

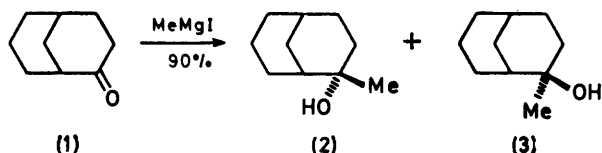
On the Stereochemistry of Grignard Addition to Bicyclo[3.3.1]nonan-2-one. Preferential Axial Attack on a Cyclohexanone System by a Bulky Nucleophile

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Bicyclo[3.3.1]nonan-2-one (1) reacts with methylmagnesium iodide to give, in a high overall yield, a 19:1 mixture of *exo*-2-methylbicyclo[3.3.1]nonan-2-ol (2) and the *endo*-epimer (3), respectively. The high propensity of compound (1) for axial attack by a bulky reagent, such as a Grignard reagent, is atypical of bridged cyclohexanones. Possibly, flattening of the bicyclo[3.3.1]nonan-2-one skeleton favours axial attack. Results of the oxymercuration–demercuration of related olefins is in accordance with this view.

BRIDGED polycyclic systems show different reactivities for *exo* vs. *endo* attack by a variety of reagents.¹ In particular, bridged cyclohexanones have been observed to undergo preferential axial attack by 'small' nucleophiles and preferential equatorial attack by large nucleophiles.²⁻⁴ This has been attributed to either steric effects¹ or to torsional effects,² or to both effects simultaneously.³

Therefore it is interesting to present here the case of a bridged cyclohexanone where axial attack by a bulky reagent, such as a Grignard reagent, predominates. In fact, compound (1)^{4e} and methylmagnesium iodide in diethyl ether, gave, in high overall yield, a 19:1 epimeric mixture of the alcohols. It will be shown later that the prevailing epimer (2) has an equatorial hydroxy-group (Scheme 1).



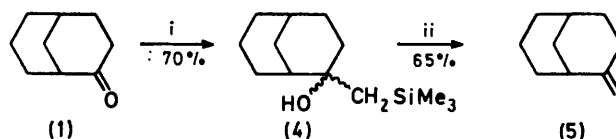
SCHEME 1

From the above mixture only the prevailing isomer (2) could be purified by preparative high-pressure liquid chromatography (h.p.l.c.) (see the Experimental section). However, we needed to isolate the other isomer to confirm the stereochemistry. Hence, we attempted to obtain the minor isomer (3) by oxymercuration–demercuration of 2-methylenebicyclo[3.3.1]nonane (5). It is known that the stereochemistry of the oxymercuration–demercuration reaction with related olefins is reversed with respect to that of the Grignard reaction on the corresponding ketones.⁵

However, compound (5) could not be obtained from the nonane (1) with either methylenetriphenylphosphorane or PhSCH_2Li ,^{6a} due to enolization of the ketone. After other unsuccessful attempts, 2-methylenebicyclo[3.3.1]nonane (5) was finally obtained by the route shown in Scheme 2, which represents a variant to a general method of olefin synthesis.^{6b} In fact, compound (4) failed to react with sodium hydride under the mild

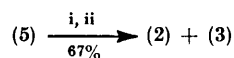
conditions suggested for similar cases.⁶ However, under forcing conditions in an autoclave, compound (4) afforded the product (5) in a 65% yield.

Oxymercuration–demercuration of compound (5) by



SCHEME 2 Reagents: i, $\text{Me}_3\text{SiCH}_2\text{MgCl}$; ii, NaH, tetrahydrofuran

standard methods⁷ afforded, in an overall fair yield, a 9:1 mixture of the alcohols (3) and (2), respectively (Scheme 3). It will be shown later that the prevailing isomer (3) has an axial hydroxy-group.



SCHEME 3 Reagents: i, $\text{Hg}(\text{OAc})_2$; ii, NaBH_4

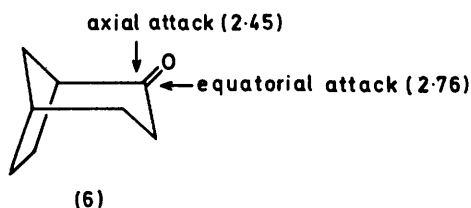
Structures (2) and (3) were assigned on the following basis. The i.r. spectrum in chloroform solution shows absorptions in the C–O stretching region at higher values for compound (2) (ν 1 003, 1 037, and 1 132 cm^{-1}) than for compound (3) (ν 972, 1 021, and 1 039 cm^{-1}), in accordance with configurational assignments⁸ for 4-isopropylcyclohexanols,⁹ bicyclo[3.3.1]nonan-2-ols,¹⁰ bicyclo[3.2.1]octan-2-ols,¹¹ and 2-methylbicyclo[3.2.1]octan-2-ols.¹² Also, in the O–H stretching region, the association band at ν 3 340–3 520 cm^{-1} is more predominant than the free OH band at ν 3 605 cm^{-1} for compound (2), in accordance with the presence of an equatorial hydroxy-group. The reverse is true for compound (3), in accordance with the axial position for OH.¹²

