PREPARATION OF DERIVATIVES OF 29-HYDROXY-30-NORLUPAN-20-ONE*

V. POUZAR and A. VYSTRČIL

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

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Hydroxy ketone *IV* was prepared from acid *I via* the corresponding chloride *II* and diazoketone *III*. Reaction of ketones *VI*, *VIII*, *X*, *XVI*, and *XVIII* with lead tetraacetate gave acetoxy ketones *V*, *XII*, *XIV*, *XIX*, and *XXII* in a 25—30% yield. During acetoxylation the hydroxy groups were protected by conversion to nitrates.

In the preceding communication[1] we have described the preparation of two derivatives of 29-hydroxy-30-norlupan-20-one; hydroxy ketone *IV* and acetoxy ketone *V*. As the side chain of the —$COCH_2OH$ type is characteristic of steroid derivatives with mineralocorticoid or glucocorticoid activity, we tried to prepare a series of lupane derivatives substituted at 19α with the same type of chain. The already described methods of preparation of compounds of this type afforded the required products in low yields only; hydroxy ketone *IV* was obtained as a by product during the ozonolysis of betulin diacetate, and that with poor reproducibility; acetoxy ketone *V* was prepared from the poorly accessible 3β,28-diacetoxy-29-bromo-30-norlupan-20-one[1].

For the first procedure we used as starting substance the chloride of dinoracid[2] *II*; when reacting with diazomethane, it gave diazoketone *III* which was then converted with sulfuric acid in tetrahydrofuran[3] to hydroxy ketone *IV* in 50% yield. Subsequent acetylation afforded acetoxy ketone *V* in an overall 30% yield. Still more advantageous was the second procedure, starting from derivatives of 30-norlupna -20-one, which are more easily accessible than dinoracids of the type *I*. Norketones *VI* and *XVI* were prepared according to literature[4]. For the preparation of substances with a free hydroxyl group in the positions 3 and 28, or with an oxo group in the position 3, these hydroxyl groups had to be protected by a group the subsequent elimination of which would not be based on base-catalysed hydrolysis. We chose the nitrate group for its easy reductive elimination with zinc in acetic acid[5]. On esterification of known[1,6,7] hydroxy ketones *VII* and *XVII* with nitric acid in acetic anhydride nitrates *VIII* and *XVIII* were obtained. Partial acetylation[8] of diol *VII* gave monoacetate *IX* which was converted to nitrate-acetate *X* using the same procedure. Using

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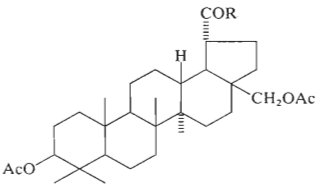
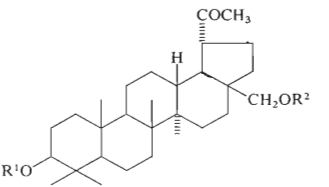
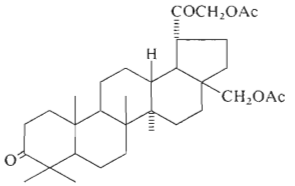


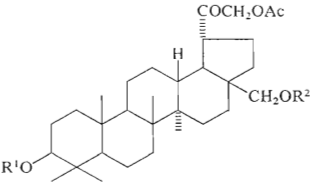
I, R = OH
II, R = Cl
III, R = CHN_2
IV, R = CH_2OH
V, R = CH_2OAc



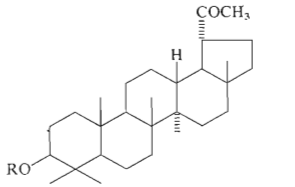
VI, $R^1 = R^2 = Ac$
VII, $R^1 = R^2 = H$
VIII, $R^1 = R^2 = NO_2$
IX, $R^1 = H$, $R^2 = Ac$
X, $R^1 = NO_2$, $R^2 = Ac$



