FUNCTIONALISATION OF THE LUPANE SKELETON USING BARTON'S REACTION*

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It was found that the photolysis of (20*S*)-20-nitrosyloxy-30-norlupane derivatives *XII* and *XVII* takes place uniformly under formation of 12-oximino derivatives *XIX* and *XXIII*; the photolysis of epimeric 20*R* nitrites *VII* and *XV* did not take place in the sense of Barton's reaction but a mixture of reaction products was formed. The conversion of oximes *XIX* and *XXIII* to ketones *XXVII* and *XXVIII* succeeded only *via* nitrimines *XXII* and *XXVI*. The structure of 12-substituted lupane derivatives *XIX*, *XX*, *XXI* and *XXVII* has been determined on the basis of their PMR spectra (analysis of ABX systems of the protons 11α, 11β, and 9α), and in the case of ketones *XXVII* and *XXVIII* it was completed by CD spectra.

In the preceding paper[1] we described the functionalisation of the ring C in the lupane skeleton by means of the angular 17β-hydroxymethyl group. The utilisation of an extracyclic functional group for these purposes is little known and therefore we were interested in which position the lupane skeleton could be substituted by means of further extracyclic functional groups, primarily those from the side chain, on $C_{(20)}$ and $C_{(29)}$. As has been shown[2-4], the substituted side chain assumes certain preferred conformations only, in dependence on steric interactions or on the configuration at $C_{(20)}$; hence, it could be considered that these distinct steric dispositions will also play a role in the selective functionalisation of certain positions of the lupane skeleton. For our first studies we made use of Barton's reaction[5-8], *i.e.* of photochemical conversion of the nitrites of 20-lupanol derivatives, (20*R*)- or (20*S*)-30-nor-lupanol, and 29,30-dinor-20-lupanol. In this part we describe the course of the photolysis of (20*R*) or (20*S*)-nitrosyloxy-30-norlupane derivatives.

As starting compound for the preparation of nitrites *XV* or *XVII* noralcohols *XIV* or *XVI* respectively were used, that are easily accessible by the known procedure[9] from betulin diacetate. For the simplification of the interpretation of the IR and PMR spectra it was further desirable to investigate the course of the photolysis of nitrites *VII* or *XII*, resp., which do not contain acetoxyl groups. The parent alcohols *VI* or *XI* were also prepared earlier[4], but by a method which did not give satisfactory

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yields. Therefore we worked out new procedures utilizing α-lupene (*I*) or 30-norlupan-20-one (*II*) as starting substances. In the first procedure α-lupene (*I*) was converted by Brown's reaction to a mixture of $C_{(20)}$-epimeric 29-lupanols *V* and *X* which gave, according to the preparative yields, a 9 : 1 mixture. For the determination of the absolute configuration at $C_{(20)}$ both alcohols *V* and *X* were converted to acids *III* or *VIII*, and corresponding methyl esters *IV* or *IX*, respectively. The comparison of the molecular rotation changes with corresponding 3β, 28-diacetoxy derivatives[10] (Table I) showed that compounds *III*, *IV* and *V* have configuration 20*R* and compounds *VIII*, *IX* and *X* have configuration 20*S*. The degradation of both 29-lupanols *V* and *X* to 30-nor-20-lupanols *VI* or *XI* was carried out in one reaction sequence *via* corresponding aldehydes and norformyloxy derivatives according to[10]: from 29-hydroxy derivative *V* a single product, noralcohol *VI*, was thus obtained, and analogously, from the epimeric 29-hydroxy derivative *X* noralcohol *XI* was obtained; from this it follows that alcohol *VI* has configuration 20*R* and the noralcohol *XI* configuration 20*S*, which is in agreement with the results obtained by PMR spectra analysis[4].

As the hydroboration of α-lupene (*I*) takes place highly stereospecifically* the above mentioned method is suitable for the preparation of (20*R*)-30-norlupanol (*VI*) only, the total yield of which calculated per starting α-lupene (*I*), is 63%. For the preparation of epimeric noralcohol *XI* the reduction of norketone *II* with sodium in boiling 1-propanol was found as most suitable, as during this reaction both noralcohols are formed in a 1 : 1 ratio, while in the reduction with complex hydrides (for example lithium borohydride) noralcohol *VI*, *i.e.* 20*R* prevails (3 : 1).

The mentioned noralcohols *VI*, *XI*, *XIV* and *XVI* were further converted to corresponding nitrites *VII*, *XII*, *XV*, and *XVII* under the effect of gaseous nitrosyl chloride at −20°C in pyridine. Their molecular rotation displays the same relationships as in the case of (20*R*)- or (20*S*)-30-norlupanol derivative esters described earlier[4]; the dependence of their UV absorption on the configuration at $C_{(20)}$ manifests itself less significantly.

During the actual course of Barton's reaction it was found that nitrites of 20*R* configuration, *i.e. VII* and *XV*, are converted to a mixture which according to thin-layer chromatography consisted of 7−10 substances. The separation of this mixture by

* From this it follows that the isopropenyl chain of the 20(29)-lupene skeleton has a rather restricted rotation around the $C_{(19)}$—$C_{(20)}$ bond. According to generally valid premises of *a*) a cisoid addition of borane to the double bond[11], and *b*) its preferred approach from the less hindered side, the highly favorised formation of the 20*R* alcohol *V* can be explained only by the assumption that the isopropenyl chain of α-lupene (*I*) must be fixed in a conformation in which the 19β*H* and the double bond $C_{(20)}$—$C_{(29)}$ are synclinal. This is in agreement with the preferred conformations of the variously modified side chain of lupane derivatives, that we proposed in our preceding papers[2,4,12,13]. This preferred conformation of the unsaturated side chain also explains the long known[14] distinct acceleration of the hydrolysis of the 28-acetoxy group in betulin diacetate by the through-space-interaction of the double bond 20(29) and the 28-acetoxy group.

