TRITERPENES. XXVII.*

CONFORMATIONAL ANALYSIS OF THE A-CYCLE
OF 1,3-DIHYDROXY DERIVATIVES OF PENTACYCLIC
TRITERPENOIDS

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Conformations of cycle A of 1α,3α-dihydroxylupane (*I*), 1α,3β-dihydroxylupane (*IV*), and their acetates *XIII*, *XVI*, as well as of 1α,3α-dihydroxy-19β,28-epoxy-18α-oleanane (*XII*) were investigated. It was found that all these substance have their A-cycle in the deformed chair conformation. The deformation (except for acetate *XIII*) may be interpreted by the reflex effect caused by 1,3-diaxial non-bonding interaction of methyl groups in the positions 4β and 10β, or 8β. and 10β respectively.

Conformational analysis of the A-cycle of 2,3-dihydroxy derivatives of triterpenoids was already carried out by a number of authors[1-4]. However, sufficient attention was not paid to 1,3-dihydroxy derivatives although some of them were found in nature[5-8]. We decided to study the conformation of pentacyclic triterpenoids: 1α,3α-dihydroxylupane (*I*), 1α,3β-dihydroxylupane (*IV*), their acetates *XIII* and *XVI*, and further 1α,3α-dihydroxy-19β,28-epoxy-18α-oleanane (*XII*).

Diols *I* and *IV* were obtained on reduction of 1α,2α-epoxy-3-lupanone (*VI*) with lithium aluminum hydride in the conventional manner. Literature data on physical constants of these substances disagree[5,9]. Our data tend towards those of Ganguly and Govindachari[5]. We also made use of the reduction of epoxy ketone *VI* for the preparation of diols *II* and *V*, using lithium aluminum deuteride as reagent. For the preparation of 1α,3α-dihydroxy-lupane-[2β-D] (*III*) we used the following procedure: 2-lupene[11] (*VII*) was oxidised with selenium dioxide in dioxane under normal pressure and in the presence of traces of water. The mentioned modification of the oxidation of unsaturated compounds with selenium dioxide was worked out in our laboratory[12]. In a number of cases it gives better results than the procedures used earlier[11,13]. We obtained 1α-hydroxy-2-lupene (*VIII*) which on epoxidation with perbenzoic acid gave 1α-hydroxy-2α,3α-epoxylupane (*IX*). The proof of its structure

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was based on the presence of an intramolecular hydrogen bond found in its IR spectrum and on the course of its reduction with lithium aluminum hydride, which gave 1α,3α-dihydroxylupane (*I*) described earlier. If 1α-hydroxy-2α,3α-epoxylupane (*IX*) was
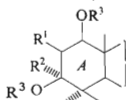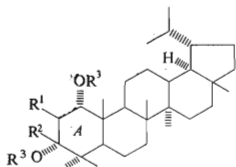
I; R^1 = R^2 = R^3 = H   *IV*; R^1 = R^2 = R^3 = H   *VI*
II; R^1 = R^2 = D, R^3 = H   *V*; R^1 = R^2 = D, R^3 = H
III; R^1 = D, R^2 = R^3 = H   *XVI*; R^1 = R^2 = H, R^3 = CH$_3$CO
XIII; R^1 = R^2 = H, R^3 = CH$_3$CO   *XVII*; R^1 = R^2 = D, R^3 = CH$_3$CO
XIV; R^1 = R^2 = D, R^3 = CH$_3$CO
XV; R^1 = D, R^2 = H, R^3 = CH$_3$CO
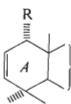
VII, R = H
VIII, R = OH

IX

X   *XI*   *XII*

XVIII; R = $\overset{\text{H}}{\underset{\text{H}}{}}$

XIX; R = $\overset{\text{CH}_3}{\underset{\text{CH}_3}{}}$
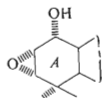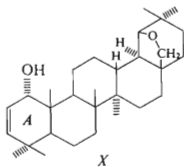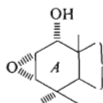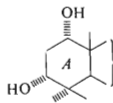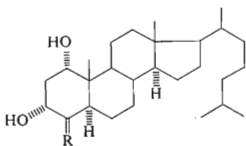
used for reduction with lithium aluminum deuteride the required monodeuterated diol III was obtained. By an analogous epoxidation of 1α-hydroxy-19β,28-epoxy-18α-olean-2-ene[14] (X) we obtained 1α-hydroxy-2α,3α; 19β,28-diepoxy-18α-oleanane (XI) which on reduction with lithium aluminum hydride gave 1α,3α-dihydroxy-19β,28-epoxy-18α-oleanane (XII). Acetates XIII[5], XIV, XV, XVI[5], and XVII were prepared by acetylation from corresponding diols.

