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Four Isomeric α-Hydroxybornanones

SVANTE THORÉN*

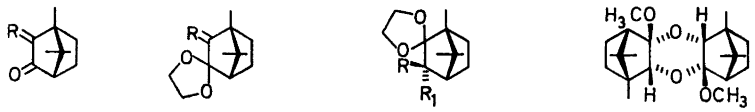
Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm 70, Sweden

Four optically active α-ketols with the bornane skeleton and the corresponding acetates have been prepared in order to study their ORD and CD behaviour.

For investigations of the chemistry of 3-bornanone (*1a*) various methods for the synthesis of this ketone were studied. During this work the 2-hydroxy-3-bornanones as well as the 3-hydroxycamphors were prepared in order to compare their ORD- and CD-curves. Recently a new synthesis of 3-bornanone [1] and the synthesis of the hitherto unknown 2-exohydroxy-3-bornanone (*9a*; see Fig. 2)[1,2] have been described in two independent investigations. Attempts to accomplish exchange dioxolanations between camphorquinone (*1b*) and the ethylene acetals of diisopropyl ketone and methylethyl ketone failed, but ethylene glycol reacted with camphorquinone to form the 3-ethylenedioxy derivative *2a* together with a small amount of the 2,3-diacetal *2b*. The structure of *2a* follows from its reduction to 3-bornanone (*1a*) according to a modified Wolff-Kishner reaction [3] and is in accord with its spectral properties. The yield of the 2,3-diacetal *2b* could be increased to about 20 % by using excess ethylene glycol and prolonged reaction time. Carefully conducted hydrolysis of the diacetal gave the crystalline ketodioxolane *3a*, which on reduction with lithium aluminium hydride afforded the alcohol *3b* whose NMR spectrum showed that the proton at C_3 is endo-oriented. (Sharp singlet at 3.42 ppm; *cf.* Ref. 4.) Hydrolysis of *3b* gave 3-exohydroxybornan-2-one (*7a*), purified *via* the semicarbazone [5] and obviously identical with the ketol described by Rupe and Müller.[5] The two α-endohydroxyketones *8a* and *10a* were prepared by reduction of camphorquinone.[6] The latter ketol was obtained *via* the bimolecular acetal *4*, and *8a* from the mother liquors of *4*. The NMR spectrum of *4* showed a broad singlet at 3.39 ppm, which indicates two exo protons in the C_2 positions, and thus two possible configurations of *4*, *4a* and *4b*. For steric reasons the latter is improbable. (Distorted dioxan ring, strong interactions between the methoxyl groups.) The configuration should therefore be that

* Present address: Division of Organic Chemistry, The Lund Institute of Technology, Chemical Centre, Box 740, S-220 07 Lund 7, Sweden.

of *4a*. Reduction of 2-endohydroxybornan-3-one (*10a*) with sodium amalgam [8] gave 3-bornanone and camphor (3:1 as shown by GLC). It has been suggested [9] that the camphor owes its formation to the alkali-catalyzed isomerization of *10a* to *8a*. However, it was found that the reduction of the acetate of *10a* (*10b*) with sodium amalgam gives almost pure 3-bornanone (*1a*).

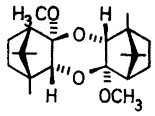


1a R=H_2 1b R=O

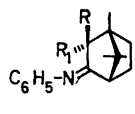
2a R=O b R=-O-CH_2-CH_2-O- c R=H_2

3a RR_1=O b R=OH; R_1=H

4a



4b



5a RR_1=O b R=OH; R_1=H

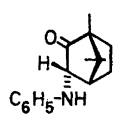


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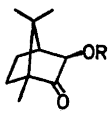
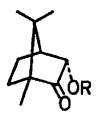
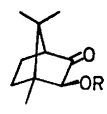
Fig. 1.



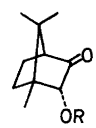
7a R=H b R=$COCH_3$



8a R=H b R=$COCH_3$



9a R=H b R=$COCH_3$



10a R=H b R=$COCH_3$

Fig. 2.