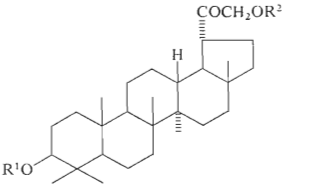
XI



XI, $R^1 = R^2 = H$
XII, $R^1 = R^2 = NO_2$
XIII, $R^1 = H$, $R^2 = Ac$
XIV, $R^1 = NO_2$, $R^1 = Ac$



XVI, R = Ac
XVII, R = H
XVIII, R = NO_2



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

the reaction of norketones *VI*, *VIII*, *X*, *XVI* and *XVIII* with lead tetraacetate in the presence of boron trifluoride etherate and methanol in benzene[9] corresponding 29-acetoxy norketones *V*, *XII*, *XIV*, *XIX* and *XXII* were obtained in 25–30% yields.

For further modifications of the model substances diol *XI* was prepared from dinitrate *XII* by elimination of the protecting groups. This diol was submitted to partial acetylation[8], leading to monoacetate *XIII*. This was also prepared by elimination of the protecting group from nitrate-acetate *XIV*. Oxidation of monoacetate *XIII* with pyridinium chlorochromate[10] gave diketone *XV*.

Further we attempted the preparation of hydroxy acetate *XXI* without the use of the protecting nitrate group. On hydrolysis of diacetate *XIX* with potassium carbonate in aqueous methanol diol *XX* was obtained in 80% yield. Partial acetylation of diol *XX* gave monoacetate *XXI* which was also prepared by elimination of the protecting group from nitrate *XXII*.

The structure of the newly prepared compounds was confirmed by an analysis of their spectra. In the IR spectra characteristic bands appear for 29-acetoxy-30-norlupan-20-one at 1750, 1230, 1055 (acetate), 1730 (keto group) and 1412 cm^{-1} (α-methylene group). In the ^{1}H-NMR spectra of the acetoxy ketones *XII* and *XV* the signals of the methylene group protons are formed for an AB system with a high value of geminal coupling constant, $J_{gem} \approx -17$ Hz, which is characteristic of the $-COCH_2OOCR$ group.

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotations were measured in chloroform on an automatic polarimeter ETL-NPL (Bendix-Ericsson) with a 1–2° accuracy. The infrared spectra were measured in chloroform on a UR-10 (Zeiss, Jena, GDR) spectrophotometer, unless stated otherwise. The ^{1}H-NMR spectra were measured on a Varian HA-100 (100 MHz) instrument in deuteriochloroform, with tetramethylsilane as internal reference; the chemical shifts are given in ppm, δ-scale. For column chromatography silica gel according to Pitra (60 to 120 μ) and for thin-layer chromatography silica gel G (Merck) were used. The reaction mixtures were worked up using the following procedures: *A*) the mixture was poured into water, the product extracted with ether, the extract washed with a saturated solution of sodium hydrogen carbonate and water; *B*) the mixture was poured onto ice, the product extracted with ether, the extract washed with dilute hydrochloric acid (1 : 4), water, a sodium hydrogen carbonate solution and water; *C*) the mixture was poured into a mixture of ice and concentrated aqueous ammonia, the product was extracted with dichloromethane, the extract washed with dilute aqueous ammonia (1 : 1) and water; *D*) the mixture was filtered through diatomaceous earth, the solid residue was washed with dichloromethane, and the combined organic fractions were washed with water (5 times), a sodium hydrogen carbonate solution and water. The organic solutions were dried over sodium sulfate. Samples for analysis were dried over phosphorus pentoxide at 80°C and 13–133 Pa (0·1–1 Torr) for 8–12 h. The identity of the samples prepared by various procedures was checked by mixture melting point determination, thin-layer chromatography and infrared spectra.

