PREPARATION OF ISOMERIC 2-METHYL-3-OXOLUPANE-28-NITRILES*

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2β-Methyl- and 2α-methyl-3-oxo derivatives of lupane-28-nitrile *XV* and *XVI* were prepared from betulin-3-acetate (*I*). The key steps of the synthesis were the condensation of ketone *VII* with formaldehyde and dimethylamine hydrochloride, conversion of the methylene ketone *VIII* formed to 3β-acetoxy-2-methylene derivative *X* and hydrogenation of the exomethylene double bond. Both 2-methyl-3-oxo derivatives, *XV* and *XVI*, are approximately equally stable; in their equilibrium mixture 47 ± 3% of the 2β-isomer were found.

In connection with the study of the conformation of the ring A in triterpenoid 3-oxo derivatives we described in our previous paper[1] the preparation of isomeric 2-methyl--3-oxo derivatives of 19β,28-epoxy-18α-oleanane. In this paper we describe the synthesis of analogous 2-methyl-3-oxo derivatives of lupane-28-nitrile *XV* and *XVI*, which are necessary for further study of the ring A conformation by means of dipole moments.

For the introduction of the methyl group in position 2 we used as starting compound 3-oxolupane-28-nitrile (*VII*) which was prepared already earlier by Lehn and Ourisson[2] by dehydration of betulonic acid amide (3-oxolupan-28-oic acid amide). The procedure used by us starts from betulin-3-acetate (*I*) and the key step for the introduction of the nitrile group into position 17 is the dehydration of 28-oximino derivative, similarly as in paper[3].

The oxidation of betulin-3-acetate (*I*) with pyridinium chlorochromate in dichloromethane led to aldehyde *II*, which was converted to oxime *III* without previous purification. Heating of oxime *III* with acetic anhydride gave the known[3] 3β-acetoxy--20(29)-lupene-28-nitrile (*IV*). On hydrogenation of derivative *IV* on Adams catalyst in acetic acid, interrupted after consumption of 1 mol of hydrogen, the saturated nitrile acetate *V* was obtained in good yield. Alkaline hydrolysis of acetate *V* gave hydroxy derivative *VI* which was oxidized with sodium dichromate in acetic acid to afford ketone *VII*.

The method used for the introduction of the methyl group into position 2 was the same as in the case of analogous derivatives of 19β,28-epoxy-18α-oleanane[1]. When submitted to Mannich reaction, ketone *VII* gave 2-methylene-3-oxo derivative *VIII*

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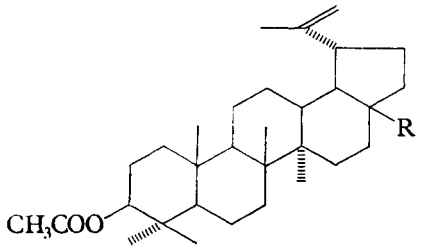
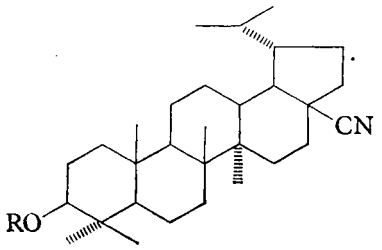
(in the presence of paraformaldehyde and dimethylamine hydrochloride in boiling dioxane). Since methylene ketone *VIII* is unstable and on attempt to purify it it gave a more polar product (probably a dimer, see also[4]), it was reduced directly with sodium borohydride to 3β-hydroxy derivative *IX*, which was stable and could be purified easily chromatographically.

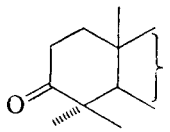


I, R = CH_2OH
II, R = CHO
III, R = CH=NOH
IV, R = CN

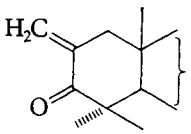


V, R = $COCH_3$
VI, R = H

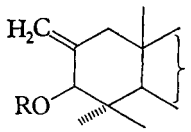
Hydrogenation of the exocyclic double bond in hydroxy derivative *IX* on Adams catalyst in acetic acid led to a mixture of isomeric 2-methyl-3-hydroxy derivatives *XI* and *XIII*. As a by-product of the reaction a mixture of ketones *XV* and *XVI* was isolated, which are formed by rearrangement of the unsaturated alcohol *IX*. The same rearrangement was also observed during the hydrogenation of an analogous derivative earlier[1]. When acetate *X* was hydrogenated under the same conditions, the rearrangement did not take place and a mixture of saturated acetates *XII* and *XIV* was



