Four Isomeric 7-Isopropyloctahydro-4*H*-inden-4-ones

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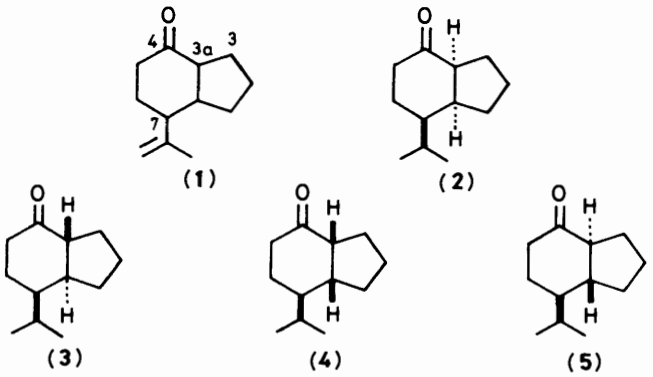
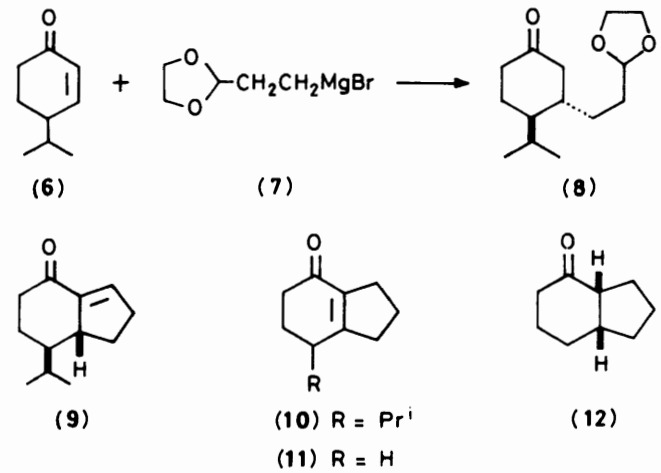
The four isomeric 7-isopropyl-4-hydrindanones (**2**)—(**5**) have been prepared and their configurations assigned, using arguments based on the results of equilibration of the two pairs of ketones and on the products formed on hydrogenation of enone precursors. Base-catalysed equilibration at *ca.* 22 °C indicates that for (**3**) $\rightleftharpoons$ (**2**), $-\Delta G \geqslant 4.5$ kcal mol^{-1} and for (**5**) $\rightleftharpoons$ (**4**), $-\Delta G$ *ca.* 0.1 kcal mol^{-1}. Possible diagnostic features in the ^{1}H n.m.r. spectra of (**2**)—(**5**) are discussed briefly.

In the course of a photochemical investigation we encountered a ketone that appeared to be one of the isomers of the 7-isopropenyl-4-hydrindanone (**1**), as we have reported elsewhere.[1] Rigorous assignment of structure and stereochemistry to this compound was possible through reduction of the side-chain double bond and correlation of the isopropyl ketone with synthetic material. Our studies led eventually to assignments for all four racemates (**2**)—(**5**) and for two of the related isopropenyl compounds, and to estimates of the free-energy difference for the equilibrium pairs (**2**)—(**3**) and (**4**)—(**5**). Determination of stereochemistry in hydrindanes has a long



history of difficulties,[2] and our results supplement the rather meagre information available for compounds of this sort.[3]

Preparation of these compounds began with 4-isopropylcyclohex-2-enone (**6**),[4] which underwent conjugate addition of the Grignard reagent (**7**)[5] in the presence of cuprous bromide–dimethyl sulphide complex to furnish (**8**). There are good



precedents for steric control in such reactions of 4-alkylcyclohexenones[6] and related systems,[7] and since only a single isomer is obtained here, assignment of the indicated *trans* stereochemistry to (**8**) is straightforward. Treatment of (**8**) with aqueous acid then furnished the expected[5] bicyclic ketone (**9**), which was smoothly isomerized to (**10**) on exposure to rhodium(III) chloride in refluxing ethanol.[8]