As regards the ^1H n.m.r. spectra, measurements in CCl_4 solution show line widths at half-height ($w_{1/2}$) of the signals due to the methyl groups at higher values for compound (2) ($w_{1/2}$ 1.5 Hz; actually the signal is split with J 0.6 Hz) than for compound (3) ($w_{1/2}$ 0.8 Hz). This is in agreement with what has been found for the 1-methyl-4-*t*-butylcyclohexanols.¹³

Another piece of supporting evidence is given by g.l.c. retention times. In fact, in accordance with the freer environment of an equatorial OH within cyclohexanols,¹⁴ compound (2) has a longer retention time (10.36 min) than compound (3) (9.58 min) under identical conditions.

Finally, whereas both the alcohols (2) and (3) resisted acetylation under a variety of conditions, compound (2) could easily be trifluoroacetylated by trifluoroacetic anhydride in the presence of pyridine.¹⁵ In contrast, compound (3) could not be trifluoroacetylated by the same reagent. In fact, although compound (3) proved to be slightly more reactive than the alcohol (2) towards trifluoroacetic anhydride, the treatment led to dehydration, giving 2-methylbicyclo[3.3.1]non-2-ene. That only compound (2) could be trifluoroacetylated is in agreement with a freer environment around an equatorial OH. Admittedly, because of rapid dehydration of compound (3), the above configurational test lacks the usual force. However, our configurational assignments for compounds (2) and (3) are strongly supported by all other evidence above.

The stereochemical outcome of the reaction of the nonanone (1) with methylmagnesium iodide described above is atypical of bridged cyclohexanones, where a much larger proportion of equatorial attack, to give the products (2) and (3) in nearly equal proportions, would have been expected. For example, with a close analogue of compound (1), such as bicyclo[3.2.1]octan-2-one (6), equatorial attack by methylmagnesium iodide was slightly preferred over axial attack (Scheme 4).^{4c}



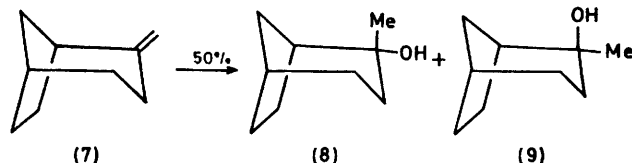
SCHEME 4 Partial relative rates for the reaction of compound (6) with methylmagnesium iodide^{4c}

Although specific studies of compound (1) are rare, there are plenty of conformational studies on bicyclo[3.3.1]nonane itself and on several of its derivatives.¹⁶ All studies lead to the conclusion that, in the absence of 3,7-*endo*-substituents, the molecule has a preferred di-chair conformation.

On the above basis, though we cannot exclude that higher energy conformations are involved in our reaction, we propose that the reacting species (1) has a di-chair conformation when attacked by a Grignard reagent. Under such circumstances, in fact, repulsion between the *endo*-3 and -7 hydrogen atoms may be sufficient to flatten the system, so as to create an unusually unhindered (for a cyclohexanone) channel for attack by the bulky reagent^{4c} along the orthogonal direction to the sp^2 plane.¹⁷ In contrast, hindrance to equatorial attack by torsional strain is not relieved. Admittedly this is

a much simplified view which, for example, does not take into account co-ordination of the carbonyl group with the metal atom.¹⁸

The above conclusions are consistent with the results obtained from the oxymercuration-demercuration of the olefins (5) and (7) (Schemes 3 and 5). In fact, in both cases the ratio of the epimeric alcohols is reversed with respect to that observed for the Grignard reaction with the corresponding ketones (Schemes 1 and 4), in



SCHEME 5 Reagents: i, $Hg(OAc)_2$; ii, $NaBH_4$. Ratio (8) : (9) is 3 : 2

accordance with expectations.⁵ Thus, in the case of compound (5), oxymercuration-demercuration occurs with nearly the same high stereoselectivity shown by the reaction of compound (1) with the Grignard reagent (Scheme 1), although with a reversed ratio of the epimers. For compound (7), oxymercuration-demercuration occurs with the same low stereoselectivity (again resulting in a reversed ratio of the epimers) shown by the reaction of compound (6) with the Grignard reagent (Scheme 4).

