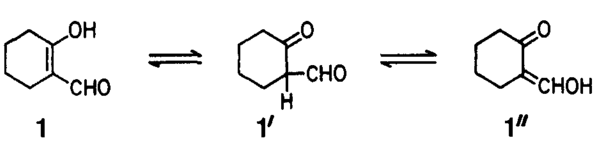
Synthesis of 2-(1-Hydroxy-2-phenylethyl)-cyclohexanone and Derivatives Thereof. A New Synthesis of 1,8-Dimethylphenanthrene

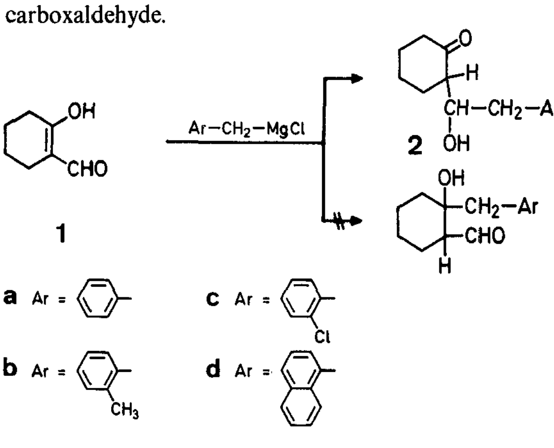
W. Wysocka, P. Canonne, L. C. Leitch*

Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada

In continuation of our earlier studies of the action of Grignard reagents on 1,3-diketones[1] we were led to examine the reaction between benzylmagnesium chloride and 2-hydroxymethylenecyclohexanone (2-formylcyclohexanone). The ^{1}H-N.M.R. spectrum of the latter indicates it exists in two enol forms according to Garbisch[2], 24% of which is present as the enol form **1″**.

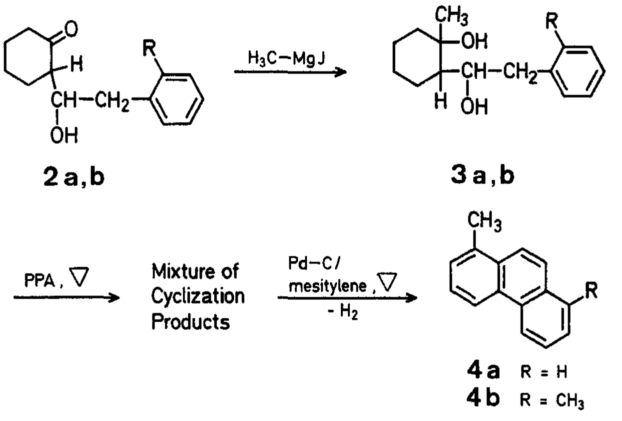


The chief reaction product obtained with benzylmagnesium chloride (Ar=C_6H_5) is 2-(1-hydroxy-2-phenylethyl)-cyclohexanone (**2a**) rather than 2-benzyl-2-hydroxycyclohexanecarboxaldehyde.

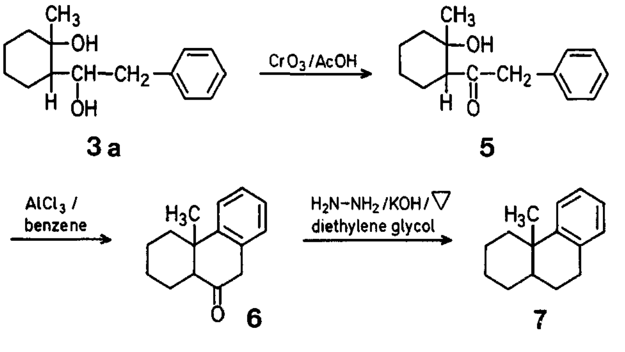


The structure of **2a** was proved by the absence of a doublet for the formyl group and a singlet for the isolated methylene of the benzyl group in the ^{1}H-N.M.R. spectrum. Furthermore, the subsequent reactions of **2a** were entirely consistent with this structure.

With methylmagnesium iodide, the ketoalcohol **2a** gave the corresponding diol **3a** which underwent cyclodehydration (cationic cyclization) with polyphosphoric acid to produce mixtures of tetrahydrophenanthrenes and probably also spiro compounds already noted by Barnes et al.[3, 4]. Dehydrogenation of these mixtures with palladium on carbon in mesitylene gave, in the case of diols **3a** and **3b**, 1-methyl- (**4a**) and 1,8-dimethylphenanthrene (**4b**), respectively. This is probably the most convenient synthesis of 1,8-dimethylphenanthrene.



Oxidation of the diol **3a** with chromium(VI) oxide in acetic acid gave the ketol **5** which could be cyclized to the ketone **6**. Wolff-Kishner reduction of **6** led to 4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**7**).