preparative chromatography afforded purer fractions, but none of them displayed in the IR spectrum an absorption characteristic of the oxime group. From this it is evident that 20*R* configuration of the nitrosyloxy group is not favourable for the usual course of Barton's reaction. Nitrites of 20*S* configuration behave in quite a different manner: photolysis of nitrite *XVII* gave a mixture from which noralcohol *XVI* was isolated in 38% yield, and the oxime to which we assign the structure *XXIII* in 30% yield. Similarly, from nitrite *XII* noralcohol *XI* was obtained in 36% yield and oxime of the supposed structure *XIX* in a 40% yield. As both $C_{(12)}$ (distance 3·1 Å) and $C_{(21)}$ (distance 2·6 Å) are in the proximity of $C_{(20)}$ it was necessary to consider the structures with the oxime group either in the position 12 or the position 21 when the structures of oximes *XIX* and *XXIII* were determined.

The decision between these possibilities was made in the following manner: Acetylation of oximes *XIX* or *XXIII* gave N-O-,20-O-diacetyl derivatives *XXI* or *XXV*, respectively, which may be partially hydrolysed to 20-O-acetyl-oximes *XX* or *XXIV*, resp. The attempts at deoximation of the oximino acetate *XXV* under the effect of chromous acetate[15], or the attempts at deoximation of oximes *XXIII* and *XXIV* with titanium(III) chloride[16] were unsuccessful. During the attempt at deoximation of 20-O-acetyloxime *XXIV* with nitrous acid in acetic acid the expected ketone (according to described analogies[17]) was not obtained. Instead a substance was isolated to which we assign the structure of nitrimine *XXVI* on the basis of its IR spectrum. In agreement with this the hydrolysis of this product took place in aqueous dioxan[18], giving rise to ketone *XVIII*. In the same manner nitrimine *XXII* and eventually ketone *XXVII* were prepared from 20-O-acetyloxime *XX*.

The structure of both ketones was proposed on the basis of the following facts: in the IR spectrum of ketone *XXVII* the carbonyl group absorption band (1712 cm^{-1}) is in the region of absorption of six-membered and larger-ring ketones; in the IR spectrum of ketone *XXVIII* the oxo group absorption band is hidden by the absorption of the acetoxyl groups. In the PMR spectra of both ketones a downfield shift of the 8β and 10β-methyl groups signal was observed and an upfield shift of the 14α-methyl signal (Table II), which is only explicable by the effect[1] of the oxo group in the position 12. In these spectra is also a significant doublet with a coupling constant 11·5 or 10·8 Hz, resp.; this signal corresponds to a hydrogen in α-position with respect to the carbonyl group (*i.e.* 13β), which neighbours in the β-position with a single additional hydrogen (18α) so that both close a dihedral angle near 180°. Further, in the spectrum of ketone *XXVII* a multiplet at 2·28 p.p.m. was found (AB part of an ABX system), which corresponds to two hydrogen atoms in the α-position to the carbonyl group; on the basis of its analysis according to[19] the coupling constant values were computed, $|J_{AB}| = 12{\cdot}1$ Hz, $J_{AX} = 13{\cdot}9$ Hz, and $J_{BX} = 3{\cdot}3$ Hz. From this it follows that only a single hydrogen is in the β-position to the carbonyl (proton X), which makes with proton A a dihedral angle close to 180° and with proton B an angle of approximately 60°. Such a distribution of hydrogen atoms is only possible

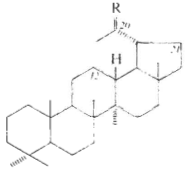
TABLE I

Molecular Rotation Differences between $C_{(20)}$-Epimeric Lupane and 3β, 28-Diacetoxylupane Derivatives

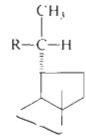
$C_{(20)}$-Substituent	Lupane			3β, 28-Diacetoxylupane[10]
	$[M]_D$ 20*S*	$[M]_D$ 20*R*	$\Delta[M]_D$ (20*S*−20*R*)	$\Delta[M]_D$ (20*S*−20*R*)
COOH	+49°	−212°	+261°	+307°
$COOCH_3$	+61°	−299°	+360°	+378°
CH_2OH	−43°	−78°	+35°	+32°

if the keto group is located in the position 12; it proves simultaneously that a change in the *trans*-annelation of the D/E rings did not take place. The values of the circular dichroism of both ketones (*XXVIII* or *XXVII*, $\Delta\varepsilon = -1{\cdot}68$ (292 nm), or $\Delta\varepsilon = -1{\cdot}54$ (293 nm), respectively) also correspond to the values that were determined[1,20,21] for 12-lupanone derivatives.

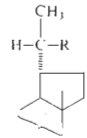
Further proofs concerning the position of the carbonyl group of ketones *XXVII* and *XXVIII* could be obtained by an analysis of the PMR spectra of their derivatives *XIX*, *XX*, *XXI*, *XXIV* and *XXV*. The double bond C=N has a similar effect as the C=O double bond, *i.e.* it causes a considerable downfield shift of the 8β and 10β--methyl signals (Table II); the 13β proton again appears as a doublet the coupling constant of which (11 – 12 Hz) confirms its antiperiplanar conformation with respect to 18αH. As regards the configuration of the oxime group (*XIX*, *XX*, *XXIII*, *XXIV*) or oximinoacetate group (*XXI*, *XXV*) Dreiding models indicate that it can be only 12*E*, because in the case of 12*Z* configuration strong non-bonding interactions with