3β,28-Diacetoxy-29-hydroxy-30-norlupan-20-one (*IV*)

A solution of 200 mg of chloride[2] *II* in 12 ml of benzene was added to a solution of diazomethane (500 mg) in ether (26 ml) under cooling at 20°C, over 30 minutes. After 26 h standing at room temperature excess diazomethane was evaporated together with solvents *in vacuo*. Yield 200 mg of amorphous diazoketone *III*. IR spectrum: 1718, 1252, 1030 (CH_3COO), 3108, 2108, 1635 ($COCHN_2$) cm^{-1}. Sulfuric acid (50%; 0·2 ml) was added into the solution of 200 mg of diazoketone *III* in 15 ml tetrahydrofuran and the mixture was stirred at room temperature for 3 h and then worked up using the procedure *A*. The residue was chromatographed on 2 preparative silica gel plates (20 × 20 cm) in light petroleum–ether (1 : 1). Yield 100 mg of hydroxy ketone *IV*, m.p. 138–141°C (methanol), $[\alpha]_D$ −16·4° (*c* 0·79) identical with that of an authentic sample[1]. Literature[1] gives m.p. 131–133°C, $[\alpha]_D$ −12·3°.

Acetate V. Acetic anhydride (1·2 ml) was added into a solution of 50 mg of hydroxy ketone *IV* in 2 ml of pyridine. After 12 h standing at room temperature the mixture was worked up according to procedure *B*. Crystallisation of the residue from light petroleum gave 35 mg of acetoxy ketone *V*, m.p. 122–128°C (under decomposition), $[\alpha]_D$ −20° (*c* 0·78), identical with a sample prepared by acetoxylation of norketone *VI*.

3β,28-Dihydroxy-30-norlupan-20-one 3,28-Dinitrate (*VIII*)

Diol[1] *VII* (720 mg) was added over 10 minutes to a mixture prepared from 7·2 ml of nitric acid (ϱ = 1·51 g/cm^3) and 54 ml of acetic anhydride at −20°C. After 40 min stirring at −10°C the mixture was worked up using procedure *C*. By crystallization of the residue from light petroleum 735 mg of dinitrate *VIII* were obtained, of m.p. 203–205°C (decomp.), $[\alpha]_D$ −6·8° (*c* 1·50). IR spectrum: 1627, 1277, 860 (ONO_2), 1707, 1354 ($COCH_3$) cm^{-1}. For $C_{29}H_{46}N_2O_7$ (534·7) calculated: 65·14% C, 8·67% H, 5·24% N; found: 65·32% C, 8·88% H, 5·40% N.

3β-Hydroxy-28-acetoxy-30-norlupan-20-one (*IX*)

Acetic anhydride (2·5 ml) was added to a solution of diol *VII* (1 000 mg) in 10 ml of pyridine and the mixture was allowed to stand at 0°C for 40 min, and then worked up according to procedure *B*. The residue was chromatographed on a silica gel column (100 g). Using a mixture of light petroleum and ether (3 : 2) 685 mg of acetate *IX* were eluted, m.p. 233–235°C (ether, $[\alpha]_D$ −23° (*c* 1·47). IR spectrum: 1733, 1246, 1032 (CH_3COO), 1714, 1369 (CH_3CO), 3616 (OH) cm^{-1}. ^{1}H-NMR spectrum: 0·763 s, 0·826 s, 0·971 s, 1·003 s, 1·022 s (5 × CH_3); 2·075 s (CH_3COO); 2·16 s (CH_3CO); 2·68 mt (19βH); 3·19 mt W = 16 Hz (3αH); 3·79 d and 4·22 d, J_{gem} = −11 Hz (28-H_2). For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·35% H; found: 76·73% C, 10·56% H.

