Reduction of Triterpenoid Ketones with Bornan-2-*exo*-yloxyaluminium Dichloride: a Convenient Preparation of Axial Triterpene Alcohols

By **Dhanonjoy Nasipuri** * and **Pranab R. Mukherjee**, Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India
Satyesh C. Pakrashi, Supreeti Datta, and **Partha P. Ghosh-Dastidar,** Indian Institute of Experimental Medicine, Calcutta 700 032, India

Reduction of 3-oxo-triterpenoids with bornan-2-*exo*-yloxyaluminium dichloride furnishes axial (3α-) alcohols as the major products (75—100%), which are easily separable from the reaction mixtures. Reduction with sodium borohydride gives mainly the 3β-alcohols (85—95%).

BORNAN-2-*exo*-YLOXYALUMINIUM DICHLORIDE (I) reduces cyclohexanone derivatives to axial alcohols with high stereoselectivity (80—98%).[1] The reagent is easy to prepare and the procedure is relatively simple.[2] The major problem attending its use is to isolate the products from the reaction mixture. If, however, the cyclohexanone system forms part of a big molecule like a triterpene or a steroid, the purification can be readily achieved by taking advantage of the volatility of the camphoraceous impurities in steam. We report here the reduction of some 3-oxo-triterpenoids (and 3-oxo-steroids) with this reagent and the isolation of the pure axial alcohols, thus providing a simple route to triterpene 3α-alcohols.

Seven triterpenoid ketones, *viz.* β-amyrone, lupenone, arborinone, methyl ursonate, methyl oleanonate, and betulonic acid lactone, [all having the common structural feature (II) for rings A and B] and friedelin [part structure (III)], and two steroidal ketones, *viz.* cholestan-3-one (now re-investigated) and 2,2-dimethylcholestan-3-one, have been studied. Reductions with the reagent (I) in large excess were carried out in ether–tetrahydrofuran at room temperature. The epimeric alcohols were quantitatively separated by column chromatography and identified by their physical properties. The results are shown in the Table, along with some data from the literature for comparison. (−)-*p*-Menthan-3-one was also reduced with this reagent and the proportions of *p*-menthan-3-ols were determined by g.l.c.

As expected, the axial alcohols predominated to the extent of 75—100% in these reductions, and often a single crystallisation of the epimeric mixture afforded the pure 3α-alcohol. In the case of friedelin (III), axial approach is severely hindered by a *syn*-axial methyl interaction, and the axial alcohol (in this case 3β) was the sole product (Table, entry 7). The equatorial isopropyl group in *p*-menthan-3-one (IV) also impedes attack from the axial side,[3,4] thereby increasing the percentage of axial alcohol (Table, entry 10) significantly. For the rest of the ketones, the percentage of axial alcohol was 80 ± 5, a value slightly lower than that in

Relative percentages of axial and equatorial alcohols from ketone reductions

		Reduction with			
		Reagent (I)			Sodium borohydride
No.	Ketone	Yield [a] (%)	Axial (%)	Equatorial (%)	Equatorial (%)
1	β-Amyrone	93	75	25	95
2	Lupenone	97	84	16	89
3	Arborinone	88 [b]	85	15	92
4	Methyl ursonate	97	79	21	94
5	Methyl oleanonate	90 [c]	80	20	90
6	Betulonic acid lactone	71 [b]	83	17	95
7	Friedelin	90 [c]	100	0	15
8	Cholestan-3-one	99	85	15	76, 85 [d]
9	2,2-Dimethylcholestan-3-one	95	75	25	95
10	(−)-*p*-Menthan-3-one	100	95	5	49 [e]
11	4-t-Butylcyclohexanone	100	90 [f]	10	83.5 [g]
12	3,3,5-Trimethylcyclohexanone	100	98 [f]	2	14 [g]

[a] Yields based on material isolated and refer to reduction with the reagent (I); reduction by $NaBH_4$ is almost quantitative. [b] Some waxy materials are isolated. [c] Some unchanged ketone survived. [d] W. G. Dauben, R. A. Micheli, and J. F. Eastman, *J. Amer. Chem. Soc.*, 1952, **74**, 3852; O. H. Wheeler and J. L. Mateos, *Chem. and Ind.*, 1957, 395. [e] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579. [f] Ref. 1. [g] P. T. Lansbury and R. E. Macleay, *J. Org. Chem.*, 1963, **28**, 1940.