I, R = CH_2
II, R = O



III, R = COOH
IV, R = $COOCH_3$
V, R = CH_2OH
VI, R = OH
VII, R = ONO



VIII, R = COOH
IX, R = $COOCH_3$
X, R = CH_2OH
XI, R = OH
XII, R = ONO
XIII, R = OAc

$C_{(20)}$ or the substituents in this position would take place. This assumption is confirmed experimentally by the IR spectra of 20-O-acetyloximes *XX* and *XXIV* which do not display an intramolecular association of the oxime hydroxy group (Table III). Further proof of the 12*E* configuration of the oxime or oximino acetate group consists in an appreciable downfield shift[17] (approx. 1·1 p.p.m.) of the neighbouring equatorial 11α hydrogen (*X*) signal which forms with the 11β(A) and 9α(B) hydrogens an ABX

TABLE II

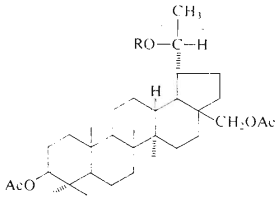
Characteristic Parameters of the PMR Spectra of 12-Substituted Lupane Derivatives

Substance	Chemical shifts, δ-scale, p.p.m.					Coupling constants, Hz	
	8βCH$_3$ Δ^a	10βCH$_3$ Δ^a	14αCH$_3$ Δ^a	13βH	11αH	$J_{13,18}$	$J_{19,20}$
XIII	1·038	0·843	0·908	—	—	—	4·1
	0·000	0·000	0·000				
XIX	1·197	0·919	0·878	2·53d	3·39[b]	10·6	≈2
	−0·159	−0·076	+0·030				
XX	1·177	0·906	0·830	2·47d	3·33[b]	11·0	4·8
	−0·139	−0·063	+0·078				
XXI	1·195	0·907	0·907	2·59d	3·14[c]	11·0	4·7
	−0·157	−0·064	+0·001				
XXVII	1·277	0·911	0·781	2·75d	2·19[f]	10·8	≈5
	−0·239	−0·068	+0·127				
XVIII[e]	1·037	0·860	0·925	—	—	—	4·0
	0·000	0·000	0·000				
XXIV	1·190	0·932	0·857	2·48d	3·30bd	10·0	[d]
	−0·153	−0·072	+0·068				
XXV	1·220	0·931	0·931	2·62d	3·11bd	12·0	[d]
	−0·183	−0·071	−0·006				
XXVIII	1·298	0·942	0·802	2·79d	—	11·5	4·8
	−0·261	−0·082	+0·123				

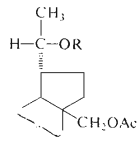
[a] The Δ values for compounds *XIX*—*XXI* and *XXVII* are referred to compound *XIII* as standard; for compounds *XXIV*, *XXV* and *XXVIII* to compound *XVIII* as standard. The sign − indicates a downfield shift of the signal: [b] X part of the ABX system, from the spectrum the position of all 6 lines can be determined; [c] X part of the ABX system, from the spectrum the position of 4 lines only can be determined, 2 external lines merge with the noise; [d] the coupling constant cannot be read from the spectrum; [e] ref.[4]; [f] AB part of the ABX system, the chemical shift value was obtained by computation.

system. In the spectra of oximes *XIX* and *XX* the X part of this system is composed of 6 lines (Table II) which were integrated according to[22] to give the following coupling constant values: $J_{AX} = -14{\cdot}3 \pm 2$ or -12 ± 2 Hz, $J_{BX} = 5{\cdot}3 \pm 2$ or $3{\cdot}4 \pm 2$ Hz, and $J_{AB} = 13 \pm 1$ Hz. These values are in good agreement with the above values obtained by analysis of ketone *XXVII*.

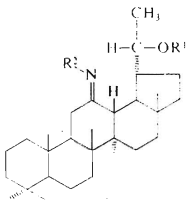
The substitution of the position $C_{(12)}$ with a bulky substituent should still more distinctly affect the conformation of the side chain than in derivatives which are unsubstituted in this position; as was shown earlier[4] in noralcohols *XI* and *XVI* and their acetates *XIII* and *XVIII* such conformers of the side chain prevail, in which the least bulky substituent, *i.e.* 20-H, is oriented into the proximity of $C_{(12)}$. From the coupling constant values $J_{19,20}$, determined for 20-acetoxy-30-norlupane derivatives substituted in $C_{(12)}$, *i.e. XX*, *XXI*, *XXVII*, and *XXVIII* (Table II), only a weak affecting of the side chain conformers population is evident. In the case of 20-hydroxy derivatives *XIX* and *XXIII* the IR spectra (Table III) indicate a strong intramolecular



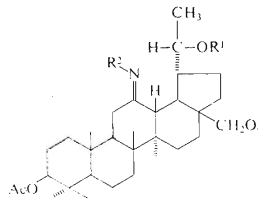
XIV, R = H
XV, R = NO



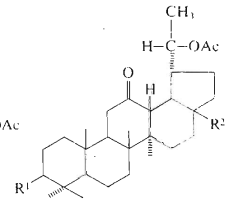
XVI, R = H
XVII, R = NO
XVIII, R = Ac



XIX, R^1 = H, R^2 = OH
XX, R^1 = Ac, R^2 = OH
XXI, R^1 = Ac, R^2 = OAc
XXII, R^1 = Ac, R^2 = NO_2



XXIII, R^1 = H, R^2 = OH
XXIV, R^1 = Ac, R^2 = OH
XXV, R^1 = Ac, R^2 = OAc
XXVI, R^1 = Ac, R^2 = NO_2



XXVII, R^1 = H, R^2 = CH_3
XXVIII, R^1 = OAc,
R^2 = CH_2OAc

TABLE III

Frequencies (cm^{-1}) of the Stretching Vibration Bands of the OH Groups

Measured with a Grating Unicam SP 700 Spectrophotometer in $2 . 10^{-3}$M solutions in tetrachloromethane.