The ketoalcohols **2c** and **2d** were prepared from 2-chlorobenzyl chloride and 1-chloromethylnaphthalene, respectively. Compound **2c** was not suitable for further syntheses but **2d** has possibilities as a starting material for the synthesis of substituted chrysenes and/or benzo[*c*]phenanthrenes.

2-Hydroxymethylenecyclohexanone (1):

This compound is prepared as described by Ainsworth[5]. Unless used immediately it should be kept in a freezer to prevent polymerization; m.p. 14.5–15°.

2-(1-Hydroxy-2-phenylethyl)-cyclohexanone (2a):

Benzylmagnesium chloride is prepared from benzyl chloride (63.2 g, 0.5 mol) and magnesium (12.0 g, 0.5 g-atom) in ether as described by Gilman and Catlin[6]. A solution of 2-hydroxymethylenecyclohexanone (20.0 g, 0.16 mol) in absolute ether (200 ml) is added dropwise to the ice-cold stirred solution of the Grignard reagent keeping the temperature below +5° (ice-bath). After the addition of the hydroxyketone, the reaction mixture is stirred at room temperature for 1–2 h, and left overnight. It is poured into ice-cold saturated ammonium chloride solution (700 ml). The ether layer is separated and dried with magnesium sulfate. Evaporation of the ether and toluene in a rotary evaporator leaves a yellow oil which crystallizes on standing for a few hours or on seeding. The crystals are shaken with a little pentane to remove oil, and filtered; yield: 18–19 g of white powder. It is recrystallized from methanol/water (2:1); yield of pure product: 16.5 g (47%); m.p. 96–97°.

$C_{14}H_{18}O_2$	calc.	C 77.03	H 8.31
(218.3)	found	76.84	8.46

I.R. ($CHCl_3$): ν_{max} = 3250 (OH); 1700 cm^{-1} (C=O).

Semicarbazone: m.p. 159–160°.

2,4-Dinitrophenylhydrazone: m.p. 159–160°.

$C_{20}H_{22}N_4O_5$	calc.	C 60.29	H 5.57	N 14.06
(398.4)	found	59.56	5.37	14.3

I.R. (mull): $\nu_{max}=3250$ cm^{-1} (broad, OH).

2-(1-Hydroxy-2-phenylethyl)-1-methylcyclohexanol (3a):
Methylmagnesium iodide is prepared from magnesium (10.8 g, 0.45 g-atom) and methyl iodide (76.5 g, 0.45 mol) in absolute ether (400 ml). To this solution, a solution of **2a** (33 g, 0.15 mol) in absolute ether (700 ml) is added dropwise with stirring. The reaction mixture is left overnight and then poured into ice-cold saturated ammonium chloride solution (1000 ml). The ether layer and ether washings are dried with magnesium sulfate. Evaporation of the ether leaves an oil which slowly crystallizes in contact with pentane. Recrystallization from hexane gives the pure product; yield: 27.0 g (77%); m.p. 87°.

$C_{15}H_{22}O_2$	calc.	C 76.88	H 9.46
(234.3)	found	76.73	9.38

I.R. (CHCl$_3$): $\nu_{max}=3400$ cm^{-1} (OH).

1-Methylphenanthrene (4a):
Diol **3a** (5 g, 0.021 mol) is mixed with polyphosphoric acid (50 g). The mixture is heated on the steam bath for 2 h and then poured onto ice. The resultant oil is taken up in ether, and the ether evaporated. Bulb-to-bulb distillation of the residue gives 1.6 g of product (b.p. 120–130°/0.1 torr) which is a mixture of several compounds as determined by T.L.C. This product mixture is heated under reflux in mesitylene (5 ml) in the presence of palladium on carbon (0.3 g) for 5 h, and then filtered. Evaporation at 0.1 torr leaves crude 1-methylphenanthrene which is purified by recrystallization from ethanol: yield: 0.50 g (32%): m.p. 120–121° (Ref.[7], m.p. 121–122°).

2-Methylbenzyl Chloride:
o-Xylene is chlorinated with sulfuryl chloride as described in Ref.[1].

2-[1-Hydroxy-2-(2-methylphenyl)-ethyl]-cyclohexanone (2b):
The Grignard reagent prepared from 2-methylbenzyl chloride (70.0 g, 0.54 mol) is treated with 2-hydroxymethylenecyclohexanone (20.0 g, 0.16 mol) as described in the preparation of **2a**. The ketoalcohol is isolated with Girard's reagent T as described earlier[1]. The crude product is purified by bulb-to-bulb distillation in a heated air bath; yield: 34.0 (91%); b.p. 110–115°/0.02 torr.

$C_{15}H_{20}O_2$	calc.	C 77.55	H 8.68
(232.3)	found	77.67	8.47

I.R. (film): $\nu_{max}=1680$ cm^{-1} (C=O).