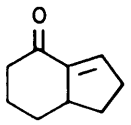
Hydrogenation of (**10**) in ethyl acetate over palladium-on-carbon gave a mixture of two hydrindanones that were assigned structures (**2**) and (**4**) [(**2**):(**4**) ~ 14:86] for the following reasons. The hydrogenation of the parent unsaturated ketone (**11**) under comparable conditions yields only the *cis*-fused product (**12**).[9] From extensive studies of solvent effects on the stereochemistry of hydrogenation of other types of 4-substituted cyclohexanones,[10] one would expect that, in ethyl acetate, approach of hydrogen to (**10**) should favour formation of (**4**) rather than (**2**). Corroborative evidence for this conclusion came from hydrogenation of (**10**) in hexane as solvent. Previous experience[10] suggests that in hexane approach to the double bond should occur primarily from the side opposite that of the isopropyl group, and indeed in this case (**2**) was the only product obtained. Influence of solvent polarity on the stereochemistry of reduction of (**10**) is then clearly established, and the selectivity in this case is actually greater than that typically observed.

These stereochemical assignments are in good accord with the results of base-catalysed equilibration of both (**3**) and (**5**), the origins of which will be described below. Treatment of (**5**) with ethanolic sodium ethoxide at room temperature gave an equilibrium mixture of (**4**) and (**5**) with the ratio (**4**):(**5**) ~ 55:45. This corresponds to a free-energy difference of only ~0.1 kcal mol^{-1} favouring the *cis* isomer, in comparison with ~0.65 kcal mol^{-1} favouring the parent (**12**) over its *trans* isomer.[11] The major effect of the isopropyl group is probably to present in both *cis* and *trans* isomers unavoidable steric interactions with the hydrogens of the adjacent cyclopentane methylene group. Similar base-catalysed equilibration of (**3**) gave an equilibrium mixture consisting entirely of (**2**) within our limit of detection ($\leqslant 0.05\%$). At equilibrium then the ratio (**2**):(**3**) is $\geqslant 99.95:0.05$, implying a free-energy difference $\geqslant 4.5$ kcal mol^{-1}. Since (**3**) necessarily has either an axial isopropyl group or a non-chair six-membered ring, its instability relative to (**2**) is understandable. It is noteworthy that the observed $\geqslant 4.5$ kcal mol^{-1} energy difference is ~1.7 kcal mol^{-1} or more greater than the sum of the conformational energy of the isopropyl group (~2.1 kcal mol^{-1})[12] and the energy difference between the parent ketone (**12**) and its *trans* isomer (~0.65 kcal mol^{-1}).[11]

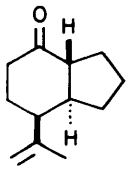
With the structures of (**2**)—(**5**) firmly established, it is instructive to examine the course of several other reductions in this series. Catalytic hydrogenation of (**9**) in ethyl acetate over palladium-on-carbon gave a small amount of (**10**) together with

a mixture (~55:45) of (**4**) and (**5**), suggesting that addition of hydrogen to (**9**) occurs about equally from each side of the molecule. The formation of *trans*-fused (**5**) from (**9**) is contrary to the behaviour of (**13**) which yields only (**12**) under similar conditions.[13]

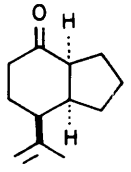
Direct hydrogenation of the photochemically derived isopropenyl ketone[1] in benzene containing tris(triphenylphosphine)rhodium(I) chloride (TTRC)[14] gave a mixture (3:2) of (**2**) and (**3**). Since (**3**) is easily converted into (**2**) on



(**13**)



(**14**)



