ISOMERIC OXIMES OF 30-NORLUPAN-20-ONE AND ITS DERIVATIVES*

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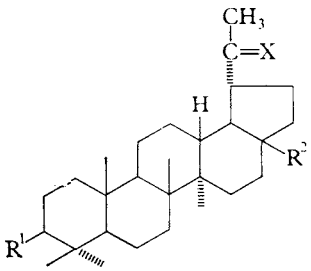
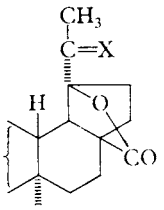
30-Norlupan-20-one (*Ib*) and its derivatives *IIb*—*Vb* were converted into 5 : 1—10 : 1 mixtures of relatively stable *E* and *Z* oximes *Ic, d*—*Vc, d*. Beckmann rearrangement of the oxime mixtures (as obtained from the oximation) afforded isomeric amides *VIII*—*XII* and *XIII*—*XVI* in the ratios 3·5 : 1 to 5 : 1. Oximes *Vc, d*, with the E-ring bridged by a lactone grouping, react with difficulty and the rearrangement was proved only for the *Z*-isomer *Vd*.

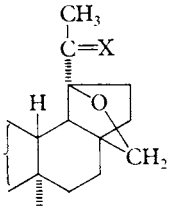
In our previous communications we have described the reactions and properties of 20(29)-lupene[1-4] and 30-norlupan-20-one[1,5-12] derivatives (*Ia*—*VIa* and *Ib*—*VIb*, respectively) which can be explained as the result of steric interactions of the side-chain with the asymmetric cyclic part of the molecule. Our present work tries to extend our knowledge by studying oximes of the mentioned ketones. In principle,





3β-OAc

V



3β-OAc

VI

I, $R^1 = H$, $R^2 = CH_3$
II, $R^1 = OAc$, $R^2 = CH_2OAc$
III, $R^1 = OCH_3$, $R^2 = CH_2OCH_3$
IV, $R^1 = OAc$, $R^2 = COOCH_3$

a X = CH_2; *b* X = O; *c* X = N—OH (*E*); *d* X = N—OH (*Z*); *e* X = N ~ OAc; *f* X = N ~ OTs

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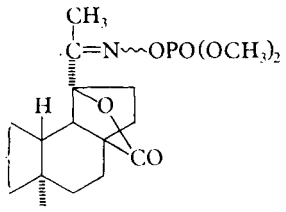
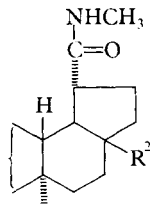
the $E-Z$ isomerism of oximes introduces a new stereogenic element into the side-chain of the compounds *Ib–VIb*. In oximes of simple methyl alkyl ketones[13] (such as pinacolone oxime) the *E*-isomer is clearly preferred. With less substituents in the α-position, or more distant alkyls, an equilibrium between the *E*- and *Z*-isomer is established. By analogy with oximes of pregnan-20-one derivatives[14], oximes of 30-norlupan-20-one (*Ib*) and its derivatives *IIb–VIb* should exist in only one isomer (of *E*-configuration).

The preparation of norketones *Ib–IIIb* was described already previously[11,15], ketone *IVb* was obtained from methyl O-acetylbetulinate (*IVa*) by the procedure described in ref.[15]. Ketone *Vb*, described by us previously[8], was prepared by a different reaction sequence: lactone *Va* was dihydroxylated with osmium tetroxide at the double bond of its side-chain to give two epimeric diols *XVII* of which the less polar isomer clearly prevailed (13 : 1). In an attempted characterization of the chromatographically separated diols by conversion into the acetates, we observed that both the diols afforded approximately the same mixture of epimeric acetates *XVIII* with the more polar acetate predominating (5 : 1). The epimeric diols *XVII* on oxidation with sodium periodate gave ketone *Vb* in a good yield.



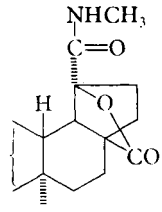
3β - OAc

VII



3β - R^1

VIII, $R^1 = H$, $R^2 = CH_3$
IX, $R^1 = OAc$, $R^2 = CH_2OAc$
X, $R^1 = OCH_3$, $R^2 = CH_2OCH_3$
XI, $R^1 = OAc$, $R^2 = COOCH_3$



3β - OAc

XII

Oximation of ketones *Ib–Vb*, as performed under standard conditions, gave invariably both isomeric oximes which were chromatographically separated (in the formulas, the letters *c* and *d* denote the first and the second eluted isomer, respectively). Contrariwise, oxime *VI* (X = N~OH), prepared from ketone *VIb* by the same procedure, was obtained[7] in only one stereoisomeric form. In addition to different adsorption on silica gel, the isomeric oximes differ also in their specific rotation which is lower for the less polar oximes *Ic–Vc* than for their more polar isomers *Id–Vd*. The oxime acetates *Ie*, *IIe*, *IVe* and *Ve* were obtained only in one stereoisomeric form. Molecular rotations of the stereoisomeric oximes, differences

between them, and molecular rotations of the corresponding acetates are given in Table I. The trend of the observed changes shows that the series of the oximes *c* and *d* are homogeneous. On the other hand, the infrared spectra are of no diagnostic significance as far as the *E*, *Z*-isomerism is concerned because the observed hydroxyl stretching frequencies are practically identical (ν(OH) 3 600 – 3 602 cm^{-1}). Configuration of the oxime group was determined on the basis of different chemical shifts of proton signals in the NMR spectra[13]. Since the 19β-proton signals for the less polar oximes *Ic* and *IVc* appear at higher field than those for their isomers *Id* and *IVd* (see Table II), the former (*Ic* and *IVc*) are assigned the *E*-configuration whereas the latter (*Id*, *IVd*) the *Z*-configuration. In hexadeuteriobenzene the differences between the 19βH signal positions are still more pronounced. For the oximes *IIc* and *IIIc* the *E*-configuration follows from the chemical shift of the N—H singlet of their trichloroacetylcarbamoyl derivatives which is identical with that of the analogous derivative of oxime *Ic* (*Ic*–*IIIc*: $\delta(C^2HCl_3)$ 9·78–9·82) whereas in the case of the isomeric oxime *Id* this signal is shifted to δ 10·20. Oximes *Vc* and *Vd* were assigned configuration on the basis of correlation of M_D values.

