

Experimental

Mercuric acetate oxidation of acetyl betulinic acid 1 : Preparation of the lactone 2

To acetyl betulinic acid (10 g) dissolved in chloroform (250 ml) was added a solution of mercuric acetate (175 g) in hot acetic acid (1.2 lit.), reaction mixture was maintained at 100° in an oil bath for 4 hours. On cooling the precipitated mercuric acetate was filtered off and the whole filtrate was diluted with water and extracted with more chloroform. The orange coloured chloroform solution was washed well with water and dried (anhydrous Na₂SO₄). Removal of chloroform gave an orange solid which was dissolved in pyridine and hydrogen sulfide was passed for three hours. The black reaction mixture was filtered from Kieselguhr and pyridine was removed under reduced pressure when a brownish black gummy product (9 gr) was obtained. It was dissolved in benzene (40 ml) and chromatographed over alumina (350 gr) column deactivated by 14 ml of 10% aqueous acetic acid. Chromatogram was developed in petroleum ether and eluted by the following solvents (Table I).

Table I

Eluent	Fractions 50 ml each	Residue left on evaporation
Petroleum ether (200 ml)	1-4	Nil
Petroleum ether (200 ml)	5-8	Yellow sulphur
Petroleum ether (300 ml)	9-14	Nil
Petroleum ether:benzene (4:1) (350 ml)	15-21	Solid, m.p. 295-8°

Further elution with more polar solvent did not afford any crystalline material

The fractions (15-21) (table I) were collected and crystallised from a mixture of chloroform and methanol to afford fine needle shaped crystals m.p. 301-2°, $(\alpha)_D + 58^\circ$. Recrystallisation did not improve the melting point.

Found : C, 77.58; H, 9.54%

Calculated for $C_{32}H_{48}O_4$: C, 77.42; H, 9.67%

I.R. (KBr) : 1780 (γ -lactone), 1730, 1245 (acetate), 1640 and 830 (vinylidene) cm^{-1} .

NMR (60 Mc) : δ 0.96, δ 0.89 and δ 0.81 (5 CH_3), δ 1.98 (3H, -O.COCH₃)
 δ 1.65 (3H, -C=C), δ 4.95, δ 5.25 (2H, vinylidene,
 δ 4.4 (\underline{H} -C-O.^{CH₃}COCH₃).

Attempted isomerisation of 2 with hydrogen chloride in chloroform

To the solution of the lactone 2 (0.2 g) in chloroform (15 ml), hydrogen chloride was passed through for 4 hours. Chloroform and HCl were removed by evaporation and the product was dissolved in ether. The ether solution was washed well with water and dried (anhydrous Na₂SO₄). Removal of ether gave a solid (0.18g). The product was recrystallised from a mixture of chloroform and methanol to afford fine needle shaped crystals, m.p. 299-301°. Mixed m.p. with 2 was found undepressed. (I.R. comparison identical with 2).

Attempted isomerisation of 2 with 98% formic acid in acetic acid

To the lactone 2 (0.2g) a mixture of acetic acid (10 ml) and formic acid (98%) (10 ml) was added and the mixture was heated for 16 hours at 100°. The reaction mixture was cooled and poured into water and the precipitated solid was collected by filtration. The brown solid (.16 g), thus obtained, was chromatographed on an active column of alumina (12 g). The chromatogram was developed in petroleum ether. The solid was dissolved in 5 ml benzene and poured into the column and eluted by the following solvents (Table II).

Table II

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum ether (100 ml)	1-2	Nil
Petroleum ether:benzene (4:1) (100 ml)	3-4	Nil
Petroleum ether:benzene (3:2) (100 ml)	5-6	Nil
Petroleum ether:benzene (2:3) (150 ml)	7-9	Solid m.p. 296-8°

Elution with more polar solvents did not afford any crystalline material.

Fraction (7-9) (Table II) were combined and crystallised from CHCl_3 -MeOH, when needle shaped crystals m.p. 301-2°, was obtained. It was found to be identical with 2 by m.m.p. and I.R. comparison.