(**15**)

enolization, it is likely that (**2**) arises in this reaction as a secondary product. If this is correct, then the photoproduct is (**14**) with the stereochemistry of (**3**). In confirmation of this conclusion, the photoproduct could be epimerized completely to (**15**) by ethoxide in ethanol, and then hydrogenation of (**15**) using TTRC in ethyl acetate yielded (**2**) as the sole product. If reduction of (**15**) was carried out over palladium-on-carbon, a mixture (3:2) of (**2**) and (**4**) was formed, indicating considerable allylic isomerization[15] in reduction of the isopropenyl group under these conditions. More extensive loss of stereochemistry at the allylic centre occurs on hydrogenation of (**14**) over palladium-on-carbon; here the product is a mixture (58:42) of (**5**) and (**3**).

Because of the problems in deducing stereochemistry in hydrindanones there is natural interest in identifying spectroscopic features of these compounds that have diagnostic value. We note that in our two pairs of ketones the bridgehead hydrogen α to the carbonyl group (3a-H) appears downfield in the ^{1}H n.m.r. spectrum of the *cis* isomer relative to its position in that of the epimeric *trans* compound: (**2**) [δ 2.61 (ddd, $J_1 \sim J_2 \sim J_3 \sim 7.1$ Hz)], (**3**) [2.55 (ddd, $J_1 = 13.1$, $J_2 \sim J_3 \sim 8.6$ Hz)], (**4**) [2.68 (ddd, $J_1 \sim J_2 \sim J_3 \sim 7.9$ Hz)], and (**5**) [~2.37 (m, 3 H)]. From spectral data already on record,[11] this same relationship appears to hold for the parent ketone (**12**) and its *trans* isomer, as well as for two other pairs of methyl-substituted 4-hydrindanones.

It has also been suggested that in *cis*-fused 4-hydrindanones the axial or equatorial configuration of 3a-H can be deduced from the vicinal coupling constants between it and the protons at C-3, with two coupling constants of ~8 Hz each for an equatorial proton and one coupling constant smaller than the other for axial 3a-H.[11] In our four hydrindanones this bridgehead proton should be axial in (**2**), (**3**), and (**5**) and equatorial in (**4**) on the basis of structure for the *trans*-fused isomers (**3**) and (**5**) and from the presumed equatorial preference of the isopropyl substituent in the *cis*-fused (**2**) and (**4**). In (**5**) the signal for 3a-H is obscured, but in the remaining ketones its multiplicity is assignable as given above. It may be seen that, regardless of configuration, in (**2**) and (**4**) both coupling constants in question ($^3J_{3,3a}$) lie in the same range and for each ketone both constants have approximately the same value. The suggested correlation then is valid for the equatorial bridgehead proton of (**4**), but it does not obtain for the axial hydrogen of (**2**).

Experimental

Materials and Equipment.—General procedures have been previously described.[1] Preparative gas chromatography (g.c.) was carried out using a Varian Aerograph Model 920 with one of the following columns: (A) 10% Carbowax 20 M, 5 ft × ¼ in, Chrom W-HP 80/100; (B) 10% OV 101, 5 ft × ¼ in, Chrom W-HP 80/100. Analytical g.c. was carried out on a Varian Aerograph Model 1400 with one of the following columns: (C) 1.5% OV 101, 5 ft × ⅛ in, Chrom G-HP 100/120; (D) 10% Carbowax 20 M, 8 ft × ⅛ in, Chrom W-HP 80/100 . The analytical g.c. employed a flame ionization detector which was interfaced to a Hewlett Packard Model 3390A integrating recorder. Flash chromatography was carried out as previously described.[16]