Compound	*XI*	*XVI*	*XIX*	*XXIII*	*XX*	*XXIV*
$C_{(20)}$–OH	3 620	3 618	3 208, 3 117	3 210, 3 120	—	—
Oxime OH	—	—	3 592	3 587	3 596	3 594

hydrogen bridge between the 20-hydroxy group and the oxime group in the position $C_{(12)}$; the formation of this hydrogen bond also changes the original conformation of the side chain as may be seen from the drop in the coupling constant $J_{19,20}$ by 2·8 Hz in comparison with the corresponding 20-O-acetyl derivative *XX*. From the values $J_{19,20}$ = 2 Hz in oxime *XIX* it may be supposed that the conformers with dihedral angles 19βH and 20H close to 90° or 270° are preferred. Of these possibilities only one suits the formation of an intramolecular hydrogen bridge (Table III), *i.e.* that conformation in which the 20-methyl group is in synclinal conformation with respect to 19βH, but also in synclinal conformation with respect to the substituent on $C_{(12)}$; the energy of the hydrogen bond evidently exceeds the non-bonding interactions of the bulky methyl group with the oxime group on $C_{(12)}$.

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotations were measured in chloroform on an automatic ETL-NPL (Bendix-Ericsson) polarimeter with a $\pm 1-2°$ precision. The infrared spectra were measured in chloroform on a UR-20 (Zeiss, Jena, GDR) apparatus; the ultraviolet spectra were measured with a Unicam SP-700 spectrophotometer. The CD curves were recorded with a Roussel-Jouan Dichrographe 185, Model II, in dioxan. The PMR spectra were measured in deuteriochloroform with tetramethylsilane as internal standard on a Varian HA-100 instrument (compounds *XXIV* and *XXV* on a Tesla 80 MHz instrument); the chemical shifts are given in p.p.m., δ-scale, for the description of the ABX systems the same symbols were used as in paper[23]. For column chromatography neutral alumina was used (Reanal, act. II) and silica gel (Spolana, Neratovice), for thin layer chromatography silica gel G (Merck) was employed. The conventional work-up of the ethereal solutions means that they were washed with dilute hydrochloric acid (1 : 4), water, saturated sodium hydrogen carbonate and water; in the cases of reduction with complex hydrides or alkali metals and in the case of hydroboration saturated ammonium sulfate solution was used instead of water. The methyl esters were prepared using an ethereal diazomethane solution. Samples for analysis were dried over phosphorus pentoxide at 80°C and 0·1–1 Torr for 8–12 hours. The identity of the samples prepared by various procedures was checked by mixture melting point determination, optical rotation, thin layer chromatography and infrared spectra.

(20*R*)-Lupan-29-oic Acid (*III*)

a) To a solution of 2·2 g of α-lupene[9] (*I*) in 100 ml of acetic acid a solution of 1·85 g of chromium trioxide in 28 ml of 90% acetic acid were added dropwise under stirring (at 67—70°C). The mixture was stirred for 1 hour at the same temperature. The excess chromium trioxide was decomposed with 20 ml of methanol and the product precipitated with 220 ml of 0·2M-HCl, filtered off under suction and washed with water. After drying in a vacuum the product was chromatographed on a silica gel column (90 g). A light petroleum–ether mixture (98 : 2) eluted 100 mg of norketone *II*, m.p. 173—174·5°C, $[\alpha]_D$ —15° (*c* 0·73); literature[9] gives m.p. 174—176°C, $[\alpha]_D$ —16°. A light petroleum–ether (95 : 5) mixture eluted 420 mg of acid *III*, m.p. 255—285°C (sublimation) (hexane–acetone), $[\alpha]_D$ —47° (*c* 0·67). IR spectrum: 3 520, 3 200—2 700, 1 750, 1 710 (COOH) cm^{-1}. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·70% C, 11·25% H. Methyl ester *IV*: m.p. 201—202°C (acetone), $[\alpha]_D$ —65·5° (*c* 0·84). IR spectrum: 1 730, 1 442 ($COOCH_3$) cm^{-1}. For $C_{31}H_{52}O_2$ (456·7) calculated: 81·52% C, 11·48% H; found: 81·38% C, 11·59% H.

b) Jones reagent (2 ml) was added into a solution of 100 ml of alcohol *V* in 12 ml of acetone and the mixture stirred at room temperature for 15 min. Excess reagent was decomposed with saturated sodium hydrogen sulfite and the reaction mixture was poured into water, the product extracted with ether, the extract washed with saturated ammonium sulfate solution and water. Crystallisation of the residue from hexane–acetone gave 50 mg of acid *III*, m.p. 254—270°C (sublimates), $[\alpha]_D$ —44·5° (*c* 0·76).

(20*R*)-Lupan-29-ol (*V*)

a) Boron trifluoride etherate (2·25 ml) was added to a solution of 1 g of α-lupene[9] in 30 ml of ether at —5°C and a solution of 500 mg of lithium aluminum hydride in 60 ml of ether was added dropwise under cooling to —10°C to the stirred solution. After 2 hours stirring at 0°C the excess hydride was decomposed with 20 ml of acetone and the reaction mixture was diluted with 20 ml of ether. After addition of a saturated sodium sulfate solution the organic layer was separated, dried and evaporated. To the residue dissolved in 50 ml of tetrahydrofuran a solution of 5 g of potassium hydroxide in 50 ml of water and 30 ml of 30% hydrogen peroxide was added dropwise at 0°C under stirring. The mixture was stirred at 0°C for 1 hour, diluted with water and the product extracted with ether. The extract was worked up in the conventional manner. The residue (1 g) was chromatographed on 10 preparative silica gel plates (20 × 20 cm) in light petroleum–ether (9 : 1), double development. The zones containing the less polar component were combined, eluted with ether and the solvent evaporated *in vacuo*. Yield, 860 mg of alcohol *V*, m.p. 150—153°C (dichloromethane–methanol), $[\alpha]_D$ —17° (*c* 0·64). IR spectrum: 1 020, 3 635 (OH) cm^{-1}. For $C_{30}H_{52}O$ (428·7) calculated: 84·04% C, 12·23% H; found: 84·23% C, 12·20% H.