Attempted isomerisation of 2 with hydrochloric acid in acetic acid

The lactone 2 (.25 g) was dissolved in AcOH (30 ml) and conc. HCl (3 ml) was added to it. The reaction mixture was heated at 100° for one hour. It was cooled and diluted with water, the brown solid (0.17 g) was collected by filtration. It was dissolved in 6 ml of benzene and poured on an active column prepared from alumina (1.5 g.). The chromatogram was developed in petroleum ether and eluted with the following solvents (Table III).

Table III

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum ether (150 ml)	1-3	Nil
Petroleum ether:benzene (4:1) (100 ml)	4-5	Nil
Petroleum ether:benzene (3:2) (100 ml)	6-7	Nil
Petroleum ether:benzene (2:3) (150 ml)	8-10	Solid, m.p. 296-9°

Further elution with more polar solvent did not afford any solid

The fractions (8-10), Table III) were combined and crystallised from CHCl_3 -MeOH, when needle shaped crystals m.p. 301-3° was obtained. It was also found to be identical with 2 by m.m.p. and I.R. comparison.

Ozonolysis of the lactone 2 : Preparation of nor-keto lactone 3

The lactone 2 (4 g) was dissolved in CHCl_3 (40 ml). A stream of ozonised oxygen was passed through it for 3 hours while the temperature was kept at 0°C. It was then treated with 2 ml of AcOH and 2 gr. Zn dust to decompose the ozonide. After decomposition the mixture was ~~then~~ extracted with ether, washed well with water and dried (anhydrous Na_2SO_4). Evaporation of the solvent gave a white solid (3.4 g). It was dissolved in benzene (25 ml) and poured on a

column prepared from silica gel (220 g). The chromatogram was developed in petroleum ether and eluted with the following solvents. (Table IV).

Table IV

Eluent	Fraction 50 ml each	Residue on evaporation
Petroleum ether (150 ml)	1-3	Nil
Petroleum ether:benzene (4:1) (200 ml)	4-7	Nil
Petroleum ether:benzene (3:2) (150 ml)	8-10	Nil
Petroleum ether:benzene (2:3) (300 ml)	11-16	White solid, m.p. 294-6°

Elution with more polar solvent did not afford any more solid

The fractions 11-16 (3.2 g, Table IV) were combined and crystallised from a mixture of chloroform and methanol when prismatic crystals, m.p. 301-3°, (α)_D - 9° (lit.¹ m.p. 317°, (α)_D - 2°) were obtained. Recrystallization did not improve the melting point.

Found : C, 74.19; H, 9.08%

Calculated for C₃₁H₄₆O₅ : C, 74.68; H, 9.23%

I.R. (CHCl₃) : 1721 (compositive for acetate and carbonyl),
1780 (γ-lactone), 1255 cm⁻¹ (acetate)

U.V. (Ethanol): λ_{\max} 275 μ ($\log \epsilon$ 1.4)
NMR (60 Mc) : δ 0.95, δ .90 and 0.85 (5 CH₃), δ 2.35 (3H, -CO.CH₃),
 δ 2.04 groups on saturated carbon) (3H, -~~e~~.COCH₃),
 δ 4.4 (1H, H-C-O-COCH₃)
Mass : 498, 438, 395, 249 m/e
O.R.D. : (ϕ)₃₀₆ - 381° (trough), (ϕ)₂₇₃ + 114° (peak) and
(ϕ)₂₃₄ - 1765° (trough)
C.D. : Negative Cotton effect with a negative maximum
at 218 μ ($\Delta \epsilon$, -7.02), 290 μ ($\Delta \epsilon$ -0.99)
R_f (Benzene:CHCl₃:1:1) : 0.55

Attempted epi-merisation of the nor-ketone 3 with 2N sulfuric acid
in ethanol solution:

To the nor-ketone 3 (200 mg) dissolved in 15 ml ethanol was added 2N H₂SO₄ (0.2 ml) and the reaction mixture was refluxed for 4 hours. The reaction mixture was cooled and diluted with water. The precipitated solid was collected by filtration. The crude product (180 mg) was acetylated with acetic anhydride (2 ml) and pyridine (2 ml). The acetylated product (170 mg) thus obtained on working up in the usual manner, was subjected to chromatography on an alumina column, prepared from alumina (12 g.) and deactivated by 0.4 ml of 10% aqueous AcOH. The chromatogram was developed in petroleum ether. The solid (170 mg) dissolved in benzene (6 ml) was put on the column and eluted by the following solvents (Table V).