3β-Hydroxy-28-acetoxy-30-norlupan-20-one 3-Nitrate (*X*)

520 mg of alcohol *IX* were added over 10 minutes to a mixture prepared from 2·5 ml of nitric acid (ϱ = 1·51 g/cm^3) and 19 ml of acetic anhydride at −20°C. After 40 minutes' stirring at −10°C the mixture was worked up by procedure *C*. Crystallization of the residue from light petroleum gave 527 mg of nitrate *X*, m.p. 201–204°C (decomp.), $[\alpha]_D$ −7·6° (*c* 1·06). IR spectrum: 1622, 1277, 862 (ONO_2), 1726, 1242, 1031 (CH_3COO), 1709, 1366 ($COCH_3$) cm^{-1}. For $C_{31}H_{49}NO_6$ (531·7) calculated: 70·02% C, 9·29% H, 2·63% N; found: 70·25% C, 9·03% H, 2·89% N.

Acetoxylation of 30-Norlupan-20-one Derivatives

Methanol (1·28 ml), boron trifluoride etherate (3·20 ml) and lead tetraacetate (535 mg) were added to a solution of 0·001 mol of norketone in 22 ml of benzene, the mixture was stirred for 8 hours and worked up using procedure *A*. The product was isolated by chromatographing the residue on 5 preparative silica gel plates (compounds *V*, *XIX*, *XXII*), or on a silica gel column (compounds *XII* and *XIV*). The starting ketone about (45%) could also be recovered from each experiment.

3β,28,29-*Triacetoxy*-30-*norlupan*-20-*one* (V): Chromatography in light petroleum–ether mixture (1 : 1) gave 132 mg of acetoxy ketone *V*, m.p. 120—126°C (decomp.; from hexane), $[\alpha]_D$ −21° (*c* 0·76). Literature[1] gives m.p.150—152°C, $[\alpha]_D$ −20°, but an authentic sample had m.p. 123 to 127°C (under decomposition). For $C_{35}H_{54}O_7$ (586·8) calculated: 71·64% C, 9·28% H; found: 71·85% C, 9·01% H.

3β,28-*Dihydroxy*-29-*acetoxy*-30-*norlupan*-20-*one* 3,28-*dinitrate* (XII): Using a mixture of light petroleum and ether (4 : 1) 160 mg of amorphous acetoxy ketone *XII* were eluted, $[\alpha]_D$ −11·4° (*c* 1·93). IR spectrum: 1627, 1276, 862 (ONO_2), 1747, 1728, 1234, 1412, 1054 ($COCH_2$. $OOCCH_3$) cm^{-1}. ^{1}H-NMR spectrum: 0·866 s (2 × CH_3); 1·003 s, 1·014 s, 1·034 s (3 × CH_3); 2·17 s (CH_3COO); 2·70 mt (19βH); 4·17 d and 4·64 d, J_{gem} = −11 Hz (28-H_2); AB system 4·66 and 4·72, J_{gem} = −17 Hz (29-H_2); 4·64 mt (3αH). For $C_{31}H_{48}N_2O_9$ (592·7) calculated: 62·82% C, 8·16% H, 4·73% N; found: 63·02% C, 8·00% H, 4·96% N.

3β-*Hydroxy*-28,29-*diacetoxy*-30-*norlupan*-20-*one* 3-*nitrate* (XIV): Amorphous acetoxy ketone *XIV* (177 mg) was eluted with a mixture of light petroleum and ether (9 : 1), $[\alpha]_D$ −10·3° (*c* 0·94), IR spectrum: 1622, 1276, 860 (ONO_2), 1726, 1237, 1030 (CH_3COO), 1741, 1726, 1412, 1237. 1053 ($COCH_2OOCCH_3$) cm^{-1}. For $C_{33}H_{51}NO_8$ (589·8) calculated: 67·21% C, 8·72% H, 2·37% N; found: 66·98% C, 9·08% H, 2·11% N.

3β,29-*Diacetoxy*-30-*norlupan*-20-*one* (XIX): Chromatography in the system light petroleum–ether (4 : 1) gave 143 mg of acetoxy ketone *XIX*, m.p. 141—150°C (decomp.; from light petroleum), $[\alpha]_D$ −14·5° (*c* 0·55). IR spectrum (tetrachloromethane): 1734, 1244, 1025 (CH_3COO), 1754, 1734, 1413, 1255, 1055 ($COCH_2OOCCH_3$) cm^{-1}. For $C_{33}H_{52}O_5$ (528·8) calculated: 74·96% C, 9·91% H; found: 75·06% C, 10·08% H.

