554. *2,3-Dimethylcyclohexanone and 2,3-Dimethylcyclohexanol*

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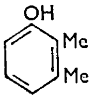
Pure specimens of *cis*- and *trans*-2,3-dimethylcyclohexanone have been prepared and their reduction products studied.

During the course of another investigation we prepared moderately large quantities of 2,3-dimethylcyclohexanone, which gave us the opportunity to study its stereoisomers and those of the corresponding alcohol. While this manuscript was being prepared, a Paper[1] by Ulery and Richards, describing these compounds, was published. We agree with the conclusions of these workers, and we present additional information drawn from reaction conditions that were somewhat different from those they describe.

Hydrogenation of 2,3-xylenol (I) over Raney nickel,[2] at elevated temperature and pressure gave a 90% yield of 2,3-dimethylcyclohexanol which was shown by gas–liquid chromatography (g.l.c.) to consist of a mixture of the four possible racemic alcohols, (II; 18%), (III; 15%), (IV; 32%), and (V; 35%) in order of increasing retention time. This result differs considerably from the largely stereospecific formation of (V; 82%) when the xylenol was reduced over platinum at low temperature and pressure.[1] These conditions would be expected to lead to kinetically controlled reaction more than those we used. Elution of the alcohols from the column during analysis by g.l.c. gave two well-defined pairs of peaks on the chromatogram, corresponding to the *trans*(Me)-alcohols, (II) and (III) and *cis*(Me)-alcohols (IV) and (V). The former pair must have arisen by inversion at the 2-carbon atom of an intermediate ketone.



(I)

Oxidation of the alcohol mixture with chromic acid in acetone gave a mixture of the ketones (VI; 44%) and (VII; 56%), which after distillation consisted of (VI; 80%) and (VII; 20%). These were readily separated by preparative g.l.c. giving the pure *trans*- (VI) and *cis*- (VII) ketones, the former being eluted first from the column. That our assignment of structure of the ketones is correct is shown (*a*) by their physical constants (see Experimental section),[cf. 1] and (*b*) by the fact that on treatment with acid or alumina, or by prolonged heating, *both* forms give the same equilibrium mixture consisting of 80—84% of the ketone (VI).[cf. 1]

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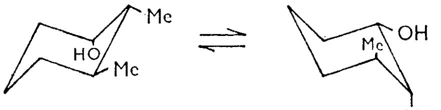
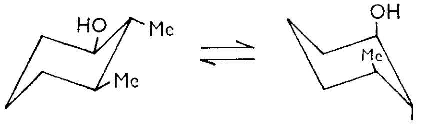
[1] H. Ulery and J. H. Richards, *J. Amer. Chem. Soc.*, 1964, **86**, 3113.

[2] E. H. Farmer and D. A. Sutton, *J.*, 1946, 10.

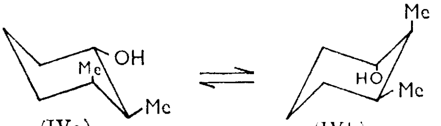
A group of French workers[3,4] obtained a 2,3-dimethylcyclohexanone (by reduction of 2,3-dimethylcyclohex-2-enone over Raney nickel followed by oxidation of the product), which was unaffected by sodium hydroxide, or sodium ethoxide, or by mineral acid. It gave the semicarbazone, m. p. 205° and oxime, m. p. 113°, of the *trans*-ketone, and on



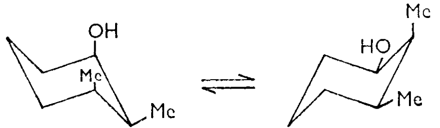
(IIa) (IIb)



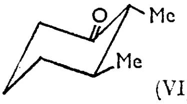
(IIIa) (IIIb)



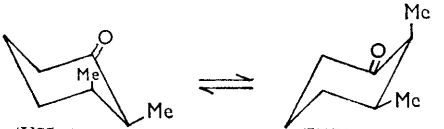
(IVa) (IVb)



(Va) (Vb)



(VI)



(VIIa) (VIIb)

Wolff–Kishner reduction it afforded *trans*-1,2-dimethylcyclohexane. On the basis of this evidence it was concluded that the ketone was *trans*-diequatorial 2,3-dimethylcyclohexanone. We believe that the ketone was an equilibrium mixture (which is unaffected by acid or base) of *trans*- and *cis*-forms and, since the *trans*-form in it preponderates, only derivatives of this form were isolated.