Synthesis of 7-Isopropyl-1,2,5,6,7,7a-hexahydro-4H-inden-4-one (**9**).—Magnesium (140 mg, 5.8 mmol) was placed in an oven-dried flask, covered with THF, and 3-bromopropanal ethylene acetal (820 mg, 4.6 mmol) was slowly added dropwise. The Grignard reagent formation commenced promptly. After all the bromide was added, the reaction mixture was warmed to 35 °C for 1 h and then cooled to −78 °C. Then CuBr·SMe_2 (240 mg, 1.15 mmol) dissolved in dimethyl sulphide (2 ml) was slowly added, and the mixture was stirred for 45 min at −78 °C. To this was added over 3 h 4-isopropylcyclohexenone[4] (500 mg, 3.6 mmol) dissolved in freshly distilled dry ether (4 ml). The solution was stirred for 9 h at −78 °C and then allowed to warm to room temperature over 11 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with aqueous $NaHCO_3$, aqueous Na_2CO_3, and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the oxo acetal (**8**) as a light yellow oil (704 mg, 81%). This material was usually carried on without further purification, but (**8**) could be isolated by preparative g.c. (column B, 190 °C); δ (300 MHz, $CDCl_3$) 4.84 (1 H, t, J 4.3 Hz), 3.9 (4 H, m), 2.4 (2 H, m), 2.3 (1 H, m), 2.0 (3 H, m), 1.85 (1 H, m), 1.6 (4 H, m), 1.4 (2 H, m), 0.99 (3 H, d, J 6.8 Hz), and 0.82 (3 H, d, J 6.8 Hz); $\nu_{max.}$(CCl_4) 2 985, 2 885, 1 695, 1 125, and 1 035 cm^{-1}. The crude oxo acetal was dissolved in THF containing aqueous HCl and rapidly stirred at room temperature for 4 days. The reaction mixture was then diluted with ether and neutralized with aqueous $NaHCO_3$. The ethereal solution was washed with water and brine, dried ($MgSO_4$), and concentrated to leave an oil; the crude material was purified by flash chromatography (hexane–ether, 5:1; R_F 0.2) to give (**9**) (90 mg, 20%). An analytical sample was prepared by preparative g.c. (Column B, 150 °C); δ (300 MHz, $CDCl_3$) 6.65 (1 H, dd, J 2.8, 5.4 Hz), 2.77 (1 H, m), 2.57 (1 H, ddd, J 2.6, 5.2, 17.3 Hz), 2.45—2.2 (4 H, m), 1.9 (2 H, m), 1.55 (2 H, m), 1.34 (1 H, tt, J 3.0, 11.3 Hz), 0.99 (3 H, d, J 6.9 Hz), and 0.87 (3 H, d, J 6.9 Hz); $\nu_{max.}$($CDCl_3$) 2 975, 2 945, 2 880, 1 675, and 1 610 cm^{-1} (Found: m/z, 178.1359. Calc. for $C_{12}H_{18}O$: M^+, 178.1358).

Isomerization of the Enone (**9**) *to 7-Isopropyl-1,2,3,5,6,7-hexahydro-4H-inden-4-one* (**10**).—Following the procedure of Barton,[8] the enone (**9**) (250 mg, 1.4 mmol) was dissolved in absolute ethanol (2 ml) and water (200 μl). $RhCl_3 \cdot 3H_2O$ (28 mg, 0.1 mmol) was then added and the solution heated at reflux for 3.5 days. The reaction mixture was diluted with water and then extracted thrice with ether. The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to provide a residue which was subjected to flash chromatography on silica gel (hexanes–ether, 3:1; R_F 0.25) to give the desired enone (**10**) (125 mg, 50%), as well as an aromatized side product (80 mg, 32%). An analytical sample of (**10**) was obtained by preparative g.c. (Column B, 160 °C); δ (300 MHz, $CDCl_3$) 2.7 (1 H, m), 2.6—2.45 (4 H, m), 2.4—2.22 (2 H, m), 2.15 (1 H, m), 2.05—1.7 (4 H, m), 1.03 (3 H, d, J 7.2 Hz), and 0.82 (3 H, d, J 6.9 Hz); $\nu_{max.}$(CCl_4) 2 985, 2 900, 1 665, 1 380, 1 250, and 855 cm^{-1} (Found: m/z, 178.1360. Calc. for $C_{10}H_{18}O$: M^+, 178.1358).