Deuterated derivatives permitted the use of the method proposed by Williamson and Johnson[15] for the interpretation of PMR spectra. We endeavoured to simplify the spectra of protons of cycle A by changing them to easily analysable AB systems by means of deuteration of positions 2 and 3. The values of the coupling constants obtained were then used for the analysis of ABX and ABXY systems of monodeuterated and nondeuterated derivatives. The PMR spectra were measured in deuteriochloroform and benzene. The results of the measurements are presented in Tables I and II. The hydroxyl protons of diols I, II, and III produced in the PMR spectra a broad singlet in the 3·14—3·20 p.p.m. region, the hydroxyl protons of diols IV and V a sharp singlet at 1·51 p.p.m. (confirmed by exchange with CD_3COOD). In order to eliminate a possible

TABLE I

PMR Data of Protons in Positions 1 and 3 of Triterpenic Derivatives

Substance	Solvent	Chemical shifts[a]		Coupling constants[a]			
		1-H	3-H	1β,2α	1β,2β	2α,3β	2β,3β
I	$CDCl_3$	3·62 t	3·47 t	∑ = 5·4		∑ = 5·4	
II	$CDCl_3$	3·61 d	—	3·1	—	—	—
	C_6H_6	3·58 d	—	3·1	—	—	—
III	$CDCl_3$	3·61 d	3·47 t	3·1	—	2·8	—
IV	$CDCl_3$	3·70 t	3·89 dd	∑ = 16·8		∑ = 6·0	
	C_6H_6	3·65 t	3·89 dd	∑ = 16·6		∑ = 5·5	
V	$CDCl_3$	3·70 d	—	3·6	—	—	—
	C_6H_6	3·56 d	—	3·3	—	—	—
XIII	$CDCl_3$	4·69 t	4·67 t	∑ = 5·3		∑ = 5·3	
	C_6H_6	4·90 t	4·90 t	∑ = 5·9		∑ = 5·9	
XIV	$CDCl_3$	4·68 d	—	3·0	—	—	—
	C_6H_6	4·88 d	—	2·8	—	—	—
XV	$CDCl_3$	4·68 d	4·66 d	b		b	
	C_6H_6	4·88 d	4·88 d	2·6	—	2·6	—
XVI	$CDCl_3$	4·83 t	4·83 dd	b	b	∑ = 16·6	
	C_6H_6	5·10 t	5·27 dd	∑ = 5·7		∑ = 16·6	
XVII	$CDCl_3$	4·83 d	—	3·5	—	—	—
	C_6H_6	5·09 d	—	3·4	—	—	—

[a] Chemical shifts in δ (p.p.m.), coupling constants in Hz; abbreviations used: d doublet, t triplet, dd doublet of doublets, ∑ sum of the values of two constants; [b] The overlapping of signals does not permit an accurate reading of coupling constants.

coupling of 1β-H and 3β-H with hydroxyl protons the measurement of diols *I*, *II*, and *III* was carried out in deuteriochloroform under addition of a trace amount of deuterioacetic acid. The position and the shape of the 2α-proton signal of diols *II* and *III* were found by multiple resonance experiments (diol *II*: doublet at 1·89 p.p.m., $J_{1\beta,2\alpha} = 3\cdot1$ Hz; diol *III*: triplet at 1·89 p.p.m., $J_{1\beta,2\alpha} + J_{2\alpha,3\beta} = 5\cdot8$ Hz). For the calculation of the dihedral angles we made use of the Williamson approach which is applied in conformational analysis of steroid derivatives[15,16]. In the case of polycyclic compounds it gives better results than the theoretically derived Karplus curve[16,17]. The dihedral angles between the protons in positions 1 and 2 of diols *I* and *IV*, and in the case of diol *I* also in positions 2 and 3, were calculated from the relationship $J = 10\cdot2 \cos^2 \varphi$, while in the case of their acetates the relationship $J = 11 \cos^2 \varphi$ was employed. The results are summarised in Table II.