Reduction of the pure *trans*-ketone (VI) over Adams catalyst in acetic acid containing hydrochloric acid gave a mixture of 2,3-dimethylcyclohexyl acetates. Alkaline hydrolysis of this mixture afforded a mixture of the alcohols (II; 84%), (III; 7%), and (V; 9%). The conditions of hydrogenation described would be expected to give an axial alcohol. We feel confident therefore that the predominant product of the reduction is *cis*-2-*trans*-3-dimethylcyclohexanol (II), which will exist largely as the conformer (IIa). Its mixture with the alcohols (III) and (V) gave a pure 3,5-dinitrobenzoate, m. p. 134·5—135·5°, in such a yield as to leave no doubt that this is the ester of the alcohol (II). The French workers[4] record a m. p. of 119—119·5° for this ester.

Reduction of the pure *trans*-ketone with potassium borohydride gave a mixture of alcohols (II; 26%) and (III; 74%). The composition of this mixture differs from that recently obtained by Ulery and Richards,[1] who found that, with borohydride, the *trans*-ketone gave a mixture of the alcohols (II; 46%) and (III; 54%). There can be little hindrance to axial approach of borohydride ion to the ketone (VI), hence an equatorial alcohol should be the predominant product with this reducing agent. Like Ulery and Richards, we therefore believe that the predominant product is *trans*-2-*cis*-3-dimethylcyclohexanol, the all-*trans*-alcohol, which will exist very largely as the conformer (IIIa). It gave a 3,5-dinitrobenzoate, m. p. 118°, in agreement with the m. p. given by the French workers,[4] who used sodium in ethanol as reducing agent, a reagent that invariably gives an equatorial alcohol.

The presence of an appreciable amount of the *cis* (Me)-alcohol (V) in the hydrogenation product of the *trans*-ketone must be a result of partial inversion of the ketone at the 2-carbon atom under the acid conditions employed

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[3] D. Capon, M. M. Claudon, R. Cornubert, H. Lemoine, R. Malzieu, and G. Vivant, *Bull. Soc. chim. France*, 1958, 837.

[4] M. M. Claudon, R. Cornubert, H. Lemoine, and R. Malzieu, *Bull. Soc. chim. France*, 1958, 843.

Reduction of the *cis*-ketone (VII) with borohydride, or hydrogenation over platinic oxide gave a mixture consisting largely of the alcohol (V; over 90%), the remainder being the alcohol (IV). Catalytic reduction of the ketone (VII) will take place from the α-side of the molecule giving the axial alcohol (Va), which will largely take up the more stable conformation (Vb), in which the hydroxyl is equatorial. In the ketone (VII) the 3-axial methyl group will hinder the approach of borohydride to the oxo-group thus leading to the axial alcohol (Va) ⟶ (Vb). The predominant product of the reduction of the ketone (VII) is thus the all-*cis*-alcohol (V),[cf. 1] which gives a 3,5-dinitrobenzoate, m. p. 65°. The remaining alcohol is *trans*-2,3-dimethylcyclohexanol, which will exist largely as the conformer (IVa), and whose 3,5-dinitrobenzoate has m. p. 80°.

We were unable to obtain the four alcohols as separate compounds by preparative g.l.c., but the two pairs (II, III) and (IV, V) were readily separated from each other in this way. Oxidation of the former pair gave pure *trans*-ketone (VI) and the latter gave pure *cis*-ketone (VII).

Equilibration of a mixture of the four alcohols with sodium ethoxide gave a mixture consisting of (II; 17·1%), (III; 69·3%), (IV; 7·7%), and (V; 5·9%). Using the quoted interaction energies of the 1,3-diaxial groups, methyl–hydrogen[5] (0·9 kcal./mole), methyl–hydroxyl[6] (2·4 kcal./mole), and hydrogen–hydroxyl[6, cf. 7] (0·48 kcal./mole), and the relationships between percentage of more stable isomer and the standard free energy difference at 80° quoted by Eliel,[8] we have calculated the percentage of each conformer (a and b) of each isomer present at equilibrium, and thence the composition of the alcohol mixture at 80°. This temperature is close to that used in our equilibration experiments. We thus arrive at the approximate theoretical equilibrium composition for the four alcohols, (II; 16·8%), (III; 74·1%), (IV; 4·3%), and (V; 4·8%).

Using similar data to those given above, and including the interaction energy[9] (0·6 kcal./mole) of an axial methyl in the 3-position to an oxo-group we calculate that at 80° the equilibrium mixture of the ketones (VI) and (VII) should consist of approximately 90% of the *trans*-form (VI).

EXPERIMENTAL

Infrared measurements were made on Nujol suspensions; analytical g.l.c. was carried out on an Aerograph Hy-Fi 600 apparatus (Wilkens Instrument & Research Inc.) and preparative g.l.c. was carried out on an Aerograph Autoprep, A-700 apparatus. Densities were measured by weighing 1 c.c. of oil; the values given are the mean of ten measurements.