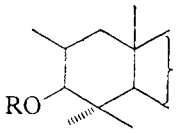
VII



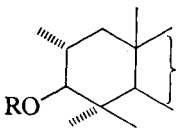
VIII



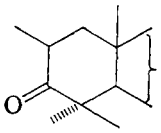
IX, R = H
X, R = $COCH_3$



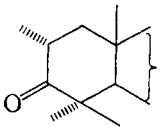
XI, R = H
XII, R = $COCH_3$



XIII, R = H
XIV, R = $COCH_3$



XV



XVI

formed, which was hydrolysed without previous separation, giving a mixture of alcohols *XI* and *XIII*. The alcohols *XI* and *XIII* were separated chromatographically. By analogy[1] the less polar alcohol was assigned the structure of 2β-methyl-3β-hydroxy derivative *XI*, and the more polar one the structure of 2α-methyl-3β-hydroxy derivative *XIII*. The configurations were further confirmed by ^{1}H NMR spectra: the coupling constant value $J_{2,3}$ (2·2 Hz) and the chemical shift of the 3α-hydrogen (2·74 ppm) in 2β-methyl derivative *XI* as well as the values of the 2α-isomer *XIII* ($J_{2,3}$ = 10 Hz; 3·29 ppm), are practically identical with the values found in analogous derivatives of 19β,28-epoxy-18α-oleanane[1]. The molecular rotation difference ($\Delta M_D = M_{D(XI)} - M_{D(XIII)} = +250°$) is also in agreement with the value found[1] in the 18α-oleanane series (+265°).

2β-Methyl-3-oxo derivative *XV* was prepared by oxidation of alcohol *XI* with sodium dichromate in acetic acid in the presence of sodium acetate. When oxidized under the same conditions alcohol *XIII* gave 2α-methyl-3-oxo derivative *XVI*. Similarly as in the 18α-oleanane series a more positive optical rotation value is characteristic of the 2β-isomer *XV* and the molecular rotation difference between the 2β-isomer *XV* and 2α-isomer *XVI* ($\Delta M_D = +566°$) is in good agreement with the value found[1] for 2-methyl-3-oxo derivatives of 19β,28-epoxy-18α-oleanane (+565°). Both 2-methyl-3-oxo derivatives, *XV* and *XVI*, are unstable and in acid medium they isomerize easily to an equilibrium mixture. From the optical rotation values it was estimated that the equilibrium mixture contains 47 ± 3% of the 2β-isomer *XV*. A similar value (51 ± 3%) was also found[1] in analogous derivatives of 19β,28-epoxy-18α-oleanane.

EXPERIMENTAL

The melting points were measured on a Kofler block and they are not corrected. Optical rotations were measured on an automatic polarimeter ETL-NPL (Bendix-Ericsson) in chloroform solution (*c* 0·3 to 1·0), with a ±2° accuracy. The infrared spectra were measured on a UR-10 (Zeiss, Jena) spectrometer in chloroform. The ^{1}H NMR spectra were measured on a Tesla BS 487A instrument at 80 MHz, in deuteriochloroform with hexamethyldisiloxane as internal reference. The chemical shifts were calculated with reference to tetramethylsilane, and they are given in ppm, δ-scale. Only characteristic signals are given in the text. In their spectra all the compounds had singlets of the five skeletal methyl groups in the 0·65—1·15 ppm region and compound with the isopropyl group on $C_{(19)}$ had two three-proton doublets (0·76—0·77 ppm, J = 6·6—6·8 Hz and 0·88 to 0·89 ppm, J = 6·7—6·9 Hz). For column chromatography neutral alumina, activity II (Reanal), was used and silica gel Silpearl of Kavalier, Votice, while for thin-layer chromatography silica gel G according to Stahl (Merck) was employed. Under the term "conventional work-up" the washing of the organic extract with water, saturated sodium hydrogen carbonate solution and water, and drying over sodium sulfate and evaporation of the solvent under reduced pressure is meant. The samples for analysis were dried under reduced pressure and over phosphorus pentoxide at 100°C.

