similar effect of bromine was observed also in the reduction of some six-membered ring bromo ketones[17].

Unfortunately, we failed to prepare other 2,3-disubstituted A(1)-nor-derivatives suitable for investigation of the ring A (such as isomeric bromohydrins, bromo ketones, *trans*-diols, *etc.*). All the attempted preparations based on addition reactions to the double bond in the olefin *VII* or on epoxide ring opening in *VIII* were unsuccessful because the reactions were accompanied with skeletal rearrangement[19].

Configuration of the bromine in *XI* follows from the above-mentioned reactions and it is confirmed also by comparison of ^1H NMR and CD spectra of *XI* and *IV*:



XV, R = H
XVI, R = $COCH_3$



XVII

whereas in the spectrum of *IV* the 2α-H doublet at δ 2·18 is broad and the 10β-methyl signal appears as a doublet ($J \sim 0{\cdot}7$ Hz), which is characteristic of long-range coupling of 10β-CH_3 with 2α-H but not with 2β-H (see ref.[3]), the $C_{(2)}H$ signal in the spectrum of *XI* is a sharp singlet (δ 3·88, $W_{1/2} \sim 0{\cdot}8$ Hz) and neither of the methyl signals is split. The CD spectrum of the ketone *IV* shows a positive Cotton effect ($\Delta\varepsilon + 2{\cdot}0$) whereas the $\Delta\varepsilon$ value for the bromo ketone *XI* is practically zero, as

predicted by the octant rule for 2α-bromine. The relatively small shift of the carbonyl stretching frequency (+8 cm^{-1}) in the infrared spectrum of *XI* (1 749 cm^{-1} in CCl_4) relative to that of *IV* (1 741 cm^{-1}) corresponds to a pseudoaxial position of the bromine[20].

The vicinal coupling constants between protons on $C_{(2)}$ and $C_{(3)}$ in the prepared hydroxy derivatives are given in Table I. For comparison, we included values found by Eady and co-workers[3] for the four possible $C_{(2)}$ and $C_{(3)}$ stereoisomeric derivatives of A(1)-nor-18α-oleanan-28→19β-olide containing a methoxycarbonyl group on $C_{(2)}$ and a hydroxy (compounds *XV*) or an acetoxy group (compounds *XVI*) on $C_{(3)}$. The $J_{2\beta,3\alpha}$ values indicate that the torsion angle between bonds to the 2β- and 3α--protons is about 90°. Also other coupling constants in all the compounds correspond to such spatial arrangement of the $C_{(3)}$—$C_{(2)}$ bond whose Newman projection is given in formula *XVII*. This means that the 2α- and 3β-hydrogen atoms in A(1)-nor--triterpenoids are pseudoaxial whereas the 2β- and 3α-hydrogens are pseudoequatorial. The pseudoaxial character of the 2α-bromine in *XI* and the formation of the 2α--alcohol *IX* in the reduction of the 2α,3α-epoxide *VIII* (β-attack by the hydride at $C_{(3)}$) also agree with this suggested spatial arrangement.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on an ETL-NPL (Bendix–Ericsson) automatic polarimeter in chloroform (*c* 0·3—0·8). Infrared spectra were taken on a UR-20 (Zeiss, Jena) spectrometer in chloroform, ^{1}H NMR spectra on a Tesla BS 487A (80 MHz) instrument in deuteriochloroform with hexamethyldisiloxane as internal standard. The chemical shifts refer to tetramethylsilane (δ_{HMDS} = 0·06) and are given in ppm (δ-scale). The coupling constants were obtained by first order analysis. The signals were identified by decoupling and gradual addition of hexadeuteriobenzene to a solu-

TABLE I

Vicinal coupling constants of $C_{(2)}$ and $C_{(3)}$ protons

Compound	Substituents	$J_{2\alpha,3\alpha}$	$J_{2\alpha,3\beta}$	$J_{2\beta,3\alpha}$	$J_{2\beta,3\beta}$
V	3α-OH	—	9·4	—	7·2
VI	3β-OH	7·2	—	1·7	—
IX	2α-OH	—	—	<0·5[a]	5·2
XII	2α-Br, 3α-OH	—	—	—	4·9
XV[b]	2-$COOCH_3$, 3-OH	7·4	9·0	1·0	7·0
XVI[b]	2-$COOCH_3$, 3-$OCOCH_3$	7·6	9·5	0·0	7·7

[a] Upper limit; no splitting observed; [b] coupling constants taken from ref.[3] for the corresponding 2,3-isomers.

tion of the measured compound in deuteriochloroform. CD spectra were recorded on a Dichrographe II (Roussel-Jouan) in dioxane. Column chromatography was carried out on silica gel Silpearl (Kavalier, Votice), thin-layer chromatography on silica gel G according to Stahl (Merck). The usual work-up procedure means extraction of the product into ether, washing the ethereal solution with water (or 5% sodium hydrogen carbonate solution or dilute hydrochloric acid and water), drying over sodium sulfate and evaporation of the solvent. The compounds were identified by their melting point, mixture melting point, thin-layer chromatography, IR and ^{1}H NMR spectra. Analytical samples were dried over phosphorus pentoxide at 100°C under diminished pressure.