Reduction of 2,3-*Xylenol*.—A mixture of the xylenol (60 g.), methanol (60 c.c.), and Raney nickel (18 g.) was hydrogenated for 18 hr. at 150° and 90 atm. The product, in ether (200 c.c.), was washed with 10% sodium hydroxide, then with water, dried, and distilled. 2,3-Dimethylcyclohexanol distilled as a colourless oil (56 g.), b. p. 178—181°, $\nu_{max.}$ 3333 cm.$^{-1}$ (OH) (Found: C, 75·0; H, 12·9. Calc. for $C_8H_{16}O$: C, 75·0; H, 12·6%).

2,3-*Dimethylcyclohexanone*.—A mixture of chromium trioxide (26·7 g.) and sulphuric acid (23 c.c.) was diluted to 100 c.c. This solution (35 c.c.) was added dropwise to the alcohol mixture (13·4 g.) in purified acetone (60 c.c.). After 2 hr., water (30 c.c.) was added, the mixture was extracted with ether, and the extract was washed with water, dried, and distilled giving the ketone (10 g.) as a red oil, which distilled as a colourless oil, b. p. 174—176°, $\nu_{max.}$ 1709 cm.$^{-1}$ (ketone) (Found: C, 76·3; H, 11·5. Calc. for $C_8H_{14}O$: C, 76·1; H, 11·2%).

Preparative separation of trans- *and* cis-*dimethylcyclohexanones*. Column: 30% Sucrose acetate hexaisobutyrate (SAIB) on Chromosorb W, 20 ft. × ¼ in. Temp., 70—130° programmed. Carrier gas, N_2 at 300 c.c./min. Injection temp., 190°. Detector temp., 220°.

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[5] W. G. Dauben and K. S. Pitzer in Newman's " Steric Effects in Organic Chemistry," Wiley, New York, 1956, ch. I; C. W. Beckett, K. S. Pitzer, and R. Pitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488.

[6] E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, 1961, **26**, 3504.

[7] E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, 1957, **79**, 5992.

[8] E. L. Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962.

[9] N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, 1962, **84**, 2201.

Collector temp., 188°. Chart speed, 10 in./hr. Cooling system, ice–salt. Sample size 0·15 c.c., automatically injected. Recovery of sample 42%.

	trans-Ketone (VI)	*cis*-Ketone (VII)
R_T	54·8 min.	58·6 min.
B. p.	33·5—34·5°/0·6 mm.	33·5—35°/0·6 mm.
d_4^{22}	0·908	0·923
n_D^{25}	1·4511	1·4548

Semicarbazones. The semicarbazones were prepared by shaking the ketone (0·2 g.) with semicarbazide hydrochloride (0·5 g.), sodium acetate (0·7 g.), and water (5 c.c.); the product was crystallised from ethanol. The *trans*-isomer had m. p. 205—206° (cf. ref. 1) (Found: C, 58·9; H, 9·5. Calc. for $C_9H_{17}N_3O$: C, 59·0; H, 9·35%). The *cis*-isomer had m. p. 179° (lit.,[1] gives m. p. 174·5—175·5°) (Found: C, 58·6; H, 9·0%).

Equilibration of the ketones. The ketones were treated as follows, and the products were submitted to analytical g.l.c. under conditions given below.

(1) The ketones were treated with sodium acetate under the conditions of formation of their semicarbazones. No equilibration took place.

(2) A mixture of equal quantities of *trans*- and *cis*-ketones was refluxed for 10 hr. The product consisted of *trans*-(78%) and *cis*-(22%) ketones.

(3) A mixture of equal quantities of the ketones (1 g.) was stirred in benzene (20 c.c.) for 12 hr. with basic alumina (5 g.). The product consisted of *trans*-(80%) and *cis*-(20%) ketones.

(4) A mixture of the pure *trans*-ketone (100 mg.) in acetone (5 c.c.) and concentrated sulphuric acid (0·5 c.c.) was refluxed for 3 min. and the product was extracted with ether. It consisted of *trans*-(80%) and *cis*-(20%) ketones. Pure *cis*-ketone gave a mixture of the same composition.

(5) 2,3-Dimethylcyclohexanone (10 g.) containing the isomers (VI; 44%) and (VII; 56%) was refluxed for 72 hr. with 2N-potassium methoxide in methanol (5 c.c.). The mixture was neutralised and extracted with ether giving an oil containing the isomers (VI; 84%) and (VII; 16%) (cf. ref. 1).

Conditions of analytical g.l.c. Column: SAIB on Chromosorb W; 10 ft. × ⅛ in. Temp. 113—114°, N_2 flow 25 c.c./min. H_2 flow 24 c.c./min. Chart speed 20 in./hr. The *trans*-ketone had R_T 14·3 min., the *cis*-ketone had R_T 17·1 min. The composition of the equilibrated products was confirmed by using a column of diethylene glycol succinate.