EXPERIMENTAL

G.l.c. was carried out on a Perkin-Elmer Sigma 3 chromatograph; i.r. spectra were run on a Perkin-Elmer 337 spectrometer; ¹H n.m.r. spectra were obtained using Varian CFT-20 (80 MHz) or Varian EM-360 (60 MHz) spectrometers and are recorded in p.p.m. with respect to Me_4Si ; preparative h.p.l.c. was performed on a Jobin-Yvon Mini-prep chromatograph (equipped with a 400×20 mm column and monitored by a Waters differential refractometer R 404); and mass spectra were measured with a Varian MAT CH7 spectrometer.

Reaction of Bicyclo[3.3.1]nonan-2-one (1) with Methylmagnesium Iodide.—Bicyclo[3.3.1]nonan-2-one (0.2 g, 1.44 mmol) and a slight excess of methylmagnesium iodide in diethyl ether gave a 19 : 1 mixture of compounds (2) and (3) (90%). H.p.l.c. on 0.2 g of this mixture [Lichroprep Si 60, 15–25 μ m, light petroleum–diethyl ether (17 : 3), 11 ml min^{-1}] gave, from the tail fractions, pure 2-methylbicyclo[3.3.1]nonan-2-ol (2) as colourless needles, 0.06 g, m.p. 82–83 °C after sublimation at 10^{-1} Torr, 35 °C (Found: C, 77.7; H, 11.8. $C_{10}H_{18}O$ requires C, 77.8; H, 11.8%); ν_{max} . ($CHCl_3$, 0.065M) 3 605 (m, free OH), 3 340–3 520 (m, associated OH), 1 429, 1 357, 1 037, 1 003, 966, 926, and 893 cm^{-1} ; $\delta(CCl_4)$ 1.67br (s, 14 H), 1.29 (d, J 0.6 Hz, w , 1.5 Hz, Me).

2-Methylenebicyclo[3.3.1]nonane (5).—Chloromethyltrimethylsilane (5.0 g, 40.8 mmol) was added, under nitrogen, to magnesium turnings (1.0 g) in dry diethyl ether. To the mixture was added a little solid iodine and after 20 min compound (1) (2.5 g, 18.12 mmol) in dry diethyl ether (10 ml) was added as drops at room temperature. After 15 min the mixture was decanted and the ethereal layer was washed with aqueous ammonium chloride, dried (Na_2SO_4), evaporated, and the residue chromatographed on a silica-

gel column (200 g). Gradient elution with benzene-diethyl ether mixtures, from 0–100% (v/v) of the ether, gave first the unchanged ketone (1) (29%) and then the crude 2-(trimethylsilyl)methylbicyclo[3.3.1]nonan-2-ols (4) in 70% yield, m.p. 55–56 °C (from pentane). G.l.c. (2.5% SE-30 on Chromosorb G AW at 100–160 °C/5 °C min⁻¹, N₂ flow rate 25 ml min⁻¹) revealed an epimeric mixture of the two alcohols (4) in a 93 : 7 ratio; $\delta(\text{CCl}_4)$ 0.13 (s, 9 H, SiMe₃), 1.13 (s, 2 H, SiCH₂), and 1.76br (s, 15 H). A solution of compound (4) (2.69 g, 11.9 mmol) in dry tetrahydrofuran (THF) (25 ml) was added to sodium hydride (500 mg, 20.8 mmol) in an autoclave and warmed, with stirring, for 10 h at 150 °C. To the mixture was then added saturated ammonium chloride (30 ml), and the whole extracted with diethyl ether. The ethereal layer was dried (Na₂SO₄), and evaporated under reduced pressure to give an oily residue which was distilled (70 °C, 20 Torr) to give 2-methylenebicyclo[3.3.1]nonane (5) in 65% yield (Found: C, 88.00; H, 12.10. C₁₀H₁₆ requires C, 88.23; H, 11.76%); $\delta(\text{CCl}_4)$ 1.76 (m, 11 H), 2.49 (m, 3 H), and 4.68 (d, J 2.2 Hz, =CH₂); on irradiation at δ 2.5 (proton at C-1) the doublet became a singlet.