From the above results it follows that all the substances investigated have their A-cycle in chair conformation which, with the exception of 1α,3α-diacetoxylupane, is deformed in such a manner that the substituents in positions 1α and 3α approach each other. The mentioned deformation may be explained by the reflex effect caused by 1,3-diaxial non-bonding interaction of the methyl groups in positions 4β and 10β. From the PMR spectra of diol *I* it follows that the reflex effect is more pronounced for values of dihedral angles between substituents at $C_{(1)}$ and $C_{(2)}$ than between those at $C_{(2)}$ and $C_{(3)}$. This may be explained by the fact that the methyl group in position 10β is exposed to a double non-bonding 1,3 diaxial interaction: the non-bonding interaction with the methyl group in position 4β is complemented by the second non-bonding interaction with the methyl group in 8β.

The cycle A of 1α,3α-diacetoxylupane (*XIII*) is also in chair conformation although on transition to the boat conformation the 1,3-diaxial non-bonding interactions of both the methyl groups at positions 4β and 10β and the acetoxy groups in positions 1α and 3α would disappear. The mentioned discrepancy is only apparent, however. The repulsion energy of diaxial non-bonding interactions is 3·7 kcal/mol for CH₃... ...CH₃ interaction[18], and 2·0 kcal/mol for AcO...OAc interaction. Their sum, *i.e.*

TABLE II

Coupling Constants and Calculated Dihedral Angles Between the Protons in the Positions 1 and 2, or 2 and 3

Substance	Coupling constants, Hz				Dihedral angles				Solvent
	1β, 2α	1β, 2β	2α, 3β	2β, 3β	1β, 2α	1β, 2β	2α, 3β	2β, 3β	
I	3·1	2·3	2·8	2·6	56·5	61·5	58·5	59·5	CDCl₃
IV	3·3	2·2	a	a	55·5	62·5	a	a	benzene
XIII	2·6	3·3	2·6	3·3	61	57	61	57	benzene
XVI	3·4	2·3	a	a	56	63	a	a	benzene

a Values of the coupling constants and the corresponding dihedral angles could not be determined.

5·7 kcal/mol, is insufficient for the change of the chair conformation of cycle A to the boat conformation. However, the non-bonding AcO...OAc interaction caused the reflex of the methyl groups in this substance not to appear any more.

1α,3α-Dihydroxy derivatives of triterpenoids have both hydroxy groups in axial conformation. An intramolecular hydrogen bond is formed between both hydroxyl groups, which may be detected in the IR spectra. Therefore we compared the values $\nu(O-H)$ of triterpenic diols I and XII and of similar steroid derivatives, *i.e.* 1α,3α-di-hydroxy-5α-cholestane (XVIII)* and 1α,3α-dihydroxy-4,4-dimethyl-5α-cholestane[19] (XIX). The values are given in Table III. As it can be supposed that the geometry of the hydrogen bond will be similar in all substances mentioned, it may be concluded that the distance O...H...O is in diols I and XII approximately equal as in compound XIX, but substantially shorter than in compound XVIII. This may be explained in accordance with the PMR data by a reflex effect of methyl groups. As it is known[10] that 1α-hydroxy derivatives of pentacyclic triterpenes absorb at 3 629 cm⁻¹ ($\nu(OH)$), while the 3α-hydroxy derivatives absorb at 3 640 cm⁻¹, and in view of the fact that the given values may also be expected in the case of corresponding, 4,4-dimethyl steroid derivatives[20], it may be concluded that in diols I and XII the proton donor for the hydrogen bond will be the hydroxy group in the position 1α, while in the case of substance XIX it will be the hydroxyl in 3α. The mentioned difference may be assigned to the effect of the methyl group in the position 8β.