When 2-endohydroxybornan-3-one (*10a*) is reduced with sodium amalgam, and carbon dioxide is simultaneously passed through the solution, 2-endo-3-exobornanediol is obtained as the main product (*cf.* Refs. 9—11). In connection with this work it was of some interest to investigate the anilino compound *6*, which can be prepared from the corresponding Schiff's base by reduction with zinc and alkali.[12] The anilino group occupies the endo position as shown by the fact that the C_3 proton gives rise to a broad doublet at 4.08 ppm. (J = 5 Hz; *cf.* Ref. 4). On reduction with sodium borohydride the above Schiff's base gave the alcohol *5b* as shown by its IR and NMR spectra. Hydrolysis of *5b* furnished 2-exohydroxybornan-3-one (*9a*). The characteristic features of

Table 1. NMR spectra [a] of the ketols *7a—10a* and their acetates.

Compound	$CDCl_3$ $\delta_{C_3 \text{ or } C_5}$	$CDCl_3$ δ_{OH}	$CDCl_3$+TFA $\delta_{C_3 \text{ or } C_5}$
7a	3.72 s	3.09	3.87 s
8a	4.28 d $J=5$ Hz	3.37	4.32 d $J=5$ Hz
9a	3.58 s	3.23	3.77 s
10a	3.87 s,b	3.25	3.92 s,b
7b	4.76 s	—	—
8b	5.26 d $J=5$ Hz	—	—
9b	4.95 s	—	—
10b	5.26 s,b	—	—

[a] Shifts are given in ppm downfield from the TMS signal; s=singlet; d=doublet; b=broadened; TFA=trifluoroacetic acid.

the NMR spectra of the four ketols *7a—10a* and their acetylation products *7b—10b* are given in Table 1.

The measurements of the ORD and CD curves were kindly performed by Professor W. Klyne and his group and the results will be discussed together with these authors in a forthcoming publication.

EXPERIMENTAL

Melting points are uncorrected. IR: oils neat, solids in KBr. The rotations were taken in chloroform (*c* 1.5 unless otherwise stated). NMR spectra were recorded on a Varian A-60 instrument in $CDCl_3$ with TMS as internal standard. The chemical shifts are given in δ-units.

3-Ethylenedioxybornan-2-one (2a). (+)Camphorquinone [13] (*1b*) (40 g), ethylene glycol (20 ml), and *p*-toluenesulphonic acid (1 g) were refluxed in benzene (600 ml) for 24 h with a Dean-Stark apparatus. The reaction mixture was dried over Na_2CO_3, filtered and the solvent evaporated. The residue (44.2 g) was distilled to give a yellow oil, b.p.$_{13}$ 113—120°, which crystallized (39.6 g). Recrystallization from light petroleum gave the 2-keto-3-acetal *2a*. The analytical sample was obtained by sublimation *in vacuo*. M.p. 81—83° (lit. 81.5—82°[1]; 88°[2]); $[\alpha]_D^{25}+66.4°$. IR ν_{max} 1755 cm^{-1}. NMR δ: 4.25 (4H, multiplet, O—CH_2—CH_2—O). (Found: C 68.5; H 8.6. $C_{12}H_{18}O_3$ requires C 68.5; H 8.6).

2,3-Bisethylenedioxybornane (2b). The residue from the above distillation (4.6 g) was crystallized from light petroleum (Norite) to give white needles of the di-acetal *2b*. The analytical sample was obtained by sublimation *in vacuo*. M.p. 61.5—62.5° (lit.[1] 55.5—56°); $[\alpha]_D^{25}$ —3.7°. The IR spectrum showed no absorption in the carbonyl region. NMR δ: 3.90 (8H, multiplet, O—CH_2—CH_2—O). (Found: C 66.0; H 8.7. $C_{14}H_{22}O_4$ requires C 66.1; H 8.7).