TABLE I

Molecular rotations (M_D) of isomeric oximes *Ic*, *d*–*Vc*, *d*, differences between them, and molecular rotations of oxime acetates *Ie*, *IIe*, *IVe* and *Ve*

M_D of oxime, adsorbed				ΔM_D	M_D of oxime acetate	
weakly		strongly				
Ic	+98	*Id*	+278	−180	*Ie*	+216
IIc	+87	*IId*	+261	−174	*IIe*	+223
IIIc	+122	*IIId*	+263	−141	—	—
IVc	+42	*IVd*	+159	−117	*IVe*	+184
Vc	−288	*Vd*	+123	−411	*Ve*	−94

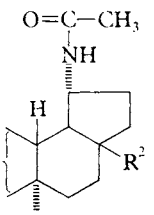
TABLE II

Signals of 19β-protons in ^1H NMR spectra of *E*,*Z*-oximes (δ scale, ppm)

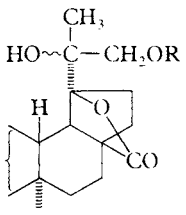
Solvent	$\delta_{19\beta H}$(oxime)		$\Delta\delta_{19\beta H}(Z - E)$
CCl_4	2·51 (*Ic*)	3·47 (*Id*)	0·96
CCl_4	3·02 (*IVc*)	4·03 (*IVd*)	1·01
$C_6{}^2H_6$	2·74 (*Ic*)	3·85 (*Id*)	1·11
$C_6{}^2H_6$	3·44 (*IVc*)	4·63 (*IVd*)	1·19

The $E : Z$ ratio for the oximation products was determined preparatively and also from specific rotation of the mixtures before separation of the isomers. For both methods the experimental error is roughly the same and both agree that the *E*-isomer predominates (5 : 1 to 10 : 1).

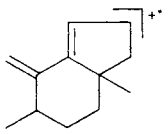
Further, we studied Beckmann rearrangement of mixtures consisting of the *E*- and *Z*-oximes in a known ratio. The rearrangement was effected by treatment with phosphorus oxychloride in pyridine at 0°C. Whereas oximes *Ic, d*–*IVc, d* were rearranged as expected (vide infra), oximes *Vc, d* gave a mixture of neutral and acidic products which, after treatment with diazomethane, were separated chromatographically. Elution afforded (in succession) 2·5% (based on the weight of the starting *Vc, d*) of ketone *Vb*, 6% of oxime *Vc, d* and 31% of a crystalline product. According to IR spectrum, the product contained a γ-lactone grouping (1 780 cm^{-1}) and an acetoxy group (1 722, 1 254 cm^{-1}) but no oximino group. Instead of this, the spectrum exhibited P=O and P=OCH_3 bands at 1 263, 1 187, and 1 047 cm^{-1}. The presence of a $P(OCH_3)_2$ group was confirmed by ^1H NMR spectrum (a doublet at δ 3·86; $J_{H,P}$ = 11·5 Hz). Thus, under the conditions employed, the oxime *Vc, d*, instead of rearranging was converted to ester–dichloride of phosphoric acid which during the work-up afforded the mixed phosphate *VII*. Therefore we tried to rearrange the oxime *Vc, d* under more vigorous conditions, *i.e.* by treatment with *p*-toluenesulfonic acid in boiling pyridine. The reaction gave oxime tosylate *Vf* (84% wt) accompanied by an amide (20% wt) whose structure *XII* was proved in connection with the Beckmann rearrangement products mentioned below. When repeating this reaction at 100°C, we isolated as the sole product (94% wt) another oxime tosylate *Vf* whose R_F differed from that of the product obtained in boiling pyridine (0·35 compared with 0·52); the difference in specific rotation was not so marked. We assume that these products represent a pair of *E*, *Z*-isomers but no configurational studies have been made in this direction.



3β -R^1



3β -OAc



a, *m/z* 162

XIII, R^1 = H, R^2 = CH_3
XIV, R^1 = OAc, R^2 = CH_2OAc
XV, R^1 = OCH_3, R^2 = CH_2OCH_3
XVI, R^1 = OAc, R^2 = $COOCH_3$

XVII, R = H
XVIII, R = Ac

Beckmann rearrangement of the oxime mixtures *Ic, d*–*IVc, d* (as obtained by the oximation) afforded mixtures of isomeric amides which were chromatographically separated: the amides (*VIII*–*XI*) representing minor reaction products, were eluted first whereas the principal products (amides *XIII*–*XVI*) were adsorbed more strongly. The amide *XIV* is already known[16]. Infrared spectra of both groups of amides differ only slightly in the region of the *I*- and *II*-amide bands (1 660–1 670 and 1 505–1 523 cm^{-1}, respectively). On the other hand, the band at 1 410 to 1 420 cm^{-1} due to symmetric deformation vibration of methyl in the CH_3—NH—CO—grouping appears only in the spectra of the less polar amides *VIII*–*XII*. The presence of this grouping was confirmed by the ^1H NMR spectrum of amide *VIII*, exhibiting a characteristic doublet of an amidic methyl at δ 2·78 (J = 4·7 Hz) and a quartet of adjacent amide proton at δ 5·96 (J = 4·7 Hz). Spectra of amides *XIII*, *XIV* and *XVI* display a characteristic singlet of an N-acetyl group (δ 1·90 to 1·92) and an amide proton doublet (δ 5·35–6·09; J = 8–9 Hz). The structure of N-methylamide *IX* was confirmed by synthesis from the known[17] 29,30-dinorlupane-20-carbonyl chloride. Further evidence came from the mass spectra. The spectra of *VIII* and *XII* as representatives of the faster eluted amides showed no significant features: in the high mass region there were ions corresponding to loss of methyl groups, acetic acid, carbon monoxide and their combinations whereas in the middle region the only more remarkable peak corresponded to the rings A and B (m/z 189)[18]. On the other hand, spectrum of the more strongly adsorbed amide *XIII* was characteristic and confirmed the presence of an acetylamino group. The dominant ion, m/z 368 ($C_{27}H_{44}$), arises from the molecular ion by McLafferty rearrangement (with the 18α hydrogen) under loss of C_2H_5NO, and is further split as 20,29,30-trinorlup-18-ene[19] to give the characteristic ion *a* (m/z 162).