3β-Acetoxy-20(29)-lupene-28-nitrile (*IV*)

A solution of 20 g of betulin-3-acetate (*I*, ref.[5]) in 150 ml of dichloromethane was poured into a stirred suspension of 10 g of pyridinium chlorochromate in 100 ml of dichloromethane. The mixture was stirred at room temperature for 2 h, then diluted with dry ether and the solution was decanted and filtered through a column of alumina (50 g). The solvents were distilled off, giving crude aldehyde *II* which was characterized only by IR spectrum: 3 080, 1 640, 892 (C=CH_2), 2 820, 2 720, 1 715 (CHO), 1 722, 1 255 (CH_3COO) cm^{-1}. Aldehyde *II* was dissolved in 250 ml of hot pyridine and hydroxylamine hydrochloride (10 g) was added to it. The mixture was heated on a boiling water bath for 2 h, cooled, diluted with water and extracted with ether. The extract was washed with dilute hydrochloric acid (1 : 4) and submitted to conventional work-up. Crude oxime *III* was dissolved in 250 ml of acetic anhydride and the solution was heated at 100 °C for 2 h. After cooling 20 ml of pyridine were added, and acetic anhydride was decomposed with water. The mixture was extracted with ether and the extract was worked up in the conventional manner. Crude nitrile *IV* (18·5 g) was chromatographed on alumina (800 g). Elution with light petroleum–benzene mixture 4 : 1 and crystallization from benzene–ethanol mixture gave 13 g of nitrile *IV*, m.p. 251–252°C, $[\alpha]_D$ +30°. Ref.[3] gives m.p. 240–242°C, $[\alpha]_{580}$ +24°. IR spectrum: 3 085, 1 644, 892 (C=CH_2), 2 240 (CN), 1 724, 1 257 cm^{-1} (CH_3COO). ^1H NMR spectrum: 1·68 s (CH_3–C=), 4·64 bs and 4·75 bs (=CH_2), 4·46 m (ΣJ = 16 Hz, 3αH). For $C_{32}H_{49}NO_2$ (479·7) calculated: 80·11% C, 10·30% H, 2·92% N; found: 79·86% C, 10·30% H, 2·70% N.

3β-Acetoxylupane-28-nitrile (*V*)

0·2 g of platinum oxide according to Adams were added to a solution of compound *IV* (10 g) in acetic acid (600 ml) and the mixture was shaken under hydrogen at room temperature till 500 ml of hydrogen were absorbed (20 min). The catalyst was filtered off, the filtrate diluted with water and extracted with ether. The extract was submitted to conventional work-up and the resulting residue was dissolved in benzene. The solution was filtered through a silica gel column (10 g). Crystallization of the residue from a benzene–ethanol mixture gave 9·5 g of compound *V*, m.p. 296–298°C, $[\alpha]_D$ +2°. IR spectrum: 2 239 (CN), 1 720, 1 257, 1 025 cm^{-1} (CH_3COO). ^1H NMR spectrum: 2·03 s (CH_3COO), 4·48 m (ΣJ = 16 Hz; 3αH). For $C_{32}H_{51}NO_2$ (481·7) calculated: 79·78% C, 10·67% H, 2·91% N; found: 79·61% C, 10·78% H, 2·79% N.

3β-Hydroxylupane-28-nitrile (*VI*)

A solution of potassium hydroxide (4 g) in ethanol (300 ml) was added to a solution of acetate *V* (9 g) in benzene (300 ml) and the mixture was refluxed for 2 h, cooled, diluted with ether, washed with water, dilute hydrochloric acid, and submitted to conventional work-up. Crystallization of the resulting residue from a mixture of benzene and ethanol gave 8·3 g of hydroxy derivative *VI*. An analytical sample was crystallized from ether–light petroleum. M.p. 241–243°C, $[\alpha]_D$ −11°. IR spectrum: 3 610, 3 480 (OH), 2 236 cm^{-1} (CN). ^1H NMR spectrum: 3·19 m (ΣJ = 16 Hz, 3αH). For $C_{30}H_{49}NO$ (439·7) calculated: 81·94% C, 11·23% H, 3·19% N; found: 81·76% C, 11·32% H, 3·04% N.

3-Oxolupane-28-nitrile (*VII*)

Sodium acetate (trihydrate, 2·5 g) and sodium dichromate dihydrate (1·0 g) were added to a solution of hydroxy derivative *VI* (0·54 g) in acetic acid (100 ml) and the mixture was stirred at room temperature for 30 min and then allowed to stand overnight. After dilution with water it was extracted with ether. The extract was worked up in the conventional manner. Crystallization

of the residue from chloroform–methanol and chloroform–heptane mixture gave ketone *VII* (0·50 g), m.p. 242–243°C, $[\alpha]_D$ +18°. Ref.[2] gives m.p. 244–245°C, $[\alpha]_D$ +18°. IR spectrum: 2 238 (CN), 1 698 cm^{-1} (CO). For $C_{30}H_{47}NO$ (437·7) calculated: 82·32% C, 10·82% H, 3·20% N; found: 82·62% C, 10·81% H, 3·05% N.