3-Ethylenedioxybornane (2c). The 2-keto-3-acetal *2a* (4 g) in triethylene glycol was reduced with N_2H_4 (40 g), $N_2H_4 \cdot 2HCl$ (16 g), and KOH (24 g) as described in Ref. 3. The distillate and the residue were combined, poured into water (3 l) and extracted with light petroleum (3 × 500 ml). The organic phase was shaken twice with water, 1 M H_2SO_4 and then with water again, dried over Na_2SO_4, filtered and evaporated. The residue, a colourless oil (2.6 g; 69 %) was essentially pure *2c* (GLC) and did not give any carbonyl absorption in IR. NMR δ: 3.85 (4H, multiplet, O—CH_2—CH_2—O). The analytical sample was distilled and had b.p.$_{13}$ 101—103°; $[\alpha]_D^{20}$ +17.8° (*c* 4.35; methanol); n_D^{27}= 1.4739. (Found: C 73.4; H 10.3. $C_{12}H_{20}O_2$ requires C 73.4; H 10.3). When *2a* contaminated with camphorquinone was used, small amounts of *bornane* were obtained in the forerun.

B.p.$_{18}$ 35°; m.p. 154–156° (sealed tube) (lit.[14] 156.5°); $[\alpha]_D$ ±0°. NMR δ: 0.83 (9H, singlet, CH_3), 1.00–1.85 (9H, multiplet). MS: m/e=138 (M^+) ($C_{10}H_{18}$).

3-Bornanone (1a). The acetal *2c* (21 g) was hydrolyzed in 2 M HCl (10 ml), H_2O (40 ml) and CH_3OH (30 ml) under reflux for 1 h. The reaction mixture was steam distilled and the distillate saturated with NaCl and extracted with ether. The ether solution gave 3-bornanone (*1a*) (15.5 g; 95 %), m.p. 175° (sealed tube) (lit.[8,1] 182°, 179–180°). The product was GLC-pure and identical (NMR, IR) with an authentic sample. $[\alpha]_D^{25}$ −34.3° (*c* 1.53; methanol) [lit.[9] $[\alpha]_D$ −40.3° (*c* 2.56; methanol)].

2-Ethylenedioxybornan-3-one (3a). The diacetal *2b* (2.0 g) was heated in 2 M HCl (8 ml) and CH_3OH (60 ml) on a water bath. The hydrolysis could conveniently be followed by TLC (SiO_2). As soon as the mixture had turned faintly yellow (after about 1 h) the reaction mixture was poured into a saturated NaCl-solution and the mixture was extracted with ether-light petroleum. After drying over sodium sulphate, the solution was concentrated and the residue recrystallized from light petroleum to give the 3-keto-2-acetal *3a* (1.1 g; 66.6 %) m.p. 39–40°. An analytical sample was obtained by sublimation *in vacuo* and had m.p. 40.5–42.5°; (lit.[1] m.p. 41.5–42°); $[\alpha]_D^{25}$ −65.6°; IR ν_{max} 1760 cm^{-1}. NMR δ: 4.10 (4H, multiplet, O–CH_2–CH_2–O). (Found: C 68.6; H 8.6. $C_{12}H_{18}O_3$ requires C 68.5; H 8.6).

3-Exohydroxy-2-ethylenedioxybornane (3b). The 3-keto-2-acetal *3a* (1 g) was treated with $LiAlH_4$ (0.10 g) in dry ether for 30 min. The excess $LiAlH_4$ was then decomposed with $Na_2SO_4 \cdot 10H_2O$, the organic phase was filtered and evaporated, and the residue distilled *in vacuo* to afford hydroxyacetal *3b* (0.65 g; 64 %). The analytical sample was obtained by sublimation *in vacuo* and had m.p. 37.5–39°; $[\alpha]_D^{25}$ −28.7°. (Found: C 67.9; H 9.4. $C_{12}H_{20}O_3$ requires C 67.9; H 9.4). IR ν_{max}: 3470 (broad, OH), 1120, 1085, 1035, 1012, 1005 (C–O) cm^{-1}. NMR δ: 3.42 (1H, singlet, C_3 endo); (the corresponding exo-proton is expected to give rise to a broadened doublet with J=*ca.* 5 Hz [4]); 2.46 (OH, singlet), 3.87 (4H, multiplet, O–CH_2–CH_2–O). The presence of the endohydroxy isomer could not be detected by NMR.