3β-*Hydroxy*-29-*acetoxy*-30-*norlupan*-20-*one* 3-*nitrate* (XXII): Chromatography in light petroleum ether mixture (9 : 1) gave 160 mg of amorphous acetoxy ketone *XXII*, $[\alpha]_D$ −4·5° (*c* 0·55). IR spectrum (tetrachloromethane): 1630, 1276, 859 (ONO_2), 1754, 1732, 1412, 1227, 1055 ($COCH_2OOCCH_3$) cm^{-1}. For $C_{31}H_{49}NO_6$ (531·7) calculated: 70·02% C, 9·29% H, 2·63% N; found: 70·22% C, 9·35% H, 2·55% N.

3β,28-Dihydroxy-29-acetoxy-20-norlupan-20-one (*XI*)

A solution of 375 mg of dinitrate *XII* in 37 ml of acetic acid was treated by addition, over one hour, of 2·5 g of zinc dust, under stirring. The stirring was continued at room temperature for 1 h and the mixture was worked up using procedure *D*. The residue was chromatographed on 4 preparative silica gel plates (20 × 20 cm) in light petroleum–acetone (7 : 3). Yield, 270 mg of diol *XI*, m.p. 193—195°C (ether), $[\alpha]_D$ −42·5° (*c* 0·73). IR spectrum: 3624, 1024 (OH), 1747, 1727, 1412, 1231, 1054 ($COCH_2OOCCH_3$) cm^{-1}. For $C_{31}H_{50}O_5$ (502·7) calculated: 74·06% C, 10·02% H; found: 73·87% C, 9·86% H.

3β-Hydroxy-28,29-diacetoxy-30-norlupan-20-one (*XIII*)

a) Zinc dust (1·5 g) was added into a solution of 185 mg of nitrate *XIV* in 21 ml of acetic acid over 1 h under stirring. After an additional hour of stirring at room temperature the mixture was worked up using procedure *D*. Chromatography of the residue on 2 preparative silica gel plates (20 × 20 cm) in light petroleum–ether (3 : 7) yielded 130 mg of alcohol *XIII*, m.p. 170 to 173°C (ether), $[\alpha]_D$ −38·2° (*c* 0·44).

b) Acetic anhydride (0·5 ml) was added to a solution of 179 mg of diol *XI* in 2 ml of pyridine and the mixture allowed to stand at 0°C for 40 min, and then worked up according to procedure *B*. The residue was chromatographed on 2 preparative silica gel plates (20 × 20 cm) in light petroleum–ether (3 : 7). The zones containing a substance of medium polarity were eluted, giving 125 mg of alcohol *XIII*, m.p. 171–173°C (ether), $[\alpha]_D$ −39·4° (*c* 0·52). IR spectrum (tetrachloromethane): 3634 (OH), 1738, 1229, 1030 (CH_3COO), 1756, 1738, 1413, 1229, 1055 ($COCH_2OOCCH_3$) cm^{-1}. For $C_{33}H_{52}O_6$ (544·8) calculated: 72·76% C, 9·62% H; found: 72·99% C, 9·75% H.