The above-mentioned evidence shows that the Beckmann rearrangement affords mainly the 19α-N-acetylamino-20,29,30-trinorlupane derivatives *XIII*–*XVI* arising from *E*-oximes. The minor products N-methyl-20,29-dinorlupane-20-carboxamides,

TABLE III

Ratios *E* : *Z* for oximes and for the corresponding Beckmann rearrangement products

Oxime	*E* : *Z*	N-Acetylamino derivative	N-Methylamide	Ratio
Ic,d	6 : 1	*VIII*	*XIII*	4 : 1
IIc,d	5 : 1	*IX*	*XIV*	3·5 : 1
IIIc,d	10 : 1	*X*	*XV*	5 : 1
IVc,d	9 : 1	*XI*	*XVI*	—

VIII–*XI*, are formed from the *Z*-oximes. The *Z*-oxime is also the precursor of the only one isolated Beckmann rearrangement product with the lactone-bridged E ring, the N-methylamide *XII*. The relative amounts of *E*- and *Z*-isomers in the starting oximes and in the corresponding Beckmann rearrangement products are compared in Table III. As seen, the starting ratios of the *E*, *Z*-oximes do not correspond to those of the products although both isomers seem to be relatively stable.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured in chloroform (*c* 0·4–0·9) on an automatic polarimeter (ETL–NPL, Bendix–Ericsson); experimental error ±2°. Infrared spectra of chloroform solutions were recorded on a UR-20 (Zeiss, Jena) spectrophotometer, more detailed spectra were taken in tetrachloromethane on an SP-700 (Unicam) instrument. The ^{1}H NMR spectra were obtained on Tesla BS-467 (60 MHz) and Varian HA-100 (100 MHz) spectrometers in deuteriochloroform with tetramethylsilane as internal standard, and on a Tesla BS-487 (80 MHz) instrument with hexamethyldisiloxane (HMDS) as internal reference. All chemical shifts refer to tetramethylsilane ($\delta_{HMDS} = 0{\cdot}06$) and are given in the δ-scale (ppm), coupling constants were obtained by analysis of the first order. Mass spectra were measured on a Varian MAT 311 spectrometer at 70 eV energy of the ionizing electrons and 1 mA of the ionizing current (ion source temperature 200°C, direct inlet at 80 to 200°C). Chromatographic separations were performed on neutral alumina (Reanal, activity II) or silica gel (Silpearl, Kavalier), preparative thin-layer chromatography (PTLC) was carried out on silica gel (Merck 60G; 10 g on a 20 × 20 cm plate, thickness 0·7 mm). Spots were detected by spraying with a 0·2% solution of morin in methanol and irradiation with UV light (254 nm). Thin-layer chromatography (TLC) was performed on Silufol UV-254 (Kavalier), and spots were detected by spraying with 10% ethanolic phosphomolybdenic acid and warming. Analytical samples were dried in vacuo over phosphorus pentoxide at 100°C. The expression "the usual work-up" means dilution of the reaction mixture with water, extraction of the product with ether, washing the ethereal extract with dilute (1 : 4) hydrochloric acid and 5% solution of sodium carbonate, drying and evaporation of the solvent. All solutions were dried over anhydrous sodium sulfate. Acetylations were carried out according to the following procedure: Acetic anhydride (1 part) was added to a solution of the sample in pyridine (2 parts), the mixture was set aside at room temperature overnight and processed as usual.

Methyl 3β-Acetoxy-20-oxo-30-norlupane-28-carboxylate (*IVb*)

A mixture of methyl O-acetylbetulinate (10 g), chloroform (60 ml), 98% formic acid (60 ml) and 30% hydrogen peroxide (30 ml) was stirred for 6 h. After dilution with water, the product was taken up in chloroform and the extract was washed with saturated solution of sodium hydrogen carbonate and water, dried and taken down. The residue was dissolved in benzene and adsorbed on alumina (200 g). After four days, the product was eluted with ether–light petroleum (1 : 1) and the eluent was distilled off. The residue (8 g) was dissolved in benzene (20 ml), chromium trioxide (3·5 g) in acetic acid (200 ml) was added and the mixture was allowed to stand overnight. Methanol (~10 ml) was added and the mixture was concentrated *in vacuo*. The almost dry residue was extracted with ether and the ethereal extract was washed with water, saturated solution of sodium hydrogen carbonate, again with water, dried and taken down, affording 7·15 g of norketone *IVb*, m.p. 202–206°C (chloroform–methanol), $[\alpha]_D$ −16·5° (reported[20] m.p. 204–206°C, $[\alpha]_D$ −16°).

