Tetrahedron Vol. 41, No. 12, pp. 2513 to 2516, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

REDUCTION OF KETONES TO EPIMERIC ALCOHOLS WITH POTASSIUM HYDROXIDE-DIETHYLENE GLYCOL

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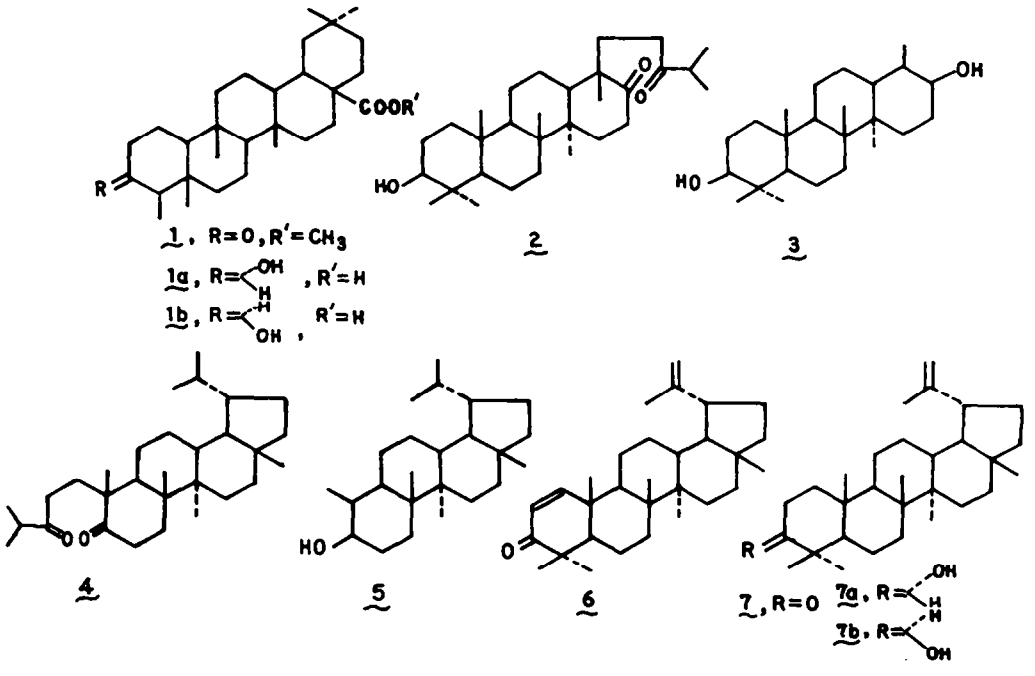
(*Received in UK* 4 *March* 1985)

Abstract - Triterpenoid ketones have been reduced to epimeric alcohols on boiling with potassium hydroxide in diethylene glycol. α,β-unsaturated ketone furnished saturated epimeric alcohols.

During the hydrolysis of 3-keto-methyl trichadenate[1] 1 with potassium hydroxide in diethylene glycol we observed that the 3-keto functional group of the triterpenoid being converted to epimeric alcohols (viz. trichadenic acid A and B[1]) 1a and 1b . A survey of the literature showed that during the degradation of hydroxydiketone 2 with potassium hydroxide in diethylene glycol, Barton et al[2] obtained the dihydroxy compound 3 . Similar observation was made by Halsall et al[3] (4 ⟶ 5). Doering et al[4,5] have reported the equillibration of ketones and alcohols in presence of their respective alkoxides under high pressure and temperature.



In order to examine the validity of the reaction on other keto compounds we carried out the reaction on a series of triterpenoid ketones (Entries 1 - 7) and one non-terpenoid ketone (Entry 8) as shown in Table I.

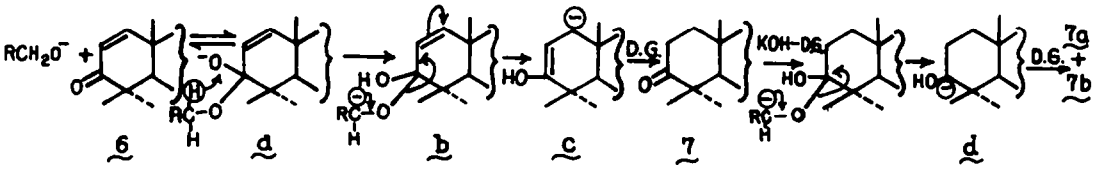
Table I

Entry No.	Ketones	Products (Yield in %)
1	Methyl trichadonate[1] 1	Trichadenic acid A[1] 1a (50) and Trichadenic acid B[1] 1b (15)
2	Friedelin[6]	Friedelanol[6] (45) and epi-friedelanol[6] (20)
3	Moretenone[7]	Moretenol[7] (50) and epi-moretenol[7] (15)
4	Taraxerone[6]	Taraxerol[6] (50) and epi-taraxerol[6] (15)
5	β-amyrone[6]	β-amyrin[6] (50) and epi-β-amyrin[6] (15)
6	Lupenone[6] 7	Lupeol[6] (50) and epi-lupeol[6] (15)
7	Glochidone[8]	Lupeol[6] (40), epi-lupeol[6](15) and lupenone[6](8)
8	Benzophenone	Benzhydrol (90)