2-Methylene-3-oxolupane-28-nitrile (*VIII*)

Dimethylamine hydrochloride (3·5 g) and paraformaldehyde (1·5 g) were added to a solution of ketone *VII* (7 g) in dioxane (300 ml) and the mixture was refluxed for 10 h. After cooling it was diluted with chloroform, filtered through a column of alumina (10 g), the filtrate was washed three times with water, dried over calcium chloride and the solvent distilled off. The residue was dissolved in benzene and the solution filtered through a column of silica gel. Ketone *VIII* (6·8 g), obtained after evaporation of benzene, was contaminated by a more polar substance. In the attempts at further chromatographic purification or crystallization the ketone *VIII* was gradually converted to a more polar substance. The same also occurred on standing of its solutions. An analytical sample of ketone *VIII*, obtained by crystallization from chloroform–methanol had m.p. 225–227°C, $[\alpha]_D$ +28°. IR spectrum: 2 236 (CN), 1 683 (CO), 1 604 cm^{-1} (C=C). For $C_{31}H_{47}NO$ (449·7) calculated: 82·79% C, 10·54% H, 3·12% N; found: 83·08% C, 10·51% H, 2·82% N.

3β-Hydroxy-2-methylenelupane-28-nitrile (*IX*)

A solution of sodium borohydride (3 g) in methanol (100 ml) was added to a solution of crude ketone *VIII* (3·0 g) in benzene (100 ml) and the mixture was allowed to stand at room temperature for three days. Ammonium chloride solution was then added to it and the organic layer separated and submitted to the conventional work-up. The residue was dissolved in benzene and chromatographed on a silica gel column (300 g). Benzene–ether mixture 19 : 1 eluted 0·4 g of non-polar substances and 2·2 g of hydroxy derivative *IX* which was crystallized from benzene–ethanol to afford a product with m.p. 247–250°C, $[\alpha]_D$ −13°. IR spectrum: 3 630, 3 480 (OH), 2 237 (CN), 3 090, 1 648, 895 cm^{-1} (C=CH_2). ^{1}H NMR spectrum: 2·30 d (J = 12·4 Hz, 1ξ-H), 3·69 bs ($W_{1/2}$ = 5 Hz, 3αH), 4·79 d ($J \sim 1$ Hz) and 5·02 bs ($W_{1/2}$ = 5 Hz, C=CH_2). For $C_{31}H_{49}NO$ (451·7) calculated: 82·42% C, 10·93% H, 3·10% N; found: 82·24% C, 10·88% H, 3·19% N.

3β-Acetoxy-2-methylenelupane-28-nitrile (*X*)

A solution of hydroxy derivative *IX* (1·41 g) in a mixture of pyridine (40 ml) and acetic anhydride (40 ml) was heated at 100 °C for 9 h and then poured into water. The precipitated material was filtered off, washed with water and dissolved in chloroform. The solution was filtered through a layer of alumina and chloroform was distilled off. Crystallization from chloroform–methanol gave acetate *X* (1·31 g), m.p. 314–316°C (under decomp.), $[\alpha]_D$ −6°. IR spectrum: 2 240 (CN), 1 740, 1 257 (CH_3COO), 1 665, 910 cm^{-1} (C=CH_2). ^{1}H NMR spectrum: 2·12 s (CH_3COO), 2·30 d (J = 12·6 Hz, 1ξ-H), 4·76 bs and 4·94 bs (C=CH_2), 4·76 bs (3αH). For $C_{33}H_{51}NO_2$ (493·8) calculated: 80·27% C, 10·41% H, 2·84% N; found: 80·06% C, 10·52% H, 2·61% N.

3β-Hydroxy-2β-methyllupane-28-nitrile (*XI*) and 3β-Hydroxy-2α-methyllupane-28-nitrile (*XIII*)

a) Adams catalyst (0·10 g PtO_2) was added to a solution of hydroxy derivative *IX* (0·70 g) in acetic acid (100 ml) and the mixture was shaken under hydrogen for 20 min. The catalyst was filtered off, the filtrate diluted with water and extracted with ether. After the conventional work-up