3β-Acetoxy-20ξ,29-dihydroxylupan-28→19β-olide (*XVII*)

Osmium tetroxide (5 g) was added to a solution of lactone *VII* (ref.[8]; 6·7 g) in anhydrous dioxane (370 ml). After standing for 7 days at room temperature, the solvent was evaporated *in vacuo*, the residue was dissolved in ethanol (115 ml), mixed with sodium sulfite (25 g) in water (230 ml) and refluxed for 2·5 h. The precipitate was filtered and extracted with hot ethanol and hot chloroform. Evaporation of solvents from the combined extracts afforded 6·54 g of diols *XVII*. A part (3·75 g) was separated by chromatography on silica gel (180 g). Elution with chloroform (3 500 ml) gave 3·09 g of diol *XVII*, m.p. 332°C (ethanol), $[\alpha]_D$ +37°. IR spectrum (tetrachloromethane): 3 588, 3 353 (OH) cm^{-1}. For $C_{32}H_{50}O_6$ (530·7) calculated: 72·41% C, 9·50% H; found: 72·20% C, 9·65% H. Further elution with chloroform–ether (1 : 1; 1 650 ml) gave 0·24 g of diol *XVII*, m.p. 290–310°C (decomposition) (chloroform–ethanol), $[\alpha]_D$ +26°. IR spectrum (tetrachloromethane): 3 596 (OH) cm^{-1}. For $C_{32}H_{50}O_6$ (530·7) calculated: 72·41% C, 9·50% H; found: 72·33% C, 9·62% H.

3β,29-Diacetoxy-20ξ-hydroxylupan-28→19β-olide (*XVIII*)

a) Acetylation of the less polar diol *XVII*, m.p. 332°C (100 mg) afforded 100 mg of mixture of epimeric acetates *XVIII*, $[\alpha]_D$ +30°.

b) Acetylation of the more strongly adsorbed diol *XVII*, m.p. 290–310°C (100 mg) gave 100 mg of mixture of epimeric acetates *XVIII*, $[\alpha]_D$ +32°.

The combined products of procedures *a*) and *b*) were separated by PTLC in benzene–ether (4 : 1). Extraction of the less polar zone gave 20 mg of the more easily eluted acetate *XVIII*, m.p. 250–252°C (ether–light petroleum), $[\alpha]_D$ +50°. IR spectrum: 1 776, 1 202, 1 153, 1 139 (γ-lactone), 1 740, 1 728, 1 257, 1 024 (CH_3COO), 3 580, 1 044 (OH) cm^{-1}; $1{\cdot}77 \cdot 10^{-3}$ mol l^{-1} solution in tetrachloromethane: 3 582 cm^{-1}, $\varepsilon^a = 108$, $\nu_{1/2} = 17$ cm^{-1}, B = 2 890, α/β = 1·25 (OH). ^{1}H NMR spectrum (100 MHz): 0·84 bs (3 CH_3), 0·89 s (CH_3), 0·93 s (CH_3), 1·32 s (CH_3), 2·03 s (CH_3COO), 2·11 s (CH_3COO), 3·97 d and 4·41 d, $J_{gem} = 11{\cdot}6$ Hz (29-H_2), 4·47 m (3α-H). For $C_{34}H_{52}O_7$ (572·8) calculated: 71·29% C, 9·15% H; found: 71·22% C, 9·03% H. Extraction of the more polar zone gave 100 mg of the more adsorbed acetate *XVIII*, m.p. 247·5–248°C (ether–light petroleum), $[\alpha]_D$ +23°. IR spectrum: 1 775, 1 154 (γ-lactone), 1 741, 1 727, 1 258, 1 024 (CH_3COO), 3 590, 1 044 (OH) cm^{-1}; $1{\cdot}8 \cdot 10^{-3}$ mol l^{-1} solution in tetrachloromethane: 3 595 cm^{-1}, $\varepsilon^a = 95$, $\nu_{1/2} = 21$ cm^{-1}, B = 3 140, α/β = 0·69 (OH). ^{1}H NMR spectrum (100 MHz): 0·84 bs (3 CH_3), 0·88 s (CH_3), 0·93 s (CH_3), 1·39 s (CH_3), 2·03 s (CH_3COO), 2·12 s (CH_3COO), 4·21 m (29-H_2), 4·47 m (3α-H). For $C_{34}H_{52}O_7$ (572·8) calculated: 71·29% C, 9·15% H; found: 71·35% C, 9·10% H.

3β-Acetoxy-20-oxo-30-norlupan-28→19β-olide (*Vb*)

A solution of sodium periodate (6·25 g) in water (45 ml) was added to a solution of epimeric diols *XVII* (5·6 g) in ethanol (2 000 ml) and the mixture was set aside for 2 days at room temperature. After removal of the solvents *in vacuo*, the residue was extracted with chloroform and the extract was washed with water, dried and taken down. The residue (5·3 g) was chromatographed on alumina (100 g) to remove polar impurities. Elution with benzene (850 ml) yielded 4·1 g of norketone *Vb* which upon crystallization from chloroform–methanol melted at 317–320°C, $[\alpha]_D$ −5° (reported[8] m.p. 319–321°C, $[\alpha]_D$ −6·2°).

General Oximation Procedure

Hydroxylamine hydrochloride (5 equivalents) was heated with a solution of the norketone (1 equivalent) in pyridine on a steam bath for 8 h and the mixture was worked up as usual.