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[2] For other methods of preparation of axial alcohols, see Y. M. Y. Haddad, H. B. Henbest, J. Husbands, and T. R. S. Mitchell, *Proc. Chem. Soc.*, 1964, 361; H. C. Brown and D. B. Bigley, *J. Amer. Chem. Soc.*, 1961, **83**, 3166.
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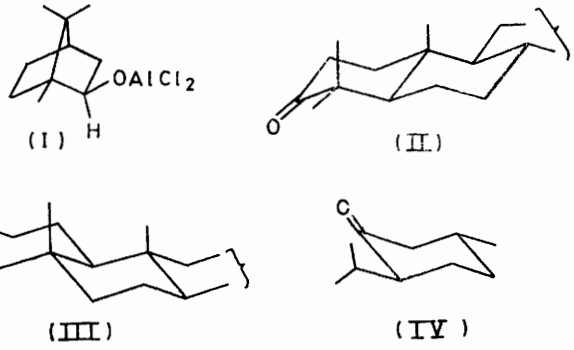
the reduction of 4-t-butylcyclohexanone (90%) (Table, entry 11).

The reduction of some of the above ketones with sodium borohydride has been reported, but the literature is often noncommittal regarding the relative percentages of epimeric alcohols. In the last column of the



(I) (II) (III) (IV)

Table we report the results of reduction of these ketones with sodium borohydride in ethanol at 0 °C. The data are in good agreement with those reported for similar systems,[5] the equatorial alcohol always predominating except in the case of friedelin, which is a hindered ketone. The six triterpenoid ketones and 2,2-dimethylcholestan-3-one, all having an adjacent *gem*-dimethyl group (Table, entries 1—6 and 9) gave a slightly higher percentage of equatorial alcohol than the ketones without such a group (Table, entries 8 and 11). This may be attributed to the steric resistance of the nearby axial methyl group to equatorial approach.[6]

EXPERIMENTAL

Specific rotations were taken for solutions in chloroform with a Hilger-Watts M-511 micro-optic photoelectric polarimeter. T.l.c. was performed on silica gel G (0.2 mm thick). (±)-Bornan-2-*exo*-ol was obtained from Aldrich Chemical Co. Light petroleum refers to the fraction of b.p. 40—60°.

Sources of the Ketones.—Most of the ketones used in the present experiments were obtained from the corresponding alcohols isolated from natural sources.[7] β-Amyrin (olean-12-en-3β-ol) was obtained from the leaves of *Enhydra fluctuans*, oleanolic acid (3β-hydroxyolean-12-en-28-oic acid) from the leaves of *Diospyros montana*, 3α- and 3β-arborinol (3-hydroxy-13β,14α-dimethyl-$\Delta^{9(11)}$-8-nor-pentacyclic triterpenes)[8] from the leaves of *Glycosmis arborea*, lupeol [lup-20(29)-en-3β-ol] and ursolic acid (3β-hydroxyurs-12-en-28-oic acid) from *Carissa carendas*, and betulinic acid [3β-hydroxylup-20(29)-en-28-oic acid] and friedelin from *Alangium lamarckii*. The oxidation of the alcohols was carried out with chromic acid according to a standard procedure.[9] 2,2-Dimethylcholestan-3-one was obtained through the courtesy of Dr. J. Husbands, Wroclaw, Poland.

*Reduction of the Ketones with Bornan-*2-exo-*yloxyaluminium Dichloride* (I).—A typical procedure is described for the reduction of β-amyrone. To an ice-cold solution of anhydrous aluminium chloride (0.44 g, 3.3 mmol) in ether (4 ml) was added ethereal 1.1M-lithium aluminium hydride (1 ml) and the mixture was stirred for 30 min. A solution of (±)-bornan-2-*exo*-ol (0.68 g, 4.4 mmol) in ether (5 ml) was added slowly. The vessel was then taken out of the ice-bath and a solution of β-amyrone (100 mg, 2.4 mmol) in ether–tetrahydrofuran was added during 10 min. The mixture was stirred for 6 h and then left at room temperature overnight. It was decomposed with cold 4N-sulphuric acid. The ethereal layer was separated, the aqueous solution was once extracted with ether, and the combined extract was washed with water, dried (K_2CO_3), and evaporated. The residue was distilled in steam until all camphoraceous matter had been removed. The crystals remaining were chromatographed on a column of neutral alumina (or silica gel). Elution with petroleum gave nothing (in some cases, it afforded some waxy material, see Table). Elution with benzene–petroleum (1 : 1) furnished 3α-hydroxyolean-12-ene (70 mg), m.p. 224—225°, $[\alpha]_D$ +71.5° (*c* 0.45) (lit.,[10] m.p. 225°, $[\alpha]_D$ +73.3°). The polarity of the solvent was gradually increased to give 3β-hydroxyolean-12-ene (23 mg), m.p. 196—198°, $[\alpha]_D$ +88.5° (*c* 0.56) (lit.,[11] m.p. 197—197.5°, $[\alpha]_D$ +88.4°). Fractions were monitored by t.l.c.