19β,28-Epoxy-3β-hydroxy-A(1)-nor-18α-oleanane-3α-carboxylic Acid (*III*)

A mixture of dibromo ketone *II* (8 g; prepared[6] from *I* in 95% yield), potassium hydroxide (53 g), benzene (100 ml) and ethanol (250 ml) was refluxed for 30 h. After concentration to half of the original volume, the mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. The extract was washed with 20% aqueous sodium hydroxide solution and the precipitated sodium salt was separated by filtration from the ethereal solution of neutral material. The sodium salt was acidified with dilute hydrochloric acid and the acid *III* was taken up in ether and worked up in the usual manner. Crystallization from chloroform–methanol afforded 4 g (63%) of *III*, m.p. 319–321°C, $[\alpha]_D$ +56° (reported[8] m.p. 318–319°C, $[\alpha]_D$ +55°). Repeated experiments using the same concentration of the hydroxide (15%) and reaction time 30–40 h afforded *III* in yields 60–65%. Shorter reaction time (5–10 h) or lower hydroxide concentration (7–12%) resulted in yields 32–48%. In these cases the neutral portion (shown by the ^{1}H NMR spectra to contain no starting dibromo ketone *II*) afforded further amounts of *III* on heating with hydroxide (total yields again 60–65%).

19β,28-Epoxy-A(1)-nor-18α-oleanan-3-one (*IV*)

a) Acid *III* (1 g) was dissolved in warm acetic acid (100 ml), cooled and shaken for 4 h with a suspension of lead tetraacetate (2 g) in acetic acid (50 ml). The mixture was diluted with water, the precipitate was filtered, dissolved in benzene and the solution was passed through a column of alumina (25 g). Benzene was distilled off and the residue crystallized from chloroform–methanol, yielding 0·75 g (83%) of ketone *IV*, m.p. 240–242°C, $[\alpha]_D$ +148° (reported[7] m.p. 244–245°C, $[\alpha]_D$ +150°, ref.[6] gives m.p. 236–238°C). ^{1}H NMR spectrum: 0·80 s, 0·87 d ($J \sim 0{\cdot}7$ Hz), 0·94 s, 0·97 s and 0·98 s ($5 \times CH_3$), 1·01 s ($2 \times CH_3$), 1·88 d ($J = 15{\cdot}7$ Hz; 2β-H), 2·18 bd ($J = 15{\cdot}7$ Hz; 2α-H), 3·53 s ($C_{(19)}H$), 3·44 d and 3·78 bd ($J = 8$ Hz; $C_{(28)}H_2$). CD spectrum: $\Delta\varepsilon$ +2·0 (309 nm).

b) A mixture of bromohydrin *XII* (30 mg) and 5% ethanolic solution of sodium hydroxide (50 ml) was refluxed for 5 h, diluted with water and worked up in the usual manner. Crystallization from ether–methanol afforded *IV* (18 mg), identical with the sample prepared under *a*).

19β,28-Epoxy-A(1)-nor-18α-oleanan-3α-ol (*V*) and
19β,28-Epoxy-A(1)-nor-18α-oleanan-3β-ol (*VI*)

a) A suspension of sodium borohydride (700 mg) in ethanol (30 ml) was added dropwise to a solution of ketone *IV* (500 mg) in a mixture of benzene (20 ml) and ethanol (20 ml). After standing for 4 h at room temperature, the mixture was diluted with water and dilute hydrochloric acid and processed as usual. Crystallization from chloroform–methanol afforded the 3β-hydroxy derivative *VI* (120 mg), m.p. 277–278°C, $[\alpha]_D$ +51° (reported[8] m.p. 274–275°C, $[\alpha]_D$ +58°).

IR spectrum: 3 630, 1 035 cm^{-1}. ^1H NMR spectrum: 0·80 s (CH_3), 0·93 s (3 × CH_3), 0·96 s (CH_3), 1·02 s (2 × CH_3), 3·51 s ($C_{(19)}H$), 3·41 d and 3·76 bd (J = 8 Hz; $C_{(28)}H_2$), 3·98 dd (J = 7·2 and 1·7 Hz; 3α-H).