Oximation of Norketone *Ib*

Oximation of norketone *Ib* (ref.[15]; 1·22 g) afforded 1·20 g of mixture of oximes *Ic*, *d*, $[\alpha]_D$ +28°. A part (330 mg) was chromatographed on silica gel (40 g). Elution with benzene containing 5% ether (100 ml) gave 240 mg of oxime *Ic*, m.p. 208–212°C (ether–light petroleum); $[\alpha]_D$ +23°. IR spectrum: 3 640, 3 310, 1 657 (C=NOH) cm^{-1}; 1·74 . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 602 cm^{-1}, ε^a = 113, $\nu_{1/2}$ = 20 cm^{-1}, B = 3 560, α/β = 1 (OH). ^{1}H NMR spectrum (100 MHz): 0·80 s (CH_3), 0·81 s (CH_3), 0·83 s (CH_3) 0·84 s (CH_3), 0·94 s (CH_3), 1·025 s (CH_3), 1·83 s (20-CH_3). Mass spectrum, *m/z* (%): 427 (M^+, 8), 411 (64), 410 (100), 396 (16), 380 (3·5), 368 (6·5), 191 (47). For $C_{29}H_{49}NO$ (427·7) calculated: 81·44% C, 11·55% H, 3·28% N; found: 81·20% C, 11·53% H, 3·66% N. Further elution with benzene–10% ether (200 ml) afforded 40 mg of oxime *Id*, m.p. 188–190°C (ether–methanol), $[\alpha]_D$ +65°. IR spectrum: 3 595, 3 275 (NOH) cm^{-1}; 1·53 . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 602 cm^{-1}; ε^a = 178, $\nu_{1/2}$ = = 19 cm^{-1}, B = 5 320, α/β = I (OH). ^{1}H NMR spectrum (100 MHz): 0·80 s (CH_3), 0·835 bs (3 CH_3), 0·95 s (CH_3), 1·03 s (CH_3), 1·83 s (20-CH_3). Mass spectrum, *m/z* (%): 427 (M^+, 21), 411 (87), 410 (98) ,396 (21), 380 (5), 368 (16), 191 (100). For $C_{29}H_{49}NO$ (427·7) calculated: 81·44% C, 11·55% H; found: 81·11% C, 11·73% H. Acetylation of the mixture *Ic*, *d* (100 mg) yielded 100 mg of oxime acetate *Ie*, m.p. 149–152°C (ether–hexane), $[\alpha]_D$ +46°. IR spectrum: 1 756, 1 635 (C=NOCOCH$_3$) cm^{-1}. For $C_{31}H_{51}NO_2$ (469·6) calculated: 79·26% C, 10·94% H; found: 79·49% C, 11·08% H.

Oximation of Norketone *IIb*

Norketone[15] *IIb* (5·2 g) afforded 4·5 g of mixture of oximes *IIc*, *d*, $[\alpha]_D$ +20°. A part of this mixture (180 mg) was subjected to PTLC (three times developed in light petroleum–ether 3 : 2). Extraction of the less polar zone gave 133 mg of oxime *IIc*, m.p. 197–198°C (ether–hexane), $[\alpha]_D$ +16°. IR spectrum: 1 724, 1 255, 1 030 (CH_3COO), 3 590, 3 320, 1 656 (C=NOH) cm^{-1}; 1·20 . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 601 cm^{-1}, ε^a = 187, $\nu_{1/2}$ = 20 cm^{-1}, B = 5 890, α/β = 1 (OH). ^{1}H NMR spectrum (100 MHz): 0·84 bs (3 CH_3), 0·95 s (CH_3), 1·03 s (CH_3), 1·82 s (20-CH_3), 2·035 s (CH_3COO), 2·06 s (CH_3COO), ≈2·61 bm (19β-H), 3·81 d and 4·29 bd, J_{gem} = 11 Hz (28-H_2), 4·48 m (3α-H). For $C_{33}H_{53}NO_5$ (543·8) calculated: 72·89% C, 9·82% H, 2·58% N; found: 72·76% C, 9·91% H, 2·90% N. Extraction of the more polar zone gave 25 mg of oxime *IId*, m.p. 225–228°C (ether), $[\alpha]_D$ +48°. IR spectrum: 1 726, 1 257, 1 030 (CH_3COO), 3 595, 3 295, 1 642 (C=NOH) cm^{-1}; 1·33 . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 601 cm^{-1}, ε^a = 184, $\nu_{1/2}$ = 21 cm^{-1}, B = 6 070, α/β = 1·09 (OH). For $C_{33}H_{53}NO_5$ (543·8) calculated: 72·89% C, 9·82% H, 2·58% N; found: 72·61% C, 9·90% H, 2·40% N.

Acetylation of the mixture *IIc*, *d* (150 mg) afforded 150 mg of oxime acetate *IIe*, m.p. 219 to 220°C (ether–light petroleum), $[\alpha]_D$ +38°. IR spectrum: 1 728, 1 254, 1 030 (CH_3COO), 1 756, 1 635 (C=NOCOCH$_3$) cm^{-1}. For $C_{35}H_{55}NO_6$ (585·8) calculated: 71·76% C, 9·46% H; found: 71·94% C, 9·55% H.

Oximation of Norketone *IIIb*

Norketone[11] *IIIb* (700 mg) afforded 700 mg of the mixture *IIIc*, *d*, $[\alpha]_D$ +26°. A part (400 mg) of the mixture was subjected to PTLC in light petroleum–ether (1 : 1). Extraction of the less polar zone afforded 332 mg of oxime *IIIc*, m.p. 148–151°C (light petroleum), $[\alpha]_D$ +25°. IR spectrum: 2 820, 1 098 (OCH_3), 3 595, 3 290 (NOH) cm^{-1}; 1·25 . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 602 cm^{-1}, ε^a = 208, $\nu_{1/2}$ = 18 cm^{-1}, B = 5 880, α/β = 1 (OH). ^{1}H NMR spectrum (100 MHz): 0·75 s (CH_3), 0·83 s (CH_3), 0·95 s (2 CH_3), 1·03 s (CH_3), 1·81 s (20-CH_3),

2·64 dd (3α-H), ≈2·60 bm (19β-H), 3·02 d and 3·47 d, J_{gem} = 9 Hz (28-H_2), 3·335 s (OCH_3), 3·35 s (OCH_3). For $C_{31}H_{53}NO_3$ (487·7) calculated: 76·33% C, 10·95% H, 2·87% N; found: 76·21% C, 10·90% H, 2·80% N. Extraction of the more polar zone gave 33 mg of oxime *IIId*, m.p. 155–158°C (ether–light petroleum), $[\alpha]_D$ +54°. IR spectrum: 2 820, 1 098 (OCH_3), 3 595, 3 285 (NOH cm^{-1}; 1·33 . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 601 cm^{-1}, ε^a = 179, $\nu_{1/2}$ = 19 cm^{-1}, B = 5 340, α/β = 1·03 (OH). For $C_{31}H_{53}NO_3$ (487·7) calculated: 76·33% C, 10·95% H, 2·87% N; found: 76·38% C, 10·85% H, 2·57% N.