b) Lithium aluminum hydride (300 mg) was added into a solution of 100 mg of methyl ester *IV* in 15 ml of tetrahydrofuran and the mixture was stirred and refluxed for 5 hours. Excess hydride was decomposed with ethyl acetate and water, the reaction mixture poured into dilute hydrochloric acid (1 : 4) and the product extracted with ether. The ethereal extract was worked up in the conventional manner. The residue was chromatographed on a preparative silica gel plate (20 × 20 cm) in light petroleum–ether (9 : 1), double development. Yield, 70 mg of alcohol *V*, m.p. 153—155°C (dichloromethane–methanol), $[\alpha]_D$ —16·8° (*c* 1·31).

(20*R*)-30-Norlupan-20-ol (*VI*)

a) Lithium borohydride (400 mg) was added into a solution of 200 mg of norketone[9] *II* in 20 ml of tetrahydrofuran and the mixture was heated under reflux for 3 hours. The excess hydride

was decomposed with water, the mixture poured into dilute hydrochloric acid (1 : 4) and extracted with ether. The extract was submitted to the conventional work-up. The residue was chromatographed on 2 preparative silica gel plates (20 × 20 cm) in light petroleum–ether (9 : 1). The zones containing the less polar component were combined, eluted with dichloromethane and the solvent was evaporated *in vacuo*. Yield, 130 mg of noralcohol *VI*, m.p. 163–164°C (light petroleum), $[\alpha]_D$ −11·5° (*c* 0·75).

b) Sodium (8·5 g) was added in portions into a refluxed and stirred solution of 1·5 g of norketone[9] *II* in 120 ml of 1-propanol over one hour and the reaction mixture was stirred and refluxed for another 30 minutes. After cooling it was poured into water, acidified with hydrochloric acid and extracted with ether. The extract was worked up in the conventional manner. The residue was chromatographed on a column of alumina (150 g). A light petroleum–ether (85 : 15) mixture eluted 700 mg of noralcohol *VI*, m.p. 163–164°C (hexane), $[\alpha]_D$ −10·8° (*c* 1·186). IR spectrum: 1029, 3636 (OH) cm^{-1}. For $C_{29}H_{50}O$ (417·7) calculated: 83·99% C, 12·15% H; found: 84·05% C, 12·26% H.

c) To a suspension of 210 mg of chromium trioxide and 170 mg of anhydrous magnesium sulfate in 10 ml of dichloromethane 0·332 ml of pyridine in 1 ml of dichloromethane were added under cooling with ice and stirring, and the mixture was stirred under cooling for another 20 minutes. Then 230 ml of alcohol *V* in 6 ml of dichloromethane were added to the complex formed and the stirring and cooling continued for another 30 minutes. After an additional 30 minutes at room temperature the reaction mixture was decomposed with 5% sodium carbonate solution and the product extracted with ether and the extract worked up. 3-Chloroperbenzoic acid (210 mg) was added to the residue dissolved in 15 ml of dichloromethane and the mixture allowed to stand for 3 days at room temperature. The solvent was evaporated *in vacuo*, the residue dissolved in benzene and introduced into a column of alumina (20 g). After two days' standing the product was eluted with ether and purified chromatographically on a preparative silica gel plate (20 × 30 cm) in light petroleum–ether (9 : 1). Yield, 117 mg of noralcohol *VI*, m.p. 162–164°C (hexane), $[\alpha]_D$ −10° (*c* 1·21).

(20*R*)-20-Nitrosyloxy-30-norlupane (*VII*)

Excess nitrosyl chloride was distilled into a solution of 200 mg of noralcohol *VI* in 5 ml of pyridine under stirring and cooling at −20°C until the reaction mixture persisted orange coloured. After 10 minutes stirring at −20°C and 5 minutes at room temperature the mixture was poured into water and the product extracted with ether. The extract was washed five times with water, dried, and evaporated under reduced pressure. The residual pyridine was eliminated by repeated distillation with light petroleum in a vacuum. Yield, 190 mg of nitrite *VII*, m.p. 168–171°C under decomposition (ether), $[\alpha]_D$ +3·8° (*c* 1·57); IR spectrum: 1641 (ONO) cm^{-1}. UV spectrum (tetrahydrofuran): λ_{max} 335 nm (ε 39·6), 345 nm (ε 59·0), 357 nm (ε 82·5), 370 nm (ε 88·7), 385 nm (ε 53·2).

(20*S*)-Lupan-29-oic Acid (*VIII*)

a) Further elution, after the isolation of acid *III* (prodedure *a*)), with the same mixture of solvents gave 370 mg of acid *VIII*, m.p. 250–280°C under sublimation (light petroleum–acetone), $[\alpha]_D$ +11° (*c* 0·65). IR spectrum: 3530, 3300–2700, 1750, 1710 (COOH) cm^{-1}. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·36% C, 11·14% H. Methyl ester *IX*: m.p. 212–214°C (acetone), $[\alpha]_D$ +13·4° (*c* 1·04). IR spectrum: 1730, 1442 ($COOCH_3$) cm^{-1}. For $C_{31}H_{52}O_2$ (456·7) calculated: 81·52% C, 11·48% H; found: 81·83% C, 11·37% H.

b) The preparation of acid *VIII* by oxidation of alcohol *X* was carried out in the same manner as the preparation of acid *III* (procedure *b*)). Crystallisation of the residue from a light petroleum–acetone mixture gave 50 mg of acid *VIII*, m.p. 256–273° (sublimation), $[\alpha]_D$ +12·6° (*c* 0·67).