28,29-Diacetoxy-30-norlupane-3,20-dione (*XV*)

Pyridinium chlorochromate (100 mg) was added into a solution of 50 mg of alcohol *XIII* in 5 ml of dichlormethane and the mixture was stirred for 1 h. It was then diluted with ether (50 ml) and filtered through a column of alumina (20 g). Evaporation of the solvents *in vacuo* gave 45 mg of amorphous chromatographically pure ketone *XV*, $[\alpha]_D$ −9·6° (*c* 0·47). IR spectrum (tetrachloromethane): 1708 (CO), 1736, 1229, 1031 (CH_3COO), 1754, 1736, 1412, 1229, 1055 ($COCH_2OOCCH_3$) cm^{-1}. ^{1}H-NMR spectrum: 0·919 s, 1·011 s, 1·021 s, 1·060 s, 1·069 s (5 × × CH_3); 2·017 s (28-$OOCCH_3$); 2·16 s (29-$OOCCH_3$); 3·805 d and 4·13 d, $J_{gem} = -11$ Hz (28-H_2); 4·66 and 4·71 AB system, $J_{gem} = -17{\cdot}5$ Hz (29-H_2). For $C_{33}H_{50}O_6$ (542·8) calculated: 73·03% C, 9·29% H; found: 72·87% C, 9·45% H.

3β-Hydroxy-30-norlupan-20-one 3-Nitrate (*XVIII*)

A solution of alcohol (1·26 g) (ref.[6,7]) in 50 ml of dichloromethane was added over 10 minutes and under stirring and cooling at −20°C to a mixture prepared from 6 ml nitric acid ($\varrho = 1{\cdot}51$ g/cm^3) and 46 ml of acetic anhydride. After 45 minutes' stirring at −10°C the mixture was worked up using procedure *C*. Crystallization of the residue from an ether–benzene mixture gave 1·2 g of nitrate *XVIII*, m.p. 220–224°C (decomp.), $[\alpha]_D$ +12·7° (*c* 0·63). IR spectrum: 1628, 1275, 859 (ONO_2), 1709, 1351 ($COCH_3$) cm^{-1}. For $C_{29}H_{47}NO_4$ (473·7) calculated: 73·53% C, 10·00% H, 2·96% N; found: 73·45% C, 9·85% C, 2·78% N.

3β,29-Dihydroxy-30-norlupan-20-one (*XX*)

A solution of potassium carbonate (150 mg) in 3 ml of water was added into a solution of diacetate *XIX* (60 mg) in 20 ml of methanol and the mixture was refluxed for 2 hours and evaporated in a vacuum. The residue was dissolved in ether and in water, the ethereal phase was washed with water, and the residue chromatographed on a preparative silica gel plate (20 × 20 cm) in benzene–acetone (9 : 1). Yield 40 mg of diol *XX*, m.p. 221–226°C (decomp.; from ether–dichloromethane), $[\alpha]_D$ −27·4° (*c* 0·47). IR spectrum: 3490, 1707 ($COCH_2OH$), 3618 (OH) cm^{-1}. For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·36% C, 10·59% H.

3β-Hydroxy-29-acetoxy-30-norlupan-20-one (*XXI*)

a) Zinc dust (1·6 g) was added in portions over 1 h and under stirring to a solution of 170 mg of nitrate *XXI* in 21 ml of acetic acid and the mixture was stirred at room temperature for another hour. The mixture was worked up using procedure *D*. When chromatographed on two preparative silica gel plates in light petroleum–ether (1 : 1) the residue afforded 123 mg of monoacetate *XXI*, m.p. 183–185°C (ether), $[\alpha]_D$ −31·9° (*c* 0·56). IR spectrum (tetrachloromethane): 1755, 1732, 1412, 1225, 1055 ($COCH_2OOCCH_3$), 3631, 1031, 1026 (OH) cm^{-1}. For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·35% H; found: 76·44% C, 10·22% H.

b) Acetic anhydride (0·2 ml) was added into a solution of 30 mg of diol *XX* in 2 ml of pyridine at 0°C. After 40 min standing at the same temperature the mixture was worked up (procedure *B*). By chromatography of the residue on a preparative silica gel plate (10 × 20 cm) in light petroleum–ether (1 : 1) monoacetate *XXI* (15 mg) was obtained, m.p. 184–186°C (ether), $[\alpha]_D$ −28·9° (*c* 0·26).

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