The remaining ketones were reduced by more or less the same procedure. Each alcohol of an epimeric pair was separated either on alumina or silica gel (column) and characterised by m.p., specific rotation, and i.r. spectrum. Most of the triterpenoid alcohols are known (see refs. 8 and 12—14), except 3α,19β-*dihydroxyolean*-28-*oic acid lactone* (epibetulinic acid lactone), obtained by reduction of betulonic acid lactone; m.p. 304—306° (Found: C, 78.6; H, 10.6. $C_{30}H_{48}O_3$ requires C, 78.9; H, 10.5%); $[\alpha]_D$ +45.0° (*c* 0.6).

2,2-Dimethylcholestan-3-one had m.p. 98—100° (lit.,[15] 111—113°) and was reduced to 3α-*hydroxy*-2,2-*dimethylcholestane*, m.p. 87° (Found: C, 83.4; H, 12.7. $C_{29}H_{52}O$ requires C, 83.65; H, 12.5%), $[\alpha]_D$ +40.5° (*c* 0.55), and 3β-hydroxy-2,2-dimethylcholestane, m.p. 147°, $[\alpha]_D$ +28.1° (*c* 0.49) (lit.,[15] m.p. 116—118°, $[\alpha]_D$ +31.0°). The big discrepancy in the m.p. of the last-named compound is possibly due to impurity in the previously reported sample.

Most of the reductions were repeated twice or thrice, sometimes reversing the order of addition of anhydrous

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aluminium chloride (see reduction of *p*-menthan-3-one).[16] The results were well reproducible.

Friedelin and methyl oleanonate were slow to be reduced. A sample of friedelin (500 mg) on reduction afforded a mixture which showed a single spot on t.l.c. However when converted into the acetate by heating with acetic anhydride and pyridine, the product exhibited two spots, one due to unchanged friedelin. It was chromatographed over silica gel and a single acetate (460 mg) was obtained which on hydrolysis gave pure friedelan-3β-ol.

Reduction of (—)-p-*Menthan-3-one*.—A solution of bornan-2-*exo*-ol (1.85 g) in ether (10 ml) was added to ethereal 0.6M-lithium aluminium hydride (5 ml), followed by a solution of (—)-*p*-menthan-3-one (460 mg). A sample taken at this moment showed no trace of *p*-menthan-3-ol. To this solution was then added dropwise a solution of anhydrous aluminium chloride (1.6 g) in ether (15 ml). The mixture was stirred for 6 h and left overnight at room temperature. The product, obtained as usual, was analysed by g.l.c. on a Carbowax 20M column ($6\frac{1}{2}$ ft × $\frac{1}{4}$ in). It showed *ca.* 95% of axial and less than 5% of equatorial alcohol.

Reduction of the Ketones with Sodium Borohydride.—In a typical experiment, β-amyrone (67 mg, 0.158 mmol) was dissolved in dry ethanol (30 ml) to which sodium borohydride (65 mg, 1.75 mmol) was added in small portions in the cold with stirring. The mixture was left in an ice-bath overnight. Ethanol was partially removed at the water-pump, the residue was diluted with water, and the organic matter was thoroughly extracted with ether. Evaporation of the extract gave a mixture of epimeric alcohols (t.l.c.). This was separated by column chromatography as before to furnish 3α-hydroxyolean-12-ene (3 mg), m.p. 223—224°, and 3β-hydroxyolean-12-ene (62 mg), m.p. 196—198°.

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