2-[1-Hydroxy-2-(2-methylphenyl)-ethyl]-cyclohexanol (3b):
The ketoalcohol **2b** (45.5 g, 0.20 mol) is added dropwise to a Grignard reagent prepared from magnesium (12.0 g, 0.5 g-atom) and methyl iodide (71.0 g, 0.5 mol) in dry ether (200 ml). Work-up as described previously for **3a** gives a nearly quantitative yield of yellow syrupy liquid which tends to undergo dehydration on distillation.

$C_{16}H_{22}O_2$	calc.	C 78.01	H 9.00
(246.4)	found	77.81	9.05

I.R. (film): $\nu_{max}=3475$ (broad, assoc. OH); 3600 cm^{-1} (free OH); C=O absent.

1,8-Dimethylphenanthrene (4b):
The diol **3b** (25 g, 0.1 mol) is heated with polyphosphoric acid (700 ml) on a steam bath for 3 h. Work-up and distillation as for **3a** gives 19.0 g of nearly colorless oil; b.p. 108°/0.05 torr. The product is a mixture of several compounds similar to that obtained in the cyclodehydration of **3a**. The product is dehydrogenated as described for the preparation of **4a**, and purified by recrystallization from methanol; yield: 12.0 g (60%); m.p. 191–192° (Ref.[8], m.p. 192°). Picrate: m.p. 152° (Ref.[8], m.p. 152°).

1-(2-Hydroxy-2-methylcyclohexyl)-2-phenylethanone (5):
Compound **3a** (25 g, 0.10 mol) is dissolved in glacial acetic acid (500 ml). A solution of chromium(VI) oxide (6.25 g in 2 ml of water) is added and the solution is stirred for 5 h. Acetic acid is removed under reduced pressure. The residue is dissolved in ether and the solution is washed with dilute sodium hydrogen carbonate solution and then water. The solvent is removed in vacuo. Bulb-to-bulb distillation of the residue gives 20.2 g (80%) of pale oil; b.p. 85–90°/0.02 torr. It is freed from a small amount of diol by chromatography on silica gel in pentane. Compound **5** is eluted with pentane/ether (10:1). The pentane is distilled off whereupon the residue crystallizes as a colorless solid; yield: 16.0 g (65): m.p. 56–57°.

$C_{15}H_{20}O_2$	calc.	C 77.55	H 8.68
(232.3)	found	77.86	8.37

^{1}H-N.M.R. (CDCl$_3$): $\delta=1.00$ (s, CH$_3$): 3.75 (s, CH$_2$); 7.33 ppm (m, H$_{arom}$).

4a-Methyl-10-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (6):
The ketoalcohol **5** (12.0 g, 0.05 mol) is cyclized with anhydrous aluminum chloride in benzene as described in Ref.[8]. Bulb-to-bulb distillation affords pure **6**; yield: 9.0 g (75%); b.p. 95–100°/0.02 torr. Semicarbazone: m.p. 220–222° (Ref.[9], m.p. 221°).

I.R. (CHCl$_3$): $\nu_{max}=1700$ cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$): $\delta=1.07$, 1.17 (3H, CH$_3$): 3.70 (s, 2H, CH$_2$): 7.20, 7.45 ppm (m, 4H$_{arom}$).

4a-Methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (7):
The ketone **6** (8.4 g, 0.04 mol) is heated for 2 h in diethylene glycol (210 ml) with potassium hydroxide (6.2 g) and anhydrous hydrazine (21 ml) at 125°. The mixture is then cooled, diluted with water (200 ml), and extracted four times with ether. The ether is evaporated and the residual oil distilled in vacuo; yield: 2.2 g (25%); b.p. 65–70°/0.01 torr.

$C_{15}H_{20}$	calc.	C 89.94	H 10.06
(200.3)	found	89.82	9.81

Dehydrogenation with palladium on carbon in mesitylene occurred with loss of the methyl group, giving *phenanthrene*; m.p. 99–100°.

2-[2-Chlorophenyl)-1-hydroxyethyl]-cyclohexanone (2c):
This hydroxyketone is prepared as described for **2b** on a 0.5 mol scale. The ketone is purified by chromatography on silica gel, eluting with pentane/ether (3:1); yield: 45%;

$C_{14}H_{12}ClO_2$	calc.	Cl 14.32
(247.7)	found	14.52

2-[1-Hydroxy-2-(1-naphthyl)-ethyl]cyclohexanone (2d):
To a Grignard reagent prepared from magnesium (36.0 g, 1.5 g-atoms) and 1-chloromethylnaphthalene (88.0 g, 0.5 mol) in ether (400 ml), 2-hydroxymethylenecyclohexanone (20.0 g, 0.16 mol) in ether (100 ml) is added with stirring while keeping the temperature at +5°. Work-up is done as in the preparation of **2b**. The product is purified by bulb-to-bulb distillation in an air bath; yield: 18.0 g (42%); b.p. 135–145°/0.2 torr.

$C_{18}H_{20}O_2$	calc.	C 80.60	H 7.52
(268.2)	found	79.21	7.23

Semicarbazone: m.p. 221–223°.

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* Please address correspondence to this author.

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