Thus from the above observation we find that the ketones are reduced to the epimeric alcohols and the formation of the equatorial isomers predominate the less thermodynamically stable axial isomers.

Mechanism:- At the high temperature of the reaction mixture, potassium hydroxide probably forms potassium-glycoxide with diethylene glycol. The glycoxide so formed may reduce the ketone in a cyclic mechanism that may be considered parallel to the action of aluminium-alcoxides in the case of Meerwein-Ponndorf -Verley reduction[9]; but in the latter case the reduction of α,β-unsaturated ketones furnish only the allylic alcohols[10] whereas in the present case the entry 7 shows that along with the keto group, the α,β-unsaturation is also reduced which cannot be explained by the cyclic mechanism. A most probable mechanism for this reduction may follow the route as depicted in the Scheme I :

Scheme I



Under the high thermal condition, the ketone undergoes nucleophilic attack by the anionic glycoxide to form the intermediate anion a that undergoes hydride ion shift forming the carbanion intermediate b ; elimination of glycolaldehyde from b furnishes the tautomeric carbanion c which subsequently acquires a proton from the solvent, the glycol to form the saturated ketone. The isolation of a small amount of the ketone, lupenone 7 from the reaction mixture as shown in entry 7 of Table I confirms the proposed mechanism. Further nucleophilic attack by the glycoxide anion on the saturated ketone in a similar path furnishes the intermediate anion d which ultimately affords the epimeric alcohols.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were run in KBr disc in Beckman-20 and UV spectra were recorded in ethanol in Beckman DU-2 Spectrophotometers. Mass spectra were run in JMS-300 instrument. All the rotations were determined in $CHCl_3$ soln. Column chromatography were performed in silica gel (BDH 60-120 mesh) and TLC were run on plates coated with silica gel G and were developed in iodine chamber. All the analytical samples were routinely dried for 36 h in vacuo. Petrol used had the b. p. 60-80° and the ether extracts were dried over anhydrous Na_2SO_4.

Treatment of methyl trichadonate 1 with KOH-diethylene glycol: Preparation of trichadenic acid A 1a and trichadenic acid B 1b : A mixture of methyl trichadonate (0.5 g) and KOH (2 g) in diethylene glycol (50 ml) was heated in a r.b. flask (100ml) in a heating mantel initially without condenser till all the moisture escaped from the mixture. When the temperature rose above 160° in the vapour phase, the condenser was fitted in the r.b. flask and the mixture was refluxed for 2h. The mixture was then cooled, acidified with dil HCl and extracted with ether. The ether extract was washed with water, dried and the solvent was removed by distillation. The residue (0.45 g) was chromatographed over silica gel column (15 g). The column on elution with benzene:ether (4:1) furnished a solid (0.085 g) which was crystallised from $CHCl_3$-MeOH to afford a solid of m.p. 334-35°, $[\alpha]_D$ +41°, IR: 3425, 1690; M^+ 458. The acetate derivative prepared by Ac_2O-Py method had the m.p. 270-71 $[\alpha]_D$ +50°, M^+ 500; IR: 1725, 1690, 1240 cm^{-1}. The acetate was identified as O-acetyl trichadenic acid B by m.m.p., co-IR and co-TLC with an authentic sample. On further elution of the column with benzene:ether (7:3) a second solid was eluted which after crystallisation from $CHCl_3$-MeOH had m.p. 289-90°, $[\alpha]_D$ + 23°; M^+ 458; IR: 3410, 1688 cm^{-1}. Acetylation of the solid with Ac_2O-Py method and workup in the usual manner furnished an acetate m.p. 251-52°, $[\alpha]_D$ + 27°, M^+ 500; IR: 1740, 1688, 1240 cm^{-1}. The acetate was identified as O-acetyl trichadenic acid A by m.m.p., co-IR and co-TLC with an authentic sample.