(20*S*)-Lupan-29-ol (*X*)

a) The zones containing the more polar component from preparative chromatography of alcohol *V* (procedure *a*)) were combined and eluted with ether. The solvent was evaporated under reduced pressure. Yield, 88 mg of alcohol *X*, m.p. 180–182°C (light petroleum), $[\alpha]_D$ −10° (*c* 0·78). IR spectrum: 1035, 3635 (OH) cm^{-1}. For $C_{30}H_{52}O$ (428·7) calculated: 84·04% C, 12·23% H; found: 84·06% C, 12·29% H.

b) The preparation of alcohol *X* by reduction of methyl ester *IX* was carried out in the same manner as the preparation of alcohol *V* (procedure *b*). Crystallisation of the residue from light petroleum gave 74 mg of alcohol *X*, m.p. 182–184°C, $[\alpha]_D$ −10° (*c* 0·50).

(20*S*)-30-Norlupan-20-ol (*XI*)

a) The zones containing the more polar component from the preparative chromatography of noralcohol *VI* (procedure *a*) were eluted with dichloromethane and the solvent was evaporated under reduced pressure. Yield, 45 mg of noralcohol *XI*, m.p. 164–166°C (light petroleum), $[\alpha]_D$ −15° (*c* 0·66).

b) Further elution with the same mixture of solvents as after the isolation of noralcohol *VI* (procedure *b*) gave 600 mg of noralcohol *XI*, m.p. 163–165°C (hexane), $[\alpha]_D$ −12·6° (*c* 1·75). IR spectrum: 1030, 3635 (OH) cm^{-1}. For $C_{29}H_{50}O$ (414·7) calculated: 83·99% C, 12·15% H; found: 84·21% C, 12·17% H.

c) The preparation of noralcohol *XI* by degradation of alcohol *X* was performed in the same manner as was the preparation of noralcohol *VI* (procedure *c*). Chromatography on a preparative silica gel plate (20 × 30 cm) with light petroleum–ether (7 : 3) afforded 126 mg of noralcohol *XI*, m.p. 163 – 165°C (hexane), $[\alpha]_D$ −14° (*c* 1·05).

(20*S*)-20-Nitrosyloxy-30-norlupane (*XII*)

The preparation of nitrite *XII* was carried out from 200 mg of noralcohol *XI* in the same manner as the preparation of nitrite *VII*. Yield, 192 mg of nitrite *XII*, m.p. 163–165°C (ether), $[\alpha]_D$ +27·9° (*c* 1·05); IR spectrum: 1640 (ONO) cm^{-1}. UV spectrum (tetrahydrofuran): λ_{max} 337 nm (ε 36·1), 347 nm (ε 51·2), 358 nm (ε 64·0), 370 nm (ε 62·8), 387 nm (ε 36·9).

(20*S*)-20-Acetoxy-30-norlupane (*XIII*)

A solution of 120 mg of noralcohol *XI* in 3 ml of pyridine and 1·5 ml of acetic anhydride was allowed to stand at room temperature for 3 days. The reaction mixture was poured onto ice and the product extracted with ether. The ethereal extract was worked up in the usual manner. The residue (123 mg) was crystallised from ether. Yield, 100 mg of acetate *XIII*, m.p. 184–185°C, $[\alpha]_D$ +2·5° (*c* 1·58). Literature[4] gives m.p. 183–185°C, $[\alpha]_D$ 0 to +3°. PMR spectrum: 0·761 s, 0·800 s (2 . CH_3), 0·843 s (2 . CH_3), 0·908 s, 1·038 s, (2 . CH_3), 1·131 d J = 6·3 Hz (20-CH_3), 1·98 s (CH_3COO), 5·17 dq $J_{20,29}$ = 6·3 Hz, $J_{19,20}$ = 4·1 Hz (20-H).

(20*R*)-3β,28-Diacetoxy-20-nitrosyloxy-30-norlupane (*XV*)

The preparation of nitrite *XV* was carried out from 200 mg of noralcohol[9] *XIV* by the same procedure used for the preparation of nitrite *VII*. Yield, 182 mg, m.p. 183–185°C under decomposition (hexane), $[\alpha]_D$ +5·7° (*c* 0·70); IR spectrum: 1730, 1260, 1038 (CH_3COO), 1647 (ONO) cm^{-1}. UV spectrum (tetrahydrofuran): λ_{max} 334 nm (ε 35·5), 344 nm (ε 52·9), 356 nm (ε 73·2), 369 nm (ε 77·2), 384 nm (ε 46·6).

(20*S*)-3β,28-Diacetoxy-20-nitrosyloxy-30-norlupane (*XVII*)

The preparation of nitrite *XVII* was carried out from 200 mg of noralcohol[9] *XVI*, in analogy to the preparation of nitrite *VII*. Yield, 185 mg of nitrite *XVII*, m.p. 220–222°C under decomp. (cyclohexane), $[\alpha]_D$ +18° (*c* 0·67); IR spectrum: 1734, 1260, 1035 (CH_3COO), 1647 (ONO) cm^{-1}. UV spectrum (tetrahydrofuran): λ_{max} 336 nm (ε 47·4), 346 nm (ε 61·3), 358 nm (ε 73·9), 371 nm (ε 71·1), 386 nm (ε 44·1).