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Table V

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum ether (100 ml)	1-2	Nil
Petroleum ether:benzene (4:1) (100 ml)	3-4	Nil
Petroleum ether:benzene (3:2) (100 ml)	5-6	Nil
Petroleum ether:benzene (2:3) (150 ml)	7-9	Solid, m.p. 299-301°

The fractions 7-9 (table V) (150 mg) were collected and crystallised from CHCl_3 - MeOH, m.p. 301-3° . The m.m.p. of this and 3 remained undepressed.

Attempted epimerisation of 3 with methanolic KOH

The norketone 3 (200 mg) dissolved in benzene (10 ml) was added to a methanolic KOH solution (5%, 10 ml) and the mixture was refluxed on water bath for 3 hours. It was then concentrated and diluted with water. The precipitated solid (155 mg) was collected by filtration. The latter was reacylated with acetic anhydride (2 ml) and pyridine (2 ml). On working up the reaction mixture in usual way, a solid (160 mg) was obtained. It was dissolved in benzene (8 ml) and put on a column prepared from alumina (15 g.) deactivated by 0.6 ml of 10% aqueous acetic acid. The chromatogram

was prepared in petroleum ether and eluted with the following solvents (Table VI).

Table VI

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum ether (100 ml)	1-2	Nil
Petroleum ether:benzene (4:1) (100 ml)	3-4	Nil
Petroleum ether:benzene (3:2) (100 ml)	5-6	Nil
Petroleum ether:benzene (2:3) (100 ml)	7-8	Solid, m.p. 298-300°

Further elution with more polar solvent did not give any solid.

Fractions 7-8 (Table VI, 130 mg) were combined and crystallised from a mixture of chloroform and methanol m.p. 301-2°.

Mixed m.p. with 3 remained undepressed.

Attempted Baeyer-Villiger oxidation of 3

The nor-ketone 3 (200 mg) dissolved in chloroform (10 ml) was added to a solution of perbenzoic acid in chloroform (10 ml) and toluene-p-sulphonic acid (30 mg). The reaction mixture was refluxed for 6 hours and kept at room temp. over night. The excess perbenzoic acid was destroyed by adding potassium iodide solution acidified with acetic acid, followed by the addition of a dilute sodium thiosulfate

solution. The chloroform layer was washed with aqueous NaOH solution and then with water and dried (Na_2SO_4). Removal of the solvent gave a solid (180 mg) which was recrystallised from chloroform-methanol, m.p. $302-3^\circ\text{C}$. Mixed m.p. with starting material 3 remained undepressed.

Modified Baeyer-Villiger oxidation of 3

The norketone 3 (150 mg) was dissolved in chloroform followed by a solution of trifluoroperoxyacetic acid. The peracid reagent was prepared from trifluoroacetic anhydride (1.2 ml), 90% hydrogen peroxide (0.16 ml) and methylene chloride (2 ml). Following a 3 hr. period of reflux, the reaction mixture was successively cooled, filtered, washed with water, dried (Na_2SO_4) and concentrated from a mixture of chloroform and methanol; m.p. $301-3^\circ$. Mixed m.p. with the starting norketone 3 remained undepressed.