EXPERIMENTAL

Melting points were measured on a Kofler block and they are not corrected. Optical rotations were measured in chloroform with a $\pm\ 2°$ precision, using a polarimeter with an objective indication ETL–NPL of Bendix-Ericsson. The PMR spectra were recorded on a Varian HA-100

TABLE III
Values of Frequencies and Molar Extinction Coefficients of $\nu_{(OH)}$ Absorption

Substance	ν, cm⁻¹		ε		$\Delta\nu$, cm⁻¹
I	3 636,	3 527	75,	118	109
XII	3 636,	3 527	76,	120	109
XVIII	3 625,	3 541	76,	105	84
XIX	3 626[a],	3 519[a]		[a]	107

[a] Lit.[15]. Molar extinction coefficients are not given.

* The sample was kindly donated by Prof. C. Tamm, Institute of Organic Chemistry, University of Basel, Switzerland.

apparatus at a 100 MHz frequency, in deuteriochloroform with tetramethylsilane as internal standard, or in benzene (δ values corrected for TMS). For identification of substances the used IR spectra were measured in chloroform on a Model UPT ČSAV-Brno spectrometer. For the study of hydrogen bonds the infrared Unicam S.P. 100 spectrometer was used; the measurements were carried out in tetrachloromethane at 27°C (conc. $1-4 . 10^{-3}$ M). Samples for analysis were dried at 100°C and 0·1 Torr pressure over phosphorus pentoxide for 8−18 h. Unless stated otherwise the reaction mixture was worked up in the following manner: The reaction mixture was poured into ether, washed gradually with water, HCl (1 : 4), 5% Na_2CO_3, and water. The ethereal layer was dried over sodium sulfate, filtered and evaporated to dryness. The residue was crystallised or chromatographed on neutral alumina (Reanal, act. II according to Brockmann).

1α,3α-Dihydroxylupane (I) and 1α,3β-dihydroxylupane (IV)

1α,2α-Epoxy-3-lupanone[4] (VI) (400 mg) and 300 mg of lithium aluminum hydride in 100 ml ether was refluxed for 5 h, then poured into ethyl acetate and worked up in the conventional manner. The crude product was chromatographed on 100 g alumina with 1 200 ml of benzene–ether mixture (3 : 1), affording 150 mg of compound I, m.p. 256°C (chloroform–methanol), $[\alpha]_D -17°$ (c 0·55). Literature[5] m.p. 250°C, $[\alpha]_D -16°$, or[9] m.p. 244−245°C, $[\alpha]_D +8·7°$. Further elution with 800 ml of benzene–ether mixture (1 : 1) gave 170 mg of compound IV. m.p. 245°C (chloroform–methanol), $[\alpha]_D -9·4°$ (c 0·63). Literature[5] gives m.p. 236−238°C, $[\alpha]_D -6·4°$.

1α,3α-Dihydroxy-lupane-[2β,3β-D$_2$] (II) and 1α,3β-dihydroxy-lupane-[2β,3α-D$_2$] (V)

Ketone[4] VI (1·3 g) and 300 mg of lithium aluminum deuteride in 200 ml of ether were refluxed under nitrogen for 5 h. The mixture was worked up as above, affording 280 mg of compound II, m.p. 255°C (chloroform–methanol); $[\alpha]_D -16·5°$ (c 0·66), and 810 mg of compound V, m.p. 244°C (chloroform–methanol); $[\alpha]_D -9·4°$ (c 0·68).

1α-Hydroxy-2-lupene (VIII)

To 2·2 g of 2-lupene[11] (VII) and 1 g of SeO_2 in 200 ml of dioxane two drops of water were added and the mixture refluxed for 13 h. The separated selenium was filtered off and the warm filtrate was poured into 1·5 l of 2·5% KOH in water. After cooling the precipitated product was filtered off and dried at 100°C. The crude product (2·05 g) was dissolved in benzene and filtered through a thin layer of alumina. Crystallisation from benzene–ethanol and recrystallisation from chloroform–methanol gave a product of m.p. 203−204°C; $[\alpha]_D +66·3°$ (c 0·65). For $C_{30}H_{50}O$ (426·7) calculated: 84·44% C, 11·81% H; found: 84·15% C, 11·50% H.