Photolysis of Nitrite *XII*

A solution of 450 mg of nitrite *XII* in 60 ml of benzene was photolysed in a sial-glass flask using a UV lamp (Tesla THK 101) for 6 hours. The photolysis was carried out under nitrogen at 16–17°C. After evaporation of benzene to dryness the residue was chromatographed on a silica gel column (50 g) using first light petroleum–ether mixture 4 : 1 for elution. The eluate weighed 60 mg and contained non-polar substances; light petroleum–ether mixture 3 : 1 eluted 150 mg of noralcohol *XI*, m.p. 162–165°C, $[\alpha]_D$ −14·7° (*c* 0·73). Further elution with the same solvent mixture gave 180 mg of amorphous oxime *XIX*; IR spectrum: 3595, 1675 (C=NOH), 3225, 3135 (OH) cm^{-1}. PMR spectrum: 0·818 s (2 . CH_3), 0·851 s, 0·878 s, 0·919 s (3 . CH_3), 1·159 d J = 7 Hz (20-CH_3), 1·197 s (8β CH_3), 2·53 d J = 10·6 Hz (13β H), 3·39 X part of the ABX system $|J_{AX} + J_{BX}|$ = = 9 Hz $2(D_+ + D_-)$ 31·4 Hz $2(D_+ - D_-)$ = 1 Hz (11α H), 3·75 dq $J_{20,29}$ = 7 Hz $J_{19,20} \approx$ ≈ 2 Hz (20-H).

(20*S*)-20-Acetoxy-12(*E*)-hydroxyimino-30-norlupane (*XX*)

A solution of 200 mg of acetate of oxime *XXI* in 5 ml of benzene was introduced into an alumina column (20 g) and allowed to stand at room temperature for 48 hours. Elution with ether gave 150 mg of oxime *XX*, m.p. 189–191°C (ether), under decomposition, $[\alpha]_D$ +99° (*c* 0·60); IR spectrum: 1725, 1263, 1055 (CH_3COO), 3600, 3443, 1667 (C=NOH) cm^{-1}. PMR spectrum: 0·804 s, 0·820 s, 0·830 s, 0·847 s, 0·906 s (5 . CH_3), 1·177 s (8β CH_3), 1·189 d J = 6·2 Hz (20-CH_3), 1·945 s (CH_3COO), 2·47 d J = 11 Hz (13β H), 3·33 X part of the ABX system $|J_{AX} + J_{BX}|$ = = 8·6 Hz $2(D_+ - D_-)$ = 6·4 Hz $2(D_+ + D_-)$ = 32 Hz (11α H), 5·50 dq $J_{20,29}$ = 6·2 Hz, $J_{19,20}$ = 4·8 Hz (20-H). For $C_{31}H_{51}NO_3$ (485·7) calculated: 76·65% C, 10·58% H, 2·88% N; found: 76·74% C, 10·87% H, 3·01% N.

(20*S*)-20-Acetoxy-12(*E*)-acetoxyimino-30-norlupane (*XXI*)

Acetic anhydride (5 ml) was added to a solution of 180 mg of oxime *XIX* in 7·5 ml of pyridine and the mixture heated at 40°C for 24 hours. It was then poured onto ice, the product extracted with ether and the extract worked up in the conventional manner. The residue was chromatographed on two preparative silica gel plates (20 × 20 cm) with light petroleum–ether (4 : 1) as developing solvent. Yield, 160 mg of acetate of oxime (*XXI*), m.p. 214–217°C (ether), $[\alpha]_D$

+74·8° (*c* 0·51); IR spectrum: 1722, 1265, 1055 (CH_3COO), 1760, 1645 (C=NOOCCH$_3$) cm^{-1}. PMR spectrum: 0·801 s, 0·814 s, 0·852 s (3 . CH_3), 0·907 s (2 . CH_3), 1·195 s (8β CH_3), 1·253 d J = 6·1 Hz (20-CH_3), 1·925 s, 2·10 s (2 . CH_3COO), 2·59 d J = 11 Hz (13β-H), 3·14 X part of the ABX system $|J_{AX} + J_{BX}|$ = 9 Hz 2($D_+ - D_-$) = 13 Hz (11α H), 5·53 dq $J_{20,29}$ = 6·1 Hz $J_{19,20}$ = 4·7 Hz (20-H). For $C_{33}H_{53}NO_4$ (527·8) calculated: 75·10% C, 10·12% H, 2·65% N; found: 75·23% C, 10·28% H, 2·73% N.

Photolysis of Nitrite *XVII*

A solution of 1·1 g of nitrite *XVII* in 100 ml of benzene was photolysed in a sial-glass flask with a UV lamp (Tesla THK 101) for 6 hours. The photolysis was carried out under nitrogen at 10–12°C. After evaporation of benzene *in vacuo* the residue was chromatographed on a silica gel column (120 g). Benzene–ether mixture (4 : 1) eluted 100 mg of non-polar substances; benzene–ether mixture (3 : 2) eluted 400 mg of noralcohol *XVI*, m.p. 259–261°C, $[\alpha]_D$ −11·5° (*c* 0·70), literature[9] gives m.p. 258·5–260·5°C, $[\alpha]_D$ −10°. Further elution with the same solvent mixture eluted 330 mg of amorphous oxime *XXIII*; IR spectrum 1730, 1260, 1035 (CH_3COO), 3595, 1675 (C=NOH), 3230, 3130 (OH) cm^{-1}.

(20*S*)-3β,20,28-Triacetoxy-12(*E*)-hydroxyimino-30-norlupane (*XXIV*)

A solution of 144 mg of acetate oxime *XXV* in 7 ml of benzene was introduced into a column of alumina (15 g) and allowed to stand at room temperature overnight. Elution of the column with ether gave 127 mg of an oily oxime *XXIV*, $[\alpha]_D$ +59·5° (*c* 0·71); IR spectrum: 1730, 1265, 1035 (CH_3COO), 3600, 3440, 1667(C=NOH) cm^{-1}. PMR spectrum: 0·857 s (3 . CH_3), 0·932 s (CH_3), 1·181 d J = 6·15 Hz (20-CH_3), 1·19 s (8β-CH_3), 1·92 s 2·01 s, 2·04 s (3 . CH_3COO), 2·48 d J = 10Hz (13β H), 3·30 d J = 12 Hz X part of the ABX system (11α H), 3·83 d and 4·32 d J_{gem} = 11 Hz (28-H_2), 4·47 mt (3α H), 5·53 mt (20-H). For $C_{35}H_{55}NO_7$ (601·8) calculated: 69·85% C, 9·21% H, 2·32% N; found: 69·65% C, 9·25% H, 2·18% N.