The mother liquors were chromatographed on silica gel (30 g). Elution with light petroleum–ether (8 : 1) afforded successively alcohol *VI* (140 mg), a mixture of alcohols *V* and *VI* (200 mg) and alcohol *V* (10 mg). The 3α-hydroxy derivative *V* melted at 241–243°C (chloroform–methanol); $[\alpha]_D$ +35° (reported[8] m.p. 233–234°C, $[\alpha]_D$ +59°). IR spectrum: 3 615, 1 032 cm^{-1}. ^1H NMR spectrum: 0·79 s and 0·81 s (2 × CH_3), 0·91–0·93 bs (5 × CH_3), 2·16 dd (J = 7·2 and 12·0 Hz; 2β-H), 3·52 s ($C_{(19)}H$), 3·43 d and 3·77 bd (J = 8 Hz; $C_{(28)}H_2$), 4·06 dd (J = 7·2 and 9·4 Hz; 3β-H).

b) A solution of 3α-acetyl-19β,28-epoxy-A(1)-nor-18α-oleanane (*XIII*; 30 mg) and 3-chloroperoxybenzoic acid (200 mg) in dichloromethane (2 ml) was allowed to stand at room temperature for 14 days. The mixture was diluted with dichloromethane, shaken with solid sodium hydrogen carbonate and filtered through basic alumina. After evaporation of the solvent, the residue was refluxed for 2 h with 2·5% potassium hydroxide solution in a benzene–ethanol (1 : 1) mixture, the mixture was diluted with water and worked up in the usual manner. The residue was purified by preparative thin-layer chromatography in light petroleum–ether (2 : 1) and crystallization from methanol, affording 19 mg of 3α-hydroxy derivative *V*, identical with the product obtained according to procedure *a*). In the same way, 3β-acetyl-19β,28-epoxy-A(1)-nor-18α-oleanane (*XIV*, 10 mg) afforded 7 mg of the 3β-hydroxy derivative *VI*, identical with the sample obtained under *a*).

c) A mixture of bromohydrin *XII* (50 mg), 10% palladium on charcoal (400 mg), powdered calcium carbonate (300 mg) and ethanol (40 ml) was shaken under hydrogen for 40 h, filtered and the solvent was evaporated. The residue was subjected to preparative thin-layer chromatography on silica gel in light petroleum–ether (2 : 1) and afforded 25 mg of *XII* and 15 mg of *V*, identical with a sample prepared under *a*).

19β,28-Epoxy-A(1)-nor-18α-olean-2-ene (*VII*)

A solution of phosphorus oxychloride (2 ml) in pyridine (10 ml) was added dropwise during 5 min to alcohol *VI* (200 mg) in boiling pyridine (20 ml). The mixture was cooled, diluted with water and worked up in the usual manner. The crude product was chromatographed on silica gel (25 g). Elution with light petroleum gave the title compound *VII* (145 mg), m.p. 216–218°C (chloroform–methanol); $[\alpha]_D$ +74° (reported[8] m.p. 209–211°C). IR spectrum: 1 035 cm^{-1}. ^1H NMR spectrum: 0·80 s (CH_3), 0·93 s (3 × CH_3), 0·97 s, 0·99 s and 1·03 s (3 × CH_3), 3·53 s ($C_{(19)}H$), 3·43 d and 3·78 bd (J = 8 Hz; $C_{(28)}H_2$), 5·46 d and 5·98 d (J = 5·7 Hz; $C_{(2)}H$ and $C_{(3)}H$). For $C_{29}H_{46}O$ (410·7) calculated: 84·81% C, 11·29% H; found: 84·63% C, 11·40% H.

2α,3α;19β,28-Diepoxy-A(1)-nor-18α-oleanane (*VIII*)

A solution of olefin *VII* (320 mg) and 3-chloroperoxybenzoic acid (250 mg) in chloroform (15 ml) was set aside at 0°C for 24 h, diluted with ether, washed with 5% solutions of potassium iodide, sodium bisulfite and sodium carbonate and with water. After drying over sodium sulfate, the solvents were evaporated and the residue was crystallized from a mixture of chloroform and methanol, affording 225 mg of epoxide *VIII*, m.p. 243–245°C, $[\alpha]_D$ +45°. IR spectrum: 1 035 cm^{-1}. ^1H NMR spectrum: 0·81 s, 0·82 s, 0·87 s and 0·93 s (4 × CH_3), 0·95 s (2 × CH_3), 1·03 s (CH_3), 2·96 d and 3·20 d (J = 2·7 Hz; $C_{(2)}H$ and $C_{(3)}H$), 3·51 s ($C_{(19)}H$), 3·41 d and 3·76 bd (J = 8 Hz; $C_{(28)}H_2$). For $C_{29}H_{46}O_2$ (426·7) calculated: 81·63% C, 10·87% H; found: 81·42% C, 11·02% H.