3-Exohydroxybornan-2-one (7a). The hydroxyacetal *3b* (530 mg) was refluxed with 2 M HCl in CH_3OH for 30 min. The reaction mixture was diluted with water and extracted with ether. After drying and evaporation a residue was obtained which was crystallized from light petroleum; the crystals were sublimed *in vacuo*. The resulting *exoketol 7a* (309 mg; 67 %), which was contaminated with the *endo isomer*, had $[\alpha]_D^{25}$ +107° (*c* 8.7; benzene), $[\alpha]_D^{25}$ +97.5° (*c* 1.2; $CHCl_3$) [lit.[5] $[\alpha]_D$ +115.8° (*c* 10; benzene)]. The ketol could be further purified *via* its semicarbazone,[5] m.p. 205–208° (lit.[5] 199–201°), which after hydrolysis with oxalic acid gave what was apparently the optically pure exohydroxy-ketone $[\alpha]_D^{25}$ +131° (*c* 10; benzene), $[\alpha]_D^{25}$ +100.7° (*c* 0.3; $CHCl_3$), m.p. 226–229° (sealed tube) (lit.[5] m.p. 210–211°). IR ν_{max}: 3440 (broad, OH), 1750 (C=O), 1124, 1108, 1076, 1016, 1003 cm^{-1}. NMR data *cf.* Table 1.

The *acetate (7b)* had m.p. 47.5–49°. (Found: C 68.7; H 8.6. $C_{12}H_{18}O_3$ requires C 68.5; H 8.6). $[\alpha]_D^{25}$ +70.0° (*c* 1.1). IR ν_{max}: 1765–1755 (broad, ester and ketone carbonyl), 1378 (CH_3COO–), 1235 (ester band), 1022 cm^{-1}. NMR data *cf.* Table 1. The bisacetal *4* was prepared (*cf.* Ref. 6) and had m.p. 149–50° and $[\alpha]_D^{25}$ +171° (lit.[6] 149–150°, and +172°, respectively). NMR shows that the proton at C_2 is in the exo position (broad singlet at 3.39).[4,7]

2-Endohydroxybornan-3-one (10a). Hydrolysis of *4* with concentrated HCl afforded *10a* which after crystallization from light petroleum and sublimation *in vacuo* had m.p. 219–220° (sealed tube), $[\alpha]_D^{25}$ +11.9° [lit.[6,2] m.p. 211°, 221°; $[\alpha]_D^{20}$ +9.05° (*c* 10; EtOH);[15] $[\alpha]_D^{25}$ +10.2° (*c* 2.1; EtOH)[2]]. IR ν_{max}: 3420 (broad, OH), 1750 (C=O), 1086, 1060, 1007 cm^{-1}. NMR data *cf.* Table 1.

The *acetate (10b)* had m.p. 60–61° (lit.[15] m.p. 61–62°); $[\alpha]_D^{25}$ +57.2°. IR ν_{max} 1752, 1740 (C=O), 1366 (CH_3COO–), 1228, 1058 (C–O) cm^{-1}. NMR data *cf.* Table 1.

3-Endohydroxybornan-2-one (8a). The mother liquor from the preparation of *4* was diluted with ether, the ether phase was neutralized by shaking with a 10 % Na_2CO_3 solution, dried and the ether evaporated. The residue was crystallized from light petroleum leaving a ketol, m.p. 192–197° (lit.[9,15] 192–195°, 197–198°), which was repeatedly crystallized from light petroleum to give pure 3-endohydroxybornan-2-one (*8a*), $[\alpha]_D^{25}$ −11.9° [lit.[15] $[\alpha]_D^{13}$ +17.3° (*c* 5; EtOH)]. IR ν_{max}: 3430 (broad, OH), 1750 (C=O), 1105, 1080, 1038, 1000 cm^{-1}. The proton at C_3 occupies the exo position as indicated by the NMR data given in Table 1.

The *acetate (8b)* had m.p. 57–58° (lit.[15] 61–62°); $[\alpha]_D^{25}$ +25.2° (*c* 1.1). IR ν_{max}: 1745 (ester and ketone C=O), 1370 (CH_3COO-), 1235 (ester band), 1015 (C–O) cm^{-1}. NMR data *cf.* Table 1.