Oxymercuration–Demercuration of the Nonane (5).—To a yellow suspension of THF (1 ml) in Hg(OAc)₂ (0.318 g, 1 mmol) dissolved in water (1 ml) was rapidly added, under N₂, compound (5) (0.136 g, 1 mmol) dissolved in THF (1 ml), whereupon the yellow colour disappeared. After 1 h, aqueous NaOH (3M, 2 ml), then 2 ml of aqueous 0.5M NaBH₄ and 3M NaOH, and finally NaCl were added to the mixture. This was extracted with diethyl ether and the residue, obtained after evaporation of the ether, was chromatographed on a silica-gel column (10 g). Gradient elution with benzene–diethyl ether [9 : 1–6 : 4 (v/v)] gave, with 67% overall yield, a ca. 9 : 1 mixture of compounds (3) and (2), respectively. G.l.c. (3 ft × 1/8 in; 8% Carbowax 20 M + 2% KOH on Chromosorb W at 160–180 °C/1 °C min⁻¹; N₂ flow rate 25 ml min⁻¹) of the above mixture followed by column chromatography gave a 9 : 1 mixture of compounds (3) and (2). H.p.l.c. of this mixture (0.15 g) under the conditions used above to obtain compound (2), gave the pure *isomer* (3) (from head fractions) as colourless prisms, 0.023 g, m.p. 91–92 °C, after sublimation at 10⁻¹ Torr, 30 °C (Found: C, 77.6; H, 11.8. C₁₀H₁₈O requires C, 77.8; H, 11.8%); ν_{max} (CHCl₃, 0.065M) 3 590 (m, free OH), 3 350–3 470 (vw, associated OH), 1 489, 1 366, 1 039, 1 021, 972, 948, 926, and 893 cm⁻¹; $\delta(\text{CCl}_4)$ 1.67br (s, 14 H) and 1.20 (s, 0.8 Hz, Me).

2-Methylenebicyclo[3.2.1]octane (7).—To a suspension of triphenylmethylphosphonium iodide (5.1 g, 12.6 mmol) in dry diethyl ether (50 ml) was added, at –20 °C and under N₂, BuⁿLi (7.5 ml of a 1.68M solution). After 20 min a solution of bicyclo[3.2.1]octan-2-one (6) (1.50 g, 12.1 mmol) in dry diethyl ether (10 ml) was added as drops. The mixture was stirred overnight, then shaken with dilute HCl and extracted with diethyl ether. Concentration of the ethereal layer under reduced pressure, removal of Ph₃PO by filtration, and evaporation gave a residue which was distilled at 33 Torr. The fraction boiling at 60 °C gave 2-methylene[3.2.1]octane (7) (0.65 g, 44%) (Found: C, 88.2; H, 11.0. C₉H₁₄ requires C, 88.45; H, 11.55%); $\delta(\text{CDCl}_3)$ 1.8 (m, 9 H), 2.5 (m, 3 H), and 4.6 (m, 2 H); ν_{max} (liquid film) 1 640 and 880 cm⁻¹; M⁺, 122.

Oxymercuration–Demercuration of Compound (7).—To a solution of Hg(OAc)₂ (0.61 g, 1.9 mmol) in water (4 ml) and THF (2 ml) was added, under N₂, 2-methylenebicyclo-

[3.2.1]octane (0.23 g, 1.9 mmol) dissolved in THF (2 ml). After 5 min, aqueous sodium hydroxide (3M, 4 ml) followed by 0.5M NaBH₄ in 3M NaOH (4 ml), was added to the mixture. This was then stirred for 1 h, NaCl added, and the whole extracted with diethyl ether. The ethereal layer was dried and evaporated to give, in 50% overall yield, a 3 : 2 crystalline mixture of the 2-methylbicyclo[3.2.1]octan-2-ols (8) and (9) (column 3 ft × 1/8 in; 15% polypropylene glycol on Chromosorb W 80–100, 128 °C, N₂ flow rate 20 ml min⁻¹).^{4c}

Trifluoroacetylation of exo-2-Methylbicyclo[3.3.1]nonan-2-ol (2).—The reaction was carried out using a 49 : 1 mixture of compounds (2) and (3) (0.105 g, 0.68 mmol) in an autoclave, by the addition of trifluoroacetic anhydride (1.5 ml) and pyridine (0.1 ml), at 60 °C for 5 h. Then (CF₃CO)₂O was evaporated off under reduced pressure. The residue was extracted with diethyl ether and washed first with 5% aqueous NaHCO₃ and then with water. The resulting solution was dried and evaporated to leave a colourless oil (0.163 g) which was distilled at 50 °C, 20 Torr to give the trifluoroacetate as a colourless oil (0.08 g); ν_{max} (liquid film) 1 768 cm⁻¹. The trifluoroacetate proved to be extremely labile giving compounds (2) and (3) and trifluoroacetic acid.

Reaction of endo-2-Methylbicyclo[3.3.1]nonan-2-ol (3) with Trifluoroacetic Anhydride.—The reaction was carried out as described above on a 99 : 1 mixture (0.15 g) of compounds (3) and (2) to give a colourless oil (0.064 g) (2-methylbicyclo[3.3.1]non-2-ene) on distillation (Found: C, 88.3; H, 11.7. C₁₀H₁₆ requires C, 88.23; H, 11.76%); $\delta(\text{CDCl}_3)$ 1.55 (m, 8 H), 1.7 (s, 3 H; Me), 2.1 (m, 4 H), and 5.5 (m, 1 H); the δ 5.5 signal became a singlet on irradiation at δ 1.6; ν_{max} (liquid film) 2 920, 2 840, 1 445, and 796 cm⁻¹; M⁺, 136.

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