19β,28-Epoxy-A(1)-nor-18α-oleanan-2α-ol (*IX*)

A mixture of epoxide *VIII* (70 mg), lithium aluminium hydride (100 mg) and ether (20 ml) was refluxed for 4 h. The excess hydride was decomposed with water, the mixture was acidified with hydrochloric acid and worked up as usual. Crystallization of the residue from chloroform–methanol afforded 55 mg of *IX*, m.p. 254–256°C, $[\alpha]_D$ +66°. IR spectrum: 3 620, 1 035 cm^{-1}. ^1H NMR spectrum: 0·75 s, 0·79 s, 0·88 s and 0·93 s (4 × CH_3), 0·99 s (2 × CH_3), 1·06 s (CH_3), 2·09 dd (J = 15·0 and 5·2 Hz; 3β-H), 3·53 s ($C_{(19)}H$), 3·44 d and 3·79 bd (J = 8 Hz; $C_{(28)}H_2$), 3·75 d (J = 5·2 Hz; 2β-H). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·01% C, 11·38% H.

19β,28-Epoxy-A(1)-nor-18α-oleanan-2-one (*X*)

A mixture of alcohol *IX* (15 mg), sodium dichromate dihydrate (7 mg), anhydrous sodium acetate (2 mg) and acetic acid (30 ml) was stirred at room temperature for 2 h. Methanol (10 ml) was added and the mixture was diluted with water and worked up in the usual manner. Crystallization from chloroform – methanol gave ketone *X* (8 mg), m.p. 232–234°C, $[\alpha]_D$ +82°, identical with a sample prepared previously[17] (m.p. 233–235°C, $[\alpha]_D$ +84°).

2α-Bromo-19β,28-epoxy-A(1)-nor-18α-oleanan-3-one (*XI*)

Bromine (560 mg) in chloroform (15 ml) was added to a solution of ketone *IV* (500 mg) in chloroform (20 ml). After standing at room temperature for 5 days, the mixture was diluted with chloroform, washed with 5% sodium bisulfite solution, 5% sodium carbonate solution, water, and dried over sodium sulfate. Chloroform was distilled off and the residue crystallized from chloroform–methanol, affording the title bromo ketone *XI* (460 mg), m.p. 226–228°C, $[\alpha]_D$ +84°. IR spectrum: 1 740, 1 035 cm^{-1}. ^1H NMR spectrum: 0·81 s and 0·94 s (2 × CH_3), 0·98 s (2 × CH_3), 1·04 s (2 × CH_3), 1·26 s (CH_3), 2·22 dd (J = 10·6 and 4·6 Hz; probably $C_{(9)}H$), 3·53 s ($C_{(19)}H$), 3·43 d and 3·79 bd (J = 8 Hz; $C_{(28)}H_2$), 3·88 s ($W_{1/2}$ = 0·8 Hz; 2β-H). CD spectrum: $\Delta\varepsilon$ +0·03 (348 nm), 0 (332 nm), −0·04 (313 nm). For $C_{29}H_{45}BrO_2$ (505·6) calculated: 68·89% C, 8·97% H; found: 68·64% C, 8·65% H.

The bromo ketone *XI* (19 mg) was obtained also by oxidation of bromohydrin *XII* (30 mg) with sodium dichromate under conditions described for the preparation of *X*.

2α-Bromo-19β,28-epoxy-A(1)-nor-18α-oleanan-3α-ol (*XII*)

A suspension of sodium borohydride (140 mg) in ethanol (10 ml) was added dropwise during 1 h to a solution of bromo ketone *XI* (100 mg) and boric acid (500 mg) in a mixture of benzene (20 ml) and ethanol (5 ml). After standing at room temperature for 4 h, the mixture was diluted with water, acidified with hydrochloric acid and worked up in the usual manner. Crystallization from chloroform–methanol yielded bromohydrin *XII* (82 mg), m.p. 212–214°C, $[\alpha]_D$ +88°. IR spectrum: 3 560, 1 035 cm^{-1}; $\nu_{(OH)}$ (in CCl_4, c 2 . 10^{-3} mol l^{-1}): 3 558 cm^{-1} (ε 67, $\Delta\nu_{1/2}$ 24 cm^{-1}). ^1H NMR spectrum: 0·80 s (CH_3), 0·93 s (3 × CH_3), 1·00 s (2 × CH_3), 1·04 s (CH_3) 3·53 s ($C_{(19)}H$), 3·44 d and 3·79 bd (J = 8 Hz; $C_{(28)}H_2$), 4·06 bd (J = 4·9 Hz; 3β-H), 4·51 d (J = 4·9 Hz; 2β-H). For $C_{29}H_{47}BrO_2$ (507·6) calculated: 68·62% C, 9·33% H; found: 68·82% C, 9·07% H.

The authors are indebted to Dr S. Hilgard for measurement of the IR *spectra and to Dr S. Vašíčková, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague, for measurement of the* CD *spectra.*

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Translated by M. Tichý.