1α-Hydroxy-2α,3α-epoxylupane (IX)

To 330 mg of substance VIII 20 ml of perbenzoic acid solution in chloroform (7 mg/1 ml) were added and the mixture was allowed to stand at −5°C for 4 days. The reaction mixture was washed with a dilute sodium carbonate solution and water, and dried over sodium sulfate. After evaporation of the solvent the residue (350 mg) was crystallised from methanol–chloroform, m.p. 229 to 232°C; $[\alpha]_D +12·3°$ (c 0·65) $\nu(OH)$ 3 553 cm^{-1} (ε 68). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·38% C, 11·57% H.

1α,3α-Dihydroxylupane (I)

150 mg of substance IX in 25 ml of ether were refluxed for 8 h with 150 mg of lithium aluminum hydride and poured into ethyl acetate. After working up the obtained substance had m.p. 255°C

(chloroform–methanol), $[\alpha]_D - 15\cdot5^\circ$ (c 0·60). Identification was carried out by comparison with the product prepared by the above described method. Compound *IX* (100 mg) and lithium aluminum deuteride (80 mg) in 25 ml of ether were refluxed under nitrogen for 5 h. After a work-up analogous to that above 1α,3α-dihydroxy-lupane-[2β-D] (*III*) was obtained, m.p. 256°, $[\alpha]_D - 15°$ (c 0·56).

1α-Hydroxy-2α3α;19β,28-diepoxy-18-oleanane (*XI*)

To 350 mg of unsaturated alcohol *X* a solution of perbenzoic acid (340 mg) in chloroform (17 ml) was added and the mixture allowed to stand at 0°C for 2 days. The solution was washed with a dilute sodium carbonate solution and water, and dried over sodium sulfate. After crystallisation from chloroform–methanol 270 mg of a substance melting at 308°C were obtained. A sample for analysis was obtained after five-fold crystallisation from a mixture of chloroform and light petroleum; m.p. 312–314°C, $[\alpha]_D + 70°$ (c 0·69ν(OH) 3552 cm^{-1} (ε 62)). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·89% C, 10·59% H; found: 78·91% C, 10·59% H.

1α,3α-Dihydroxy-19β,28-epoxy-18α-oleanane (*XII*)

Substance *XI* (110 mg) was extracted into a solution of 100 mg of lithium aluminum hydride. The mixture was refluxed for 5 h and allowed to stand at room temperature for 12 h. After pouring it into ethyl acetate the reaction mixture was further worked up. The residue was chromatographed on 10 g of alumina, act. IV. Elution with benzene–ether (3 : 1; 40 ml) gave 90 mg of a compound, m.p. 270°C (ethyl acetate). After double crystallisation from chloroform–light petroleum a sample was obtained, m.p. 273—275°C; $[\alpha]_D + 46\cdot5°$ (c 0·69), identical with a product described in literature[10].

1α,3α-Diacetoxylupane (*XIII*), 1α,3α-Diacetoxylupane-[2β,3β-D₂] (*XIV*), 1α,3α-Diacetoxylupane-[2β-D] (*XV*), 1α,3β-Diacetoxylupane (*XVI*), and 1α,3β-Diacetoxy-lupane-[2β,3α-D₂] (*XVII*)

The diol was dissolved in pyridine, the solution diluted with an equal amount of acetic anhydride and allowed to stand at room temperature for several days. After the conventional work-up the acetates were crystallised from chloroform–methanol mixture. Substance *XIII*, m.p. 191—195°C, $[\alpha]_D - 19°$ (c 0·54); lit.[5] gives 158—160°C. Substance *XIV*, m.p. 198—199°C, $[\alpha]_D - 18\cdot0°$ (c 0·62). Substance *XV*, m.p. 191—193°C, $[\alpha]_D - 15\cdot5°$ (c 0·65). Substance *XVI*, m.p. 244—246°C, $[\alpha]_D + 10\cdot6°$ (c 0·76); lit.[5] gives m.p. 238—242°C, $[\alpha]_D + 9\cdot8°$. Substance *XVII*, m.p. 246°C, $[\alpha]_D + 9\cdot2°$ (c 0·65).

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