Oximation of Norketone *IVb*

Norketone *IVb* (3 g) afforded 2·9 g of the mixture *IVc, d*, $[\alpha]_D$ +11°. A part (300 mg) of the mixture was separated by PTLC in benzene–ether (4 : 1). Extraction of the less polar zone gave 242 mg of oxime *IVc*, m.p. 244–246°C (ether–light petroleum), $[\alpha]_D$ +8°. IR spectrum: 1 731, 1 441, 1 160, 1 032 ($COOCH_3$), 1 731, 1 265, 1 032 (CH_3COO), 3 605, 3 300 (NOH) cm^{-1}; 2·0. . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 600 cm^{-1}, ε^a = 107, $\nu_{1/2}$ = 20 cm^{-1}, B = = 3 350, α/β = 0·91 (OH). ^{1}H NMR spectrum (tetrachloromethane, 60 MHz): ≈0·81 s (CH_3), 0·83 bs (2 CH_3), 0·91 s (2 CH_3), 1·80 s (20-CH_3), 1·97 s (CH_3COO), 3·62 s ($COOCH_3$), 3·02 bm (19β-H), 4·38 m (3α-H). For $C_{32}H_{51}NO_5$ (529·7) calculated: 72·55% C, 9·70% H, 2·64% N; found: 72·27% C, 9·80% H, 2·71% N. Extraction of the more polar zone gave 41 mg of oxime *IVd*, m.p. 245–248°C (ether–light petroleum), $[\alpha]_D$ +30° IR spectrum: 1 731, 1 442, 1 160, 1 033 ($COOCH_3$), 1 731, 1 264, 1 033 (CH_3COO), 3 610, 3 425, 3 280, 1 655 (C=NOH) cm^{-1}; 2·3 . . 10^{-3} mol l^{-1} solution in tetrachloromethane: 3 600 cm^{-1}, ε^a = 93, $\nu_{1/2}$ = 20 cm^{-1}, B = = 2 940, α/β = 0·97 (OH). ^{1}H NMR spectrum (tetrachloromethane, 60 MHz): 0·81 s (CH_3), 0·84 s (2 CH_3), 0·92 s (2 CH_3), 1·77 s (20-CH_3), 1·99 s (CH_3COO), 3·64 s ($COOCH_3$), ≈4·03 bm (19β-H), 4·55 m (3α-H). For $C_{32}H_{51}NO_5$ (529·7) calculated: 72·55% C, 9·70% H, 2·64% N; found: 72·33% C, 9·92% H, 2·88% N.

Acetylation of the mixture *IVc,d* (100 mg) afforded 100 mg of oxime acetate *IVe*, m.p. 135 to 138°C (ether–light petroleum), $[\alpha]_D$ +20°. IR spectrum: 1 731, 1 441, 1 161, 1 033 ($COOCH_3$), 1 731, 1 262, 1 033 (CH_3COO), 1 766, 1 644 (C=NOCOCH$_3$) cm^{-1}. For $C_{34}H_{53}NO_6$ (571·8) calculated: 71·42% C, 9·34% H, 2·45% N; found: 71·68% C, 9·52% H, 2·62% N.

Oximation of Norketone *Vb*

Norketone *Vb* (4·27 g) gave 4·20 g of mixture *Vc,d*, $[\alpha]_D$ +16°. A part (1·5 g) of the mixture was chromatographed on alumina (160 g). Elution with ether + 0·5% methanol (210 ml) afforded 120 mg of oxime *Vc*, m.p. 293–295°C (decomposition) (chloroform–methanol), $[\alpha]_D$ −56°. IR spectrum: 1 778, 1 197, 1 155, 1 142 (γ-lactone), 1 724, 1 258, 1 024 (CH_3COO), 3 590, 3 295 (NOH) cm^{-1}; 9·54 . 10^{-4} mol l^{-1} solution in tetrachloromethane: 3 598 cm^{-1}, ε^a = 213, $\nu_{1/2}$ = 21 cm^{-1}, B = 7 030, α/β = 0·71. For $C_{31}H_{47}NO_5$ (513·7) calculated: 72·48% C, 9·22% H, 2·73% N; found: 72·43% C, 9·20% H, 2·92% N.

The same solvent mixture (140 ml) further eluted 200 mg of the mixture of oximes *Vc,d*. Finally, 770 ml of ether + 0·5% methanol and 140 ml of ether + 1% methanol eluted 1 120 mg of oxime *Vd*, m.p. 288–292°C (decomposition) (chloroform–methanol), $[\alpha]_D$ +24°. IR spectrum: 1 778, 1 174, 1 154, 1 142 (γ-lactone), 1 721, 1 258, 1 021 (CH_3COO), 3 585, 3 290 (NOH) cm^{-1}; saturated solution in tetrachloromethane: 3 598 cm^{-1}, $\nu_{1/2}$ = 20 cm^{-1}, α/β = 0·78 (OH). For $C_{31}H_{47}NO_5$ (513·7) calculated: 72·48% C, 9·22% H, 2·73% N; found: 72·67% C, 9·44% H, 2·84% N.

Acetylation of *Vc,d* (1·1 g) gave 1·1 g of oxime acetate *Ve*, m.p. 275–277°C (benzene–heptane), $[\alpha]_D$ −17°. IR spectrum: 1 777, 1 200, 1 151, 1 141 (γ-lactone), 1 722, 1 254, 1 023 (CH_3COO), 1 777, 1 638 (C=NOCOCH$_3$) cm^{-1}. For $C_{33}H_{49}NO_6$ (555·7) calculated: 71·32% C, 8·89% H, 2·52% N; found: 71·25% C, 9·06% H, 2·69% N.