Reductions of 10a and 10b. (i) The ketol *10a* (2 g) was reduced with Na-amalgam (2 %; 100 g) in H_2O as reported in the literature.[8] After steam distillation a mixture (1.5 g) of 3-bornanone (*1a*) and camphor in a ratio of 3:1 was obtained. (ii) The reaction above was repeated with simultaneous bubbling of carbon dioxide through the reaction mixture. Steam distillation afforded *1a* in low yield. The residue, however, gave large amounts of a compound identified as a diol. M.p., optical rotation, and NMR (in pyridine-D_2O) data[9–11] confirm the 2-endo-3-exobornanediol structure. (iii) The keto ester *10b* (15 g) was shaken with Na-amalgam (14 g Na/500 g Hg) and water for 3 h. After standing over night the reaction mixture was worked up and afforded almost pure 3-bornanone (*1a*) (9.8 g; 90 %). M.p. 181–183°, $[\alpha]_D^{25}$ −51.1° (*c* 10; benzene) [lit.[9] $[\alpha]_D$ −57.4° (*c* 0.9; benzene)].

2-Exohydroxy-3-(N-phenylimino)bornane (5b). When the Schiff's base (*5a*), obtained from camphorquinone and aniline,[12] (2 g) was reduced with $NaBH_4$ (0.5 g) in methanol-water a vigorous reaction took place. As soon as the reaction mixture had become colourless (5 min) it was poured into a water-acetic acid mixture and extracted with ether. The organic phase was washed with dilute bicarbonate, water, and dried over Na_2SO_4. Evaporation gave a residue (1.73 g) that was crystallized twice from hexane-benzene to give the imino alcohol *5b* (0.62 g), m.p. 136–138°. The product was sublimed *in vacuo* to yield crystals, m.p. 139–140°. (Found: C 79.0; H 8.6; N 5.7. $C_{16}H_{21}NO$ requires C 79.0; H 8.7; N 5.8). $[\alpha]_D^{25}$ +129° (*c* 1.65). IR: No absorption due to carbonyl. ν_{max}: 1690, 1680 (C=N), 1600, 1588, 1495 (aromat), 1105 (C–O) cm^{-1}. NMR δ: 4.44 (1H, C_2endo; broadened doublet, $J=3$ Hz which collapses to a sharp singlet at δ 4.34 on addition of TFA), 3.92 (OH, broadened doublet), 2.44 (1H, C_4, multiplet, appears as a broad doublet at δ 2.79 with $J=4.5$ Hz on addition of TFA).

Reduction of *5a* with zinc in alkali afforded *3-anilinobornan-2-one (6)* as reported in the literature.[12] M.p. 76–79°; $[\alpha]_D^{25}$ +119° (lit.[12] m.p. 80°; $[\alpha]_D$ +127°). NMR δ: 4.08 (1H, broadened doublet, $J=5$ Hz. $CDCl_3$ solution with TFA present; C_3 proton in exo position).

2-Exohydroxybornan-3-one (9a). The imino alcohol *5b* (0.84 g) in 15 ml 2 M HCl was maintained at room temp. for 24 h and then the reaction mixture was diluted with water and repeatedly extracted with ether. The organic phase was washed with water, dried and evaporated, and the residue sublimed *in vacuo* in a tube with gradient heating to give ketol *9a* (0.17 g) m.p. 204–205° (sealed tube) (lit.[1,2] 206–207°; 228–230°); $[\alpha]_D^{25}$ −129.5° (*c* 1.6). IR ν_{max}: 3440 (broad, OH), 1745 (C=O), 1100 (C–O) cm^{-1}. NMR data *cf.* Table 1. (Found: C 71.5; H 9.6. $C_{10}H_{16}O_2$ requires C 71.4; H 9.6).

The *acetate (9b).* The pure (GLC) non-crystalline compound had $[\alpha]_D^{25}$ −148.8°. IR ν_{max}: 1755, 1745 (ketone and ester carbonyls), 1360 (CH_3COO-), 1235 (broad, ester band), 1080 (C–O) cm^{-1}. NMR data *cf.* Table 1. (Found: C 68.4; H 8.7. $C_{12}H_{18}O_3$ requires C 68.5; H 8.6).

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