Conversion of friedelin to epi-friedelanol and friedelanol: A mixture of friedelin (0.5 g) and KOH (2 g) in diethylene glycol (50 ml) was boiled in a r.b. flask (100 ml) in a heating mantel without condenser till the temperature of the escaping vapour started registering temperature above 160° when the condenser was fitted in. The mixture was allowed to reflux for 2 h and then cooled. The mixture was then acidified with dil HCl, extracted with ether, washed the ether extract with water and dried (Na_2SO_4). The solvent was removed and the residue (0.45 g) was chromatographed over silica gel (15 g). Elution of the chromatogram with benzene:Petrol (1:4) afforded a solid that was crystallised from $CHCl_3$-MeOH to furnish crystals m.p. 278-80°, $[\alpha]_D$ + 20°, IR: 3610 cm^{-1}. The acetate prepared by Ac_2O-Py method had m.p. 291-92°, $[\alpha]_D$ + 38°, IR: 1730, 1240 cm^{-1}; M^+ 470 was found identical (m.m.p., co-IR and co-TLC) with an authentic sample of epi-friedelanol acetate. Further elution of the column with benzene:petrol (3:2) furnished another solid that was crystallised from $CHCl_3$-MeOH had m.p. 300-302°, $[\alpha]_D$ + 18°; IR: 3620 cm^{-1}; its acetate prepared by Ac_2O-Py method had the m.p. 315-16°, $[\alpha]_D$ - 10°; IR: 1730, 1240 cm^{-1} was found identical with an authentic sample of friedelanol acetate by comparison of their m.p., TLC and IR spectra.

Reduction of moretenone to epi-moretenol and moretenol: Moretenone (0.5 g) and KOH (2 g) was mixed with diethylene glycol (50 ml) taken in a r.b. flask(100 ml) and heated as described before. The solid (0.45 g) obtained after usual workup was chromatographed. Elution of the chromatogram with benzene:petrol (1:4) yielded a solid (0.08 g) that was crystallised from MeOH ; the crystals had m.p. 223-24°, $[\alpha]_D$ - 2°, IR: 3460, 3080, 1640,890 cm^{-1}; M^+ 426; its acetate prepared by Ac_2O-Py method had m.p. 231-32°, $[\alpha]_D$- 18°; IR: 3070, 1725, 1640, 890 cm^{-1}; M^+ 468. The acetate was identical (m.m.p., co-IR and co-TLC) with an authentic sample of epi-moretenyl acetate. Further elution of the column with benzene:petrol (2:3) gave a solid (0.25 g) which on crystallisation from $CHCl_3$-MeOH furnished crystals of m.p. 228-30°, $[\alpha]_D$ + 27°; IR: 3480, 3070, 1640, 890 cm^{-1}; M^+ 426; the acetate prepared by Ac_2O-Py method had m.p. 276-78°, $[\alpha]_D$ + 20°; IR: 3070, 1725, 1640, 1250, 885 cm^{-1}; M^+ 468 was identified as moretenyl acetate by comparison of m.p., IR and TLC with an authentic sample.

Reduction of taraxerone to epi-taraxerol and taraxerol: A mixture of taraxerone (0.5 g) and KOH (2 g) in diethylene glycol (50 ml) was refluxed for 2 h as described above. The solid (0.45 g) obtained after usual workup was absorbed in a chromatogram (15 g) and the column on elution with benzene:petrol (1:4) yielded a solid (0.08 g). The solid on crystallisation from $CHCl_3$-MeOH furnished crystals m.p. 262-64°, $[\alpha]_D$ - 18°, IR: 3470, 810 cm^{-1}; M^+ 426; its acetate prepared by Ac_2O-Py method had m.p. 202-203°, $[\alpha]_D$ - 25°; IR: 1730, 1240, 820 cm^{-1}; M^+ 468 was identical in its m.p., TLC and IR with an authentic sample of epi-taraxeryl acetate. The chromatogram on further elution with benzene:petrol (3:2) yielded a solid (0.25 g) which on crystallisation from $CHCl_3$-MeOH furnished crystals of m.p. 278-79°, $[\alpha]_D$ + 3°, IR: 3460, 815 cm^{-1}. The solid on acetylation with Ac_2O-Py method formed acetate of m.p. 297-99°, $[\alpha]_D$ + 8°; IR: 1730, 1240, 820 cm^{-1}; M^+ 468 which was identical (m.m.p., co-IR and co-TLC) with an authentic specimen of taraxeryl acetate.