Hydrogenation of the Enone (**9**) *over* 5% Pd-C.—The enone (**9**) (75 mg) was dissolved in ethyl acetate (3 ml) and a catalytic amount of 5% Pd-C was added; the mixture was then rapidly stirred under an atmosphere of hydrogen until uptake of hydrogen ceased (*ca.* 2h). The reaction mixture was filtered through Celite and then analysed by g.c. and ^{1}H n.m.r. spectrometry. The hydrindanones (**4**) and (**5**) were observed in a ratio of ~55:45 together with ~10% of (**10**). The hydrindanones (**4**) and (**5**) were separated by preparative g.c. (Column A, 155 °C); for (**4**) δ (300 MHz, $CDCl_3$) 2.68 (1 H, ddd, *J ca.* 8.0, 8.0, 8.0 Hz), 2.47—2.18 (3 H, m), 2.0 (1 H, m), 1.9—1.4 (7 H, m), 1.27 (1 H, m), 1.15 (1 H, m), 0.98 (3 H, d, *J* 6.9 Hz), and 0.86 (3 H, d, *J* 6.9 Hz); $\nu_{max.}$(CCl_4) 2 950, 2 860, and 1 705 cm^{-1} (Found: *m/z*, 180.1512. Calc. for $C_{12}H_{20}O$: M^+, 180.1514); for (**5**) δ (300 MHz, $CDCl_3$) 2.45—2.23 (3 H, m), 2.05—1.87 (3 H, m), 1.83—1.4 (8 H, m), 0.97 (3 H, d, *J* 7.0 Hz), and 0.81 (3 H, d, *J* 7.0 Hz); $\nu_{max.}$($CDCl_3$) 2 950, 2 890, 2 860, 1 700, 1 375, and 1 090 cm^{-1} (Found: *m/z*, 180.1511. Calc. for $C_{12}H_{20}O$: M^+, 180.1514).

Hydrogenation of the Enone (**10**) *over the* 10% Pd-C.—The enone (**10**) (20 mg) was dissolved in ethyl acetate (2 ml) and a catalytic amount of 10% Pd-C was added; the mixture was then rapidly stirred under an atmosphere of hydrogen for 3 h. The reaction mixture was passed through a pad of Florisil and the solvent was evaporated under reduced pressure. Isolation of the products by preparative g.c. (Column A, 155 °C) and analysis by ^{1}H n.m.r. spectrometry showed a 14:86 mixture of (**2**) and (**4**). Repeating the above procedure with hexane as solvent gave (**2**) as essentially the sole product, as determined by g.c. and ^{1}H n.m.r. spectrometry.

Hydrogenation of the Enone (**14**) *over Wilkinson's Catalyst.*—The enone (**14**) (*ca.* 50 mg) was dissolved in N_2-purged benzene (2 ml) and a catalytic amount of TTRC was added; the mixture was then rapidly stirred under an atmosphere of hydrogen for 30 h. The reaction mixture was then passed through a pad of Florisil. Analysis of the hydrogenation mixture by analytical g.c. (Column C) showed the two hydrogenation products (**2**) (57%) and (**3**) (43%). These were isolated by preparative g.c. (Column A, 155 °C); for (**3**) δ (300 MHz, $CDCl_3$) 2.55 (1 H, ddd *J* 8.6, 8.6, 13.1 Hz), 2.27 (2 H, m), 2.11 (1 H, m), 2.0—1.43 (10 H, m), 1.04 (3 H, d, *J* 6.0), and 1.03 (3 H, d, *J* 6.5 Hz); $\nu_{max.}$(CCl_4) 2 955, 2 875, and 1 710 cm^{-1} (Found: *m/z*, 180.1514. Calc. for $C_{12}H_{20}O$: M^+, 180.1514); for (**2**) δ (300 MHz, $CDCl_3$) 2.61 (1 H, ddd *J* ~ 7.0, 7.0, 7.0 Hz), 2.54 (1 H, m), 2.35 (3 H, m), 2.05 (1 H, m), 1.8—1.35 (7 H, m), 1.11 (1 H, m), 0.98 (3 H, d, *J* 6.6 Hz), and 0.96 (3 H, d, *J* 6.6 Hz); $\nu_{max.}$($CDCl_3$) 2 955, 2 900, 2 875, 1 980, 1 700, 1 465, and 1 380 cm^{-1} (Found: *m/z*, 180.1512. Calc. for $C_{12}H_{20}O$: M^+, 180.1514).