2,3-*Dimethylcyclohexanols*.—(1) *Reduction of the* trans-*ketone* (VI). (*a*) The ketone (VI) (500 mg.) in glacial acetic acid (15 c.c.) containing hydrochloric acid (0·75 c.c.) was hydrogenated for 12 hr. over Adams catalyst (0·3 g.). The solvent was removed in a vacuum giving an oil (400 mg.), which was refluxed for 12 hr. with methanolic potassium hydroxide (10%; 15 c.c.), and the product was worked up in the usual way. On submission to g.l.c. as described below it was shown to contain the alcohols (II; 84%), (III; 7%), and (V; 9%). The mixture (0·2 g.) was warmed for 30 min. with 3,5-dinitrobenzoyl chloride (0·4 g.), then washed with sodium hydrogen carbonate solution (5%) and crystallised from methanol giving the 3,5-dinitrobenzoate of the alcohol (II) as fine needles (0·25 g.), m. p. 134·5—135·5° [lit.[4] gives m. p. 119—119·5°], $\nu_{max.}$ 1718 (ester) 1276, 1171, and 1130 cm.$^{-1}$ (Found: C, 55·6; H, 5·7. Calc. for $C_{15}H_{18}N_2O_6$: C, 55·9; H, 5·6%). (*b*) A mixture of ketone (700 mg.) in methanol–water (4 : 1; 20 c.c.) and potassium borohydride (500 mg.) was set aside overnight. It was acidified with 10% hydrochloric acid (20 c.c.) and extracted with ether giving a product containing the alcohols (II; 26%) and (III; 74%). Treatment with 3,5-dinitrobenzoyl chloride as before gave the 3,5-dinitrobenzoate of the alcohol (III) (50% yield) as needles (MeOH), m. p. 118° (cf. ref. 4); $\nu_{max.}$ 1724, 1276, 1174, and 1156 cm.$^{-1}$ (Found: C, 56·15; H, 5·7. Calc. for $C_{15}H_{18}N_2O_6$: C, 55·9; H, 5·6%).

(2) *Reduction of the* cis-*ketone* (VII). Reduction of this ketone in the manner described under (1a, b) afforded a mixture of alcohols consisting of (V; 91%) and (IV; 9%). This mixture yielded the 3,5-*dinitrobenzoate* of the alcohol (V), as plates (light petroleum), m. p. 65°; $\nu_{max.}$ 1721, 1274, 1172, and 1153 cm.$^{-1}$ (Found: C, 55·4; H, 5·7. $C_{15}H_{18}N_2O_6$ requires C, 55·9; H, 5·6%).

3,5-*Dinitrobenzoate of the alcohol* (IV). Partial separation, by preparative g.l.c., of the products obtained from the hydrogenation of 2,3-xylenol gave a mixture of alcohols containing (IV; 60%) and (V; 40%). This mixture gave a gummy 3,5-dinitrobenzoate. This (500 mg.) was absorbed on neutral alumina and eluted with a mixture of benzene and ether (4 : 1) giving the 3,5-*dinitrobenzoate of the alcohol* (IV) as plates (light petroleum), m. p. 80°; $\nu_{max.}$ 1724, 1285, 1176, and 1126 cm.$^{-1}$ (Found: C, 55·7; H, 5·5. $C_{15}H_{18}N_2O_6$ requires C, 55·9; H, 5·6%). This material (200 mg.) when refluxed for 10 hr. with 10% methanolic potash (10 c.c.) gave the alcohol (IV), which was shown by g.l.c. to consist of a single compound.

Conditions for the preparative separation of the 2,3-*dimethylcyclohexanols.* Column: 30% SAIB on Chromosorb P., 10 ft. × $\frac{3}{8}$ in. Temp. 130°. N_2 flow 300 c.c./min. Chart speed 10 in./hr. Sample size 0·25 c.c. automatically injected. R_T; (II, III), 37·3 min.; (IV, V), 51 min.

Conditions for the analysis of the 2,3-*dimethylcyclohexanols by g.l.c.* Column: 30% SAIB on Chromosorb W., 10 ft. × $\frac{1}{8}$ in. Temp. 113—114°. N_2 flow 25 c.c./min. H_2 flow 25 c.c./min. Chart speed 20 in./hr. R_T; (II), 17·7 min.; (III), 19·0 min.; (IV), 24 min.; (V) 26 min. The composition of the mixture was confirmed by the use of a column of diethylene glycol succinate.

Equilibration of the mixture of alcohols. The mixture (10 g.), obtained from the hydrogenation of 2,3-xylenol, was refluxed for 48 hr. with sodium (1 g.) in ethanol (5 c.c.). The product was neutralised and extracted with ether, and the extract was washed with water. Removal of solvent gave an oil, which was shown to contain the alcohols in the amounts shown (II; 17·1%), (III; 69·3%), (IV; 7·7%), and (V; 5·9%). This composition was unchanged after further refluxing for 1 week.

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