the product was chromatographed on a silica gel column (300 g). Elution with light petroleum–ether 4 : 1 gave gradually: 200 mg of a mixture of ketones *XV* and *XVI*, $[\alpha]_D$ +21°, the IR spectrum corresponds to the superposition of the spectra of ketones *XV* and *XVI*. 240 mg of 2β-methyl derivative *XI*, m.p. 232–233°C (chloroform–methanol), $[\alpha]_D$ +36°, IR spectrum: 3 630, 3 540 (OH), 2 237 cm^{-1} (CN). ^1H NMR spectrum: 0·97 d ($J \sim 7$ Hz, 2β-CH_3), 3·29 d ($J = 2{\cdot}2$ Hz, 2αH). For $C_{31}H_{51}NO$ (453·7) calculated: 82·06% C, 11·33% H, 3·09% N; found: 82·37% C, 11·39% H, 2·99% N. 190 mg of 2α-methyl derivative *XIII*, m.p. 235–236°C (chloroform–methanol), $[\alpha]_D$ −19°, IR spectrum: 3 640, 3 610, 3 500 (OH), 2 249 cm^{-1} (CN). ^1H NMR spectrum: 0·97 d ($J \sim 7$ Hz, 2α-CH_3), 2·74 d ($J = 10{\cdot}0$ Hz, 2β-H). For $C_{31}H_{51}NO$ (453·7) calculated: 82·06% C, 11·33% H, 3·09% N; found: 82·32% C, 11·39% H, 2·87% N.

b) Hydrogenation of acetate *X* (0·60 g) in acetic acid (250 ml) and the working up of the reaction mixture were carried out as under *a*). A mixture of acetates *XII* and *XIV* was obtained (0·60 g), which was hydrolyzed without previous separation by refluxing with potassium hydroxide (0·85 g) in a mixture of benzene (20 ml) and ethanol (30 ml) for 10 h. The reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid and water and filtered through a layer of alumina. The mixture of derivatives *XI* and *XIII* obtained (0·53 g) was separated chromatographically as under *a*). Yield, 0·30 g of 2β-methyl derivative *XI* and 0·20 g of 2α-methyl derivative *XIII*; both substances were identical with the preparations described under *a*).

2β-Methyl-3-oxolupane-28-nitrile (*XV*)

A mixture of hydroxy derivative *XI* (0·56 g), anhydrous sodium acetate (0·56 g), sodium dichromate dihydrate (0·80 g) and acetic acid (80 ml) was stirred at room temperature for 4·5 h. Methanol (5 ml) was added and the mixture poured into water, extracted with ether and the ethereal extract was worked up in the conventional manner. Crystallization of the residue from benzene–heptane gave 0·49 g of ketone *XV*, m.p. 238–240°C, $[\alpha]_D$ +102°. IR spectrum: 2 240 (CN), 1 708 cm^{-1} (CO). ^1H NMR spectrum: 0·99 d ($J = 6{\cdot}4$ Hz, 2β-CH_3), 2·82 m ($\Sigma J = 39$ Hz, 2αH). For $C_{31}H_{49}NO$ (451·7) calculated: 82·42% C, 10·93% H, 3·10% N; found: 82·36% C, 11·02% H, 3·03% N.

2α-Methyl-3-oxolupane-28-nitrile (*XVI*)

Oxidation of hydroxy derivative *XIII* (0·44 g) was carried out in the same manner as in the preceeding experiment. Yield, 0·38 g of 2α-methyl ketone *XVI*, m.p. 229–231°C (benzene–heptane), $[\alpha]_D$ −23°. IR spectrum: 2 240 (CN), 1 700 cm^{-1} (CO). ^1H NMR spectrum: 1·02 d ($J = 6{\cdot}4$ Hz, 2α-CH_3), 2·74 m ($\Sigma J = 38$ Hz, 2β-H). For $C_{31}H_{49}NO$ (451·7) calculated: 82·42% C, 10·93% H, 3·10% N; found: 82·30% C, 11·01% H, 2·92% N.

Isomerization of Ketones *XV* and *XVI*

Hydrochloric acid (36%, 0·14 ml) was added to a solution of ketone *XV* or *XVI* (50 mg) in chloroform (4 ml) and the mixture was allowed to stand at room temperature for 43 h. After dilution with chloroform and conventional work-up the residue was converted to a crystalline state by addition of a few drops of light petroleum and then dried at 100°C for 3 h. The equilibrium mixture of ketones *XV* and *XVI* obtained in this manner had $[\alpha]_D$ +36° ± 2° (average value of ten independent measurements).

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REFERENCES

1. Klinot J., Světlý J., Kudláčková D., Buděšínský M., Vystrčil A.: This Journal *44*, 211 (1979).
2. Lehn J. - M., Ourisson G.: Bull. Soc. Chim. Fr. *1962*, 1133.
3. Wrzeciono U., Dembczynska H.: Rocz. Chem. *43*, 1407 (1969); Chem. Abstr. *72*, 32 075 (1970).
4. Miller T. C.: J. Org. Chem. *30*, 2922 (1965).
5. Ruzicka L., Lamberton A. H., Christie E. W.: Helv. Chim. Acta *21*, 1706 (1938).

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