Beckmann Rearrangement of *Ic,d*

A cold solution of phosphorus oxychloride (4 ml) in pyridine (10 ml) was added dropwise to a stirred and cooled (−15°C) solution of oximes *Ic,d* (1·30 g) in pyridine (10 ml). After standing for 24 h at 0°C the mixture was poured on a mixture of ice (200 g) and concentrated hydrochloric acid (40 ml). The precipitate was filtered, washed with water until the filtrate was neutral, dried at 100°C (1·28 g) and chromatographed on alumina (120 g). Elution with ether (210 ml) gave 0·25 g of amide *VIII*, m.p. 272·5°C (ether–hexane), $[\alpha]_D$ 0°. IR spectrum: 3 520, 3 400, 1 661, 1 523, 1 420 ($CONHCH_3$) cm^{-1}; $2{\cdot}38 \cdot 10^{-3}$ mol l^{-1} solution in tetrachloromethane: 3 468 cm^{-1}, $\varepsilon^a = 126$, $\nu_{1/2} = 12$ cm^{-1}, B = 2 380, $\alpha/\beta = 1{\cdot}14$ (NH). ^{1}H NMR spectrum (100 MHz): 0·75 s (CH_3), 0·79 s (CH_3), 0·82 s (CH_3), 0·84 s (CH_3), 0·97 s (CH_3), 1·01 s (CH_3), 2·78 d, $J_{CH_3,NH} = 4{\cdot}7$ Hz (N—CH_3), 5·96 bq, $J_{NH,CH_3} = 4{\cdot}7$ Hz (NH). Mass spectrum, *m/z* (%): 427 (M^+, 99), 412 (48), 396 (5), 292 (28), 274 (11), 246 (10), 236 (22·5), 222 (27), 220 (34), 208 (47), 191 (100). For $C_{29}H_{49}NO$ (427·7) calculated: 81·44% C, 11·55% H, 3·28% N; found: 81·65% C, 11·45% H, 3·38% N. Further 180 ml of ether eluted 1·01 g of amide *XIII*, m.p. 278 to 278·5°C (benzene–heptane), $[\alpha]_D$ +16°. IR spectrum: 3 495, 3 380, 1 660, 1 520 ($NHCOCH_3$) cm^{-1}; $2{\cdot}30 \cdot 10^{-3}$ mol l^{-1} solution in tetrachloromethane: 3 442 cm^{-1}, $\varepsilon^a = 79$, $\nu_{1/2} =$ = 17 cm^{-1}, B = 2 110, $\alpha/\beta = 0{\cdot}65$ (NH). ^{1}H NMR spectrum (100 MHz): 0·79 s (2. CH_3), 0·84 bs (2. CH_3), 0·93 s (CH_3), 1·02 s (CH_3), 1·90 s (>N—$COCH_3$), 4·04 m, $J_{19,NH} \approx 8$ Hz (19-H), 5·68 bd, $J_{NH,19} \approx 8$ Hz (NH). Mass spectrum, *m/z* (%): 427 (M^+, 4), 412 (12·5), 368 ($C_{27}H_{44}$, 95), 353 (16), 259 (10), 215 (8), 191 (100), 176 (60), 162 (78). For $C_{29}H_{49}NO$ (427·7) calculated: 81·44% C, 11·55% H, 3·28% N; found: 81·38% C, 11·27% H, 3·45% N.

Beckmann Rearrangement of *IIc,d*

The reaction was performed with 200 mg of oxime mixture *IIc,d* in the same way as described for *Ic,d*. The products were separated by PTLC in ether + 1% methanol. Extraction of the less polar zone gave 26 mg of an amorphous amide, $[\alpha]_D$ +3°, identical with the amide *IX*. From the more polar zone 90 mg of amide *XIV* was obtained, m.p. 192—195 °C (ether), $[\alpha]_D$ +19°. IR spectrum: 1 726, 1 255, 1 031 (CH_3COO), 3 440, 1 663, 1 520 ($NHCOCH_3$) cm^{-1}. ^{1}H MNR spectrum (100 MHz): 0·84 bs (3. CH_3), 0·94 s (CH_3), 1·03 s (CH_3), 2·02 s (CH_3COO), 2·04 s (CH_3COO), 1·90 s (CH_3CONH), 5·35 d, $J_{NH,19} = 9$ Hz (NH), 4·45 m (3α-H), 3·73 d and 4·24 d, $J_{gem} = 11$ Hz (28-H_2). (Reported[16] m.p. 193—195°C, $[\alpha]_D$ + 18·6°).

Beckmann Rearrangement of *IIIc,d*

The oxime mixture *IIIc,d* (250 mg) was rearranged analogously as described for *Ic,d* and the products were separated by PTLC in ether + 1% methanol. The less polar zone yielded 22 mg of amide *X*, m.p. 245—246°C (ether), $[\alpha]_D$ +2°. IR spectrum: 2 825, 1 098 (OCH_3), 3 470, 3 350, 1 666, 1 521, 1 415 ($CONHCH_3$) cm^{-1}. For $C_{31}H_{53}NO_3$ (487·7) calculated: 76·33% C, 10·95% H; found: 76·45% C, 10·85H H. The more polar zone afforded 113 mg of amide *XV*, m.p. 252 to 254°C (ether), $[\alpha]_D$ +22°. IR spectrum: 2 825, 1 098 (OCH_3), 3 440, 3 340, 1 660, 1 518 ($NHCOCH_3$) cm^{-1}. For $C_{31}H_{53}NO_3$ (487·7) calculated: 76·33% C, 10·95% H, 2·87% N; found: 76·44% C, 11·12% H, 2·69% N.