(20*S*)-3β,20,28-Triacetoxy-12(*E*)-acetoxyimino-30-norlupane (*XXV*)

Five ml of acetic anhydride were added to a solution of 200 mg of oxime *XXIII* in 7·5 of pyridine and the mixture was heated at 40°C for 24 hours. After pouring the mixture onto ice it was extracted with ether and the extract worked up. The residue was chromatographed on 2 preparative silica gel plates (20 × 20 cm) with light petroleum–ether (1 : 1). Yield 200 mg of oily acetate of oxime (*XXV*); $[\alpha]_D$ +72·8° (*c* 0·73). IR spectrum: 1730, 1260, 1035 (CH_3COO), 1760, 1650 (C=NOOCCH$_3$) cm^{-1}; PMR spectrum: 0·861 s (2 . CH_3), 0·931 s (2 . CH_3), 1·22 s (8β-CH_3), 1·25 d J = 6·1 Hz (20-CH_3), 1·88 s, 2·00 s, 2·025 s, 2·075 s (4 . CH_3COO), 2·62 d J = 12 Hz (13β H), 3·11 d J = 10 Hz X part of the ABX system (11α H), 3·80 d and 4·30 d J_{gem} = 11 Hz (28-H_2), 4·50 mt (3α H), 5·56 mt (20-H). For $C_{37}H_{57}NO_8$ (643·8) calculated: 69·02% C, 8·91% H, 2.17% N; found: 69·32% C, 9·03% H, 2·14% N.

(20*S*)-20-Acetoxy-30-norlupan-12-one (*XXVII*)

To a solution of 230 mg of oxime *XX* in 6 ml of dichloromethane and 22 ml of acetic acid 10 ml of a saturated aqueous sodium nitrite solution was added dropwise over one hour and the mixture was stirred at room temperature for 1 hour. Additional 5 ml of saturated aqueous sodium nitrite solution were added to the mixture over 1 hour and the stirring was continued at room temperature for another hour. The raction mixture was poured into water and the product extracted with

dichloromethane. The extract was washed with water, sodium hydrogen carbonate solution and water. The residue was dissolved in 25 ml of dioxan, additioned with 10 ml of water and refluxed for 10 hours. The mixture was poured into water and extracted with dichloromethane. Crystallisation of the residue from ether gave 53 mg of ketone *XXVII*, m.p. 215—217°C, $[\alpha]_D - 6°$ (*c* 0·65). IR spectrum: 1720 inflexion, 1267, 1057 (CH_3COO), 1712 (CO) cm^{-1}; PMR spectrum: 0·774 s, 0·781 s, 0·821 s, 0·854 s, 0·911 s (5 . CH_3), 1·277 s (8β-CH_3), 1·309 d $J = 6·5$ Hz (20-CH_3), 1·945 s (CH_3COO), 2·28 AB part of the ABX system $|J_{AX} + J_{BX}| = 17·2$ Hz $2D_+ = 23$ Hz $2D_- = 15$ Hz (11-H_2), 2·75 d $J = 10·8$ Hz (13β H), 5·23 bp $J_{20,30} = 6·6$ Hz $J_{19,20} \approx 5$ Hz (20-H). CD (dioxan): $\Delta\varepsilon - 1·54$ (293 nm). For $C_{31}H_{50}O_3$ (470·7) calculated: 79·10% C, 10·70% H; found: 79·26% C, 10·66% H.

(20*S*)-3β,20,28-Triacetoxy-30-norlupan-12-one (*XXVIII*)

A saturated aqueous solution of sodium nitrite (10 ml) was added dropwise to a solution of 170 mg of oxime *XXIV* in 20 ml of acetic acid over one hour and the mixture was stirred at room temperature for one hour. Additional 5 ml of saturated aqueous sodium nitrite solution was added over one hour to the mixture which was stirred at room temperature for another hour. The reaction mixture was poured into water and extracted with dichloromethane. The extract was washed with water, sodium hydrogen carbonate solution and water. The residue was chromatographed on 2 preparative silica gel plates (20 × 20 cm) with light petroleum–ether (1 : 1). Yield 125 mg of amorphous nitrimine *XXVI*. IR spectrum: 1730, 1265, 1036 (CH_3COO), 1640, 1570, 1320 (C=NNO_2). A solution of 125 mg of nitrimine *XXVI* in 17 ml of dioxan and 10 ml of water was refluxed for 6 hours and the mixture poured into water and extracted with dichloromethane. The residue was chromatographed on a column of alumina (20 g). Light petroleum–ether mixture (1 : 1) eluted 77 mg of amorphous ketone *XXVIII*, $[\alpha]_D - 1·7^0$ (*c* 0·58). IR spectrum: 1730, 1260, 1035 (CH_3COO), 1715 inflexion (CO) cm^{-1}. PMR spectrum: 0·802 s (CH_3), 0·862 s (2 . CH_3), 0·942 s (CH_3), 1·298 s (8β-CH_3), 1·307 d $J = 6·4$ Hz (20-CH_3), 1·94 s, 2·035 s, 2·065 s (3 . CH_3COO), 2·38 mt (11-H_2), 2·79 d $J = 11·5$ Hz (13β H), 3·78 d and 4·24 bd $J_{gem} = 11$ Hz (28-H_2), 4·48 mt (3α H), 5·23 bp $J_{20,29} = 6·4$ Hz $J_{19,20} = 4·8$ Hz (20-H). CD (dioxan): $\Delta\varepsilon - 1·68$ (292 nm). For $C_{35}H_{54}O_7$ (586·8) calculated: 71·64% C, 9·28% H; found: 71·29% C, 9·52% H.

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