Hydrogenation of the Enone (**14**).—The enone (**14**) (50 mg) was dissolved in methanol (2 ml) and a catalytic amount of 10% Pd-C was added; the mixture was then rapidly stirred under a hydrogen atmosphere for 2 h. The solution was then filtered through Celite. Analysis of the hydrogenation mixture by analytical g.c. (Column C, 140 °C) showed 2 peaks corresponding to the hydrindanones (**5**) (58%) and (**3**) (42%). Isolation of the products by preparative g.c. (Column A, 155 °C) and analysis by ^{1}H n.m.r. spectrometry confirmed the structural assignments.

Epimerization of the Enone (**14**).—A catalytic amount of sodium was added to absolute ethanol (10 ml) and after all the sodium had reacted, the enone (**14**) (105 mg, 0.59 mmol) in absolute ethanol (2 ml) was added. The solution was stirred for 16 h at room temperature after which the reaction mixture was diluted with water and extracted with pentane. The pentane extracts were washed with saturated aqeuous NH_4Cl, aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give (**16**) as a clear oil (97 mg, 92%); δ (300 MHz, $CDCl_3$) 4.79 (1 H, s), 4.64 (1 H, s), 2.67 (3 H, m), 2.4 (3 H, m), 1.93 (2 H, m), 1.80 (3 H, s), 1.5 (4 H, m), and 1.1 (1 H, m); $\nu_{max.}$(CCl_4) 3 110, 2 985, 2 895, 1 710, 1 640, 890, and 850 cm^{-1} (Found: *m/z*, 178.1362. Calc. for $C_{12}H_{18}O$: M^+, 178.1358).

Hydrogenation of the Enone (**15**) *over Wilkinson's Catalyst.*—The enone (**15**) (10 mg, 0.06 mmol) was dissolved in argon-purged benzene (1 ml) and a catalytic amount of TTRC was added. The solution was then rapidly stirred under a hydrogen atmosphere for 36 h after which it was filtered through a pad of Florisil and evaporated. The hydrogenated product (**2**) was isolated by preparative g.c. (Column A, 155 °C) and analysed by ^{1}H n.m.r. spectrometry.

Epimerization of the Hydrindanone (**3**).—A catalytic amount of sodium was added to absolute ethanol (1 ml). After the hydrogen evolution had ceased, the hydrindanone (**3**) (20 mg) in absolute ethanol (2 ml) was added and the reaction mixture was stirred for 48 h at room temperature. It was then diluted with water and extracted with pentane. The pentane extracts were washed with aqueous NH_4Cl, aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). Examination of the reaction mixture by analytical g.c. showed one peak corresponding to the hydrindanone (**2**). Isolation of the product and examination of its 300 MHz ^{1}H n.m.r. spectrum confirmed this assignment.

Equilibration of the Hydrindanones (**4**) *and* (**5**).—The same procedure was carried out as described above for the epimerization of (**3**) except that the hydrindanone (**4**) (20 mg) was used. Examination of the reaction mixture by analytical g.c. (Column D, 150 °C) after 2 and 3 days showed an equilibrium mixture consisting of 45% (**4**) and 55% (**5**).

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