Conversion of β-amyrone to epi-β-amyrin and β-amyrin: A mixture of β-amyrone (0.5 g) and KOH (2 g) in diethylene glycol (50 ml) was refluxed as described above. The solid (0.45 g) obtained after usual work-up was chromatographed over silica gel (15 g). Elution of the column with benzene:petrol (1:4) gave a solid that was crystallised from MeOH. The crystals had m.p. 220-22°, $[\alpha]_D$ + 70°; IR: 3540, 820 cm^{-1}; M^+ 426; its acetate (Ac_2O-Py) had m.p. 125-26°, $[\alpha]_D$ + 55°; IR: 1730, 1240, 810 cm^{-1}; M^+ 468 was identified (m.m.p., co-IR, and co-TLC) with an authentic sample of epi-β-amyrin acetate). Further elution of the column with benzene:Petrol (2:3) furnished a solid (0.25 g) which was crystallised from $CHCl_3$-MeOH. The crystals had m.p. 197-98°, $[\alpha]_D$ + 80°; IR: 3500, 810 cm^{-1}; Ac_2O-Py

method of acetylation formed an acetate m.p. 237-38°, $[\alpha]_D$+ 79°; IR: 1730, 1240, 820 cm^{-1}; M^+ 468 which was identical (m.m.p., co-IR and co-TLC) with an authentic sample of β-amyrin acetate.

Reduction of lupenone to epi-lupeol and lupeol: A mixture of lupenone (0.5 g) and KOH (2 g) in diethylene glycol (50 ml) was refluxed for 2 h as described above. The product (0.45 g) obtained after usual manner was chromatographed over silica gel (15 g). Elution of the chromatogram with petrol furnished a solid (0.08 g) that was crystallised from MeOH to afford crystals m.p. 200-201°, $[\alpha]_D$ + 17°; IR: 3320, 3060, 1640, 880 cm^{-1}; the acetate prepared with Ac_2O-Py had m.p. 159-60°; $[\alpha]_D$ - 5°; IR: 3060, 1730, 1640, 1250, 880 cm^{-1} was identical (m.m.p., co-IR and co-TLC) with an authentic sample of epi-lupenyl acetate. Further elution with benzene:petrol (2:3) and crystallisation of the solid with $CHCl_3$-MeOH furnished a solid of m.p. 214-16°, $[\alpha]_D$ + 26°; IR: 3340, 1640, 890 cm^{-1} which on acetylation with Ac_2O-Py formed an acetate m.p. 215-17°; IR: 1730, 1640, 1240, 880 cm^{-1} that was identical (m.m.p., co-IR and co-TLC) with lupenyl acetate.

Reduction of glochidone to lupenone, epi-lupeol and lupeol: A mixture of glochidone (0.5 g) and KOH (2 g) in diethylene glycol (50 ml) was refluxed for 2 h as in the previous cases. The product(0.45 g) obtained after usual workup was absorbed in a column of silica gel (15 g). Elution of the chromatogram with petrol furnished a solid (0.04 g) that was crystallised from $CHCl_3$-MeOH to afford fine crystals of m.p. 168-69°; IR: 1700, 1640,880 cm^{-1}; UV: no absorption between 220 - 270 nm; M^+ 424 was identified as lupenone by comparison of m.p., IR and TLC with an authentic specimen. Further elution with petrol furnished solid (0.08 g) that was crystallised from MeOH to give crystals m.p. 199-200°; $[\alpha]_D$ + 18°; IR: 3320, 3060, 1640, 880 cm^{-1}; M^+ 426 was directly compared with an authentic sample of epi-lupeol and was found identical. Elution of the column with benzene:petrol (2:3) yielded a solid (0.20 g)that crystallised from $CHCl_3$-MeOH to afford crystals of m.p. 215-16°, $[\alpha]_D$ + 24°, IR: 3340, 1640, 890 cm^{-1}; the acetate prepared with Ac_2O -Py had m.p. 214-15°: IR 1730, 1640, 1240, 880 cm^{-1} was found identical (m.m.p., co-IR and co-TLC) with an authentic specimen of lupenyl acetate.

Reduction of benzophenone to benzhydrol: A mixture of benzophenone (0.5 g) and KOH (2 g) in diethylene glycol (50 ml) was refluxed for 2 h as in the previous cases. After usual workup the solid (0.45 g) was chromatographed over silica gel (15 g) and elution of the column with benzene:petrol (3:2) furnished solid that was crystallised from $CHCl_3$-MeOH to afford crystals of m.p. 67-68°, IR: 3350, 1605, 1280, 1050,1030, 940, 920, 860, 765, 750, 700 cm^{-1}; M^+ 168. It was found identical (m.m.p., co-IR and co-TLC) with an authentic sample of benzhydrol.

Acknowledgements:- We thank Dr. A. Duffield, Biomedical Mass Spectrometry Unit, The University of New South Wales, Australia for the mass spectra; the Director, CDRI Lucknow for the mass spectra and optical rotations; Dr. S. K. Sengupta, EIPW Calcutta also for the optical rotations, and the CSIR (New Delhi) and the University of North Bengal for financial support.

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