Beckmann Rearrangement of *IVc,d*

The reaction was performed with 50 mg of *IVc,d* as described for *Ic,d* and the products were separated by PTLC in ether + 1% methanol. The less polar zone gave amide *XI*, m.p. 260 to 263°C (methanol), $[\alpha]_D$ −4·5°. IR spectrum: 1 725, 1 435, 1 165, 1 025 ($COOCH_3$), 1 725, 1 255,

1 025 (CH_3COO), 3 460, 1 665, 1 525, 1 410 ($CONHCH_3$) cm^{-1}. For $C_{32}H_{51}NO_5$ (529·7) calculated: 72·55% C, 9·70% H; found: 72·26% C, 9·80% H. The more polar zone gave amide *XVI*, m.p. 286–288°C (methanol), $[\alpha]_D$ +7°. IR spectrum: 1 725, 1 435, 1 170, 1 025 ($COOCH_3$), 1 725, 1 260, 1 025 (CH_3COO), 3 430, 1 670, 1 520 ($NHCOCH_3$) cm^{-1}. ^1H NMR spectrum: (80 Hz): 0·84 bs (3. CH_3), 0·90 s (CH_3), 0·94 s (CH_3), 1·92 s (>N—$COCH_3$), 2·035 s (CH_3COO), 3·66 s ($COOCH_3$), 4·47 m (3α-H), 6·09 bd, $J_{NH,19}$ = 8·8 Hz (NH). For $C_{32}H_{51}NO_5$ (529·7) calculated: 72·55% C, 9·70% H, 2·64% N; found: 72·30% C, 9·82% H, 2·78% N.

Beckmann Rearrangement of *Vc,d*

a) The reaction was carried out with 3·95 g of oxime mixture *Vc,d* as described for oximes *Ic,d*. The reaction product (2 g) was methylated with ethereal diazomethane and chromatographed on silica gel (100 g). Elution with ether–light petroleum (1 : 1; 300 ml) afforded norketone *Vb* (94 mg). Further elution with the same solvent mixture recovered the starting oximes *Vc,d* (240 mg). Ether +2% methanol (1 600 ml) eluted 1 210 mg of the mixed phosphate *VII*, m.p. 239–241·5°C (chloroform–light petroleum), $[\alpha]_D$ 0°. IR spectrum: 1 780, 1 187, 1 150, 1 140 (γ-lactone), 1 722, 1 254, 1 025, (CH_3COO), 1 263 (P=O), 1 187, 1 047 (P—O—CH_3) cm^{-1}. ^1H NMR spectrum (100 MHz): 0·85 bs (3. CH_3), 0·88 s (CH_3), 0·95 s (CH_3), 2·12 s (20-CH_3), 3·86 d, $J_{H,P}$ = 11·5 Hz ($P(OCH_3)_2$), 2·03 s (CH_3COO), 4·46 m (3α-H). For $C_{33}H_{52}NO_8P$ (621·7) calculated: 63·75% C, 8·43% H, 2·25% N, 4·98% P; found: 63·69% C, 8·62% H, 2·42% N, 5·23% P.

b) To a solution of oxime mixture *Vc,d* (90 mg) in pyridine (4 ml) was added *p*-toluenesulfonyl chloride (200 mg) and the mixture was refluxed for 3 h. After the usual work-up procedure, the crude product was chromatographed on silica gel (20 g). Elution with light petroleum +20% ether (60 ml) afforded 76 mg of oxime *p*-toluenesulfonate *Vf*, R_F 0·52 (TLC in light petroleum–ether 2 : 3), m.p. 165–166°C (ether–light petroleum), $[\alpha]_D$ −37°. IR spectrum: 1 779, 1 150, 1 138 (γ-lactone), 1 721, 1 254, 1 023 (CH_3COO), 1 192, 1 179 (*p*-toluenesulfonyl) cm^{-1}. For $C_{38}H_{53}NO_7S$ (667·9) calculated: 68·33% C, 8·00% H, 2·10% N, 4·80% S; found: 68·03% C, 8·22% H, 2·41% N, 4·90% S. Light petroleum–ether (1 : 1) (150 ml) and ether (60 ml) eluted 18 mg of amide *XII*, m.p. 349°C (chloroform–heptane), $[\alpha]_D$ +39°. IR spectrum: 1 780, 1 171, 1 150 (γ-lactone), 1 721, 1 255, 1 026 (CH_3COO), 3 455, 1 678, 1 548, 1 417 ($CONHCH_3$) cm^{-1}. Mass spectrum *m/z* (%): 513 (M^+, 3·4), 453 (51), 438 (20), 410 (37), 384 (28), 371 (16), 344 (11), 262 (23), 204 (20), 189 (100).

c) To a solution of oxime mixture *Vc,d* (52 mg) in pyridine (3 ml) was added *p*-toluenesulfonyl chloride (100 mg) and the mixture was heated for 3 h on a steam bath. After usual processing, the product was chromatographed on silica gel (15 g). Elution with light petroleum–ether (1 : 1, 180 ml) afforded 49 mg of oxime *p*-toluenesulfonate *Vf*, m.p. 224–226°C (ether–light petroleum), R_F 0·35 (TLC in light petroleum–ether 2 : 3), $[\alpha]_D$ −42°. IR spectrum: 1 780, 1 150, 1 139 (γ-lactone), 1 721, 1 253, 1 022 (CH_3COO), 1 191, 1 178 (*p*-toluenesulfonyl) cm^{-1}. For $C_{38}H_{53}NO_7S$ (667·9) calculated: 68·33% C, 8·00% H, 2·10% N; found: 68·22% C, 7·89% H, 2·27% N.

N-Methyl-3β,28-diacetoxy-29,30-dinorlupane-20-carboxamide (*IX*)

Gaseous methylamine was introduced for 1 h into a solution of 29,30-dinorlupane-20-carbonyl chloride[17] (150 mg) in benzene (70 ml). After standing overnight at room temperature, the mixture was worked up as usual to give 125 mg of amorphous amide *IX*; $[\alpha]_D$ +2°. IR spectrum: 1 726, 1 254, 1 030 (CH_3COO), 3 470, 3 350, 1 668, 1 523, 1 414 ($CONHCH_3$) cm^{-1}. For $C_{33}H_{53}NO_5$ (543·8) calculated: 72·89% C, 9·82% H, 2·58% N; found: 72·98% C, 9·95% H, 2·88% N.

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