Base catalysed reaction of 3 with K.t. butoxide in t-butyl alcohol: Preparation of 18

The nor-keto lactone 3 (200 mg) dissolved in dry benzene (10 ml (10 ml) was added to a solution of 0.060 gr of potassium in 8 ml of dry tertiary butyl alcohol and the whole reaction mixture was refluxed for 4 hours. The solvent was removed and water was added followed by acidification with hydrochloric acid (10%, 5 ml). The crude product (140 mg) thus obtained was crystallised twice from acetone when constant melting product 18 was obtained, m.p. $258-60^\circ$.

Found : C, 76.02; H, 9.46%
C₂₉H₄₄O₄ required : C, 76.31; H, 9.64%
I.R. (Nujol) : 3600 (OH), 1755 (γ lactone and carbonyl) cm⁻¹.
U.V. (Ethanol) : λ_{max} 280 mμ (ε 84)

Acetylation of 18 : Preparation of 19

The compound 18 (200 mg) was acetylated with acetic anhydride (2 ml) and pyridine (2 ml) in the usual manner. The solid obtained by usual work up was crystallised from a mixture of chloroform and methanol when fine needle shaped crystals m.p. 300-2°, (α)_D - 24° was obtained.

Found : C, 74.17; H, 9.28%
C₃₁H₄₆O₅ required : C, 74.68; H, 9.23%
I.R. : 1765 (γ lactone), 1725 (acetate and ketone) and 1240 cm⁻¹ (acetate)
U.V. (ethanol) : λ_{max} 290 mμ (ε 90)
N.M.R. (60 Mc) : δ 1.40 (3H, singlet CH₃-C-O-C)
δ 2.04 (3H, singlet CH₃-C(=O)-O-C), δ 4.4 (1H, multiplet AcO-C-), δ 9.95 and δ 1.0 (5 CH₃ group on saturated carbon).
O.R.D. : (φ)₃₃₅ - 1794° (trough), (φ)₂₉₅ + 1480° (peak), and (φ)₂₄₀ - 1380° (trough)
C.D. : 318-308 mμ (Δε, -1.56), 250-2 mμ, (Δε, -0.16), 220 mμ (Δε, -3.12)

R_f (Benzene:CHCl₃ : 0.63
(1:1)

Mass : 498, 438, 249 m/e

Hydrolysis of 19 : Preparation of 18

The compound 19 (100 mg) was hydrolysed with methanolic alkali (10%, 10 ml) under reflux for 3 hours. After concentrating the reaction mixture, it was diluted with water. A solid (80 mg) was obtained which on crystallisation from acetone afforded crystals of m.p. 257-9°c. This hydrolysed product was found to be identical with 18 (m.m.p. and I.R. comparison).

Hydrogenation of 2 : Preparation of 9

A solution of the lactone 2 (200 mg) dissolved in a mixture of ethyl acetate and acetic acid (10 ml each) was shaken in an atmosphere of hydrogen in presence of PtO₂ catalyst at room temperature for 3 hours. After hydrogenation was complete the catalyst was removed by filtration and the filtrate was concentrated to a small volume and diluted with water. The solid precipitate, thus obtained, was crystallised twice from chloroform and methanol mixture to afford fine needle shaped crystals of 9, m.p. 296-8°, (α)_D + 45° (lit.¹ m.p. 299-300° (α)_D + 49°).

Found : C, 76.86; H, 10.21%

Calculated for C₃₂H₅₀O₄ : C, 77.06; H, 10.04%

I.R. (KBr) : 1780 (γ lactone), 1735 and 1240 cm⁻¹ (acetate)
band for vinylidene group was absent

C.D. : Negative lactone Cotton effect with a maximum at 216 μ ($\Delta\epsilon$, -6.05).

L.A.H. reduction of 11 : Preparation of 20

The nor-keto lactone 11 (0.3 g.) was dissolved in dry tetrahydrofuran (80 ml) and to it LAH (1.2 g.) was added. The reaction mixture was then refluxed for 4 hours. Excess LAH was destroyed by ethyl acetate and a saturated aqueous solution of sodium sulphate was added dropwise until inorganic salts coagulated at which point anhydrous sodium sulfate was added. The supernatant solution was decanted and the residue was washed with fresh ether. The combined ether solutions were washed with water, dried evaporated and the crystalline residue was recrystallized from 95% ethanol to give the tetra-ol 20 m.p. 281-3° (α)_D + 20°.

Found: C, 75.58; H, 10.98%

Calculated for : C₂₉H₅₀O₄ C, 75.32; H, 10.82%

I.R. (Nujol) : 3420 cm^{-1} (hydroxyl)

U.V. (Ethanol) : Optically transparent in the region 220-300 μ

Attempted glycol cleavage of 20 with sodium periodate

The tetraol 20 (150 mg) was dissolved in methanol (25 ml) and to it NaIO₄ solution (5 ml prepared from 1 gr. of NaIO₄ dissolved in 30 ml water), was added and the reaction mixture was kept at room temperature for 48 hours. After concentration on water bath it was diluted with water. The precipitated solid was collected by filtration and crystallised from 95% ethanol m.p. 281-2°.

It was found to be identical with the starting material (by m.m.p. and I.R. comparison).

Attempted glycol cleavage of tetra-ol-20 with lead tetraacetate at room temperature

A solution of the tetra-ol 20 (200 mg) in glacial acetic acid (10 ml) was added to a solution of $\text{Pb}(\text{OAc})_4$ (400 mg) in acetic acid (10 ml). The reaction mixture was kept at room temperature for 24 hours. The excess $\text{Pb}(\text{OAc})_4$ was destroyed by ethylene glycol (2 ml) and then diluted with water, extracted with ethyl acetate, washed with Na_2CO_3 solution and water until neutral. The solvent was removed and the solid thus obtained was recrystallised from 95% ethanol to afford crystals m.p. $289-2^\circ$.

It was found to be identical with the starting material (m.m.p. and I.R. comparison).

Glycol cleavage of tetra-ol 20 by lead tetra acetate oxidation at 120° : Preparation of tris nor-ketone 21

A solution of the tetra-ol 20 (400 mg) in glacial acetic acid (20 ml) was added to a solution of $\text{Pb}(\text{OAc})_4$ (1 gr.) in acetic acid (25 ml) and the reaction mixture was kept at 120°C for 3 hours. Excess $\text{Pb}(\text{OAc})_4$ was destroyed by adding ethylene glycol (2 ml). It was diluted with water, extracted with chloroform, washed with Na_2CO_3 solution and then with water until neutral. Remove of the Gummy solid, (280 mg) thus obtained, by evaporating the solvent was

hydrolysed with methanolic alkali (10%) for 3 hours. After concentrating somewhat the reaction mixture was diluted with water. The precipitated solid (220 mg) was collected by filtration. It was dissolved in benzene (10 ml) and poured on the column, prepared from alumina (20 gr.), deactivated by 0.6 ml of 10% aqueous acetic acid. The chromatogram was developed with petroleum ether and eluted with the following solvent (Table VII).

Table VII

Eluent	Fraction 50 ml each	Residue on evaporation
Petroleum ether (150 ml)	1-3	Nil
Petroleum ether:benzene (3:1) (150 ml)	4-6	Nil
Petroleum ether:benzene (2:2) (100 ml)	7-8	Nil
Petroleum ether:benzene (1:3) (100 ml)	9-10	Nil
Benzene (100 ml)	11-12	Nil
Benzene:chloroform (3:1) (100 ml)	13-14	Nil
Benzene:chloroform (2:2) (150 ml)	15-17	Solid

Elution with more polar solvent did not afford any solid.

The fractions 15-17 (table VII) were combined and crystallised from methanol to furnish crystals, m.p. 240-2°, (α)_D + 32°.

Found : C, 77.57; H, 10.51%
Calculated for $C_{27}H_{44}O_3$: C, 77.88; H, 10.57%
U.V. (Ethanol) : λ max 285 m μ (ϵ 75)
I.R. ($CHCl_3$) : 1740 (cyclopentanone) and 3310 cm^{-1}
(hydroxy group).

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