

368. *Epimeric Alcohols of the cycloHexane Series. Part VIII.*
Inactive 2- and 4-Methylcyclohexanol.

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Details are given of the separation and purification of the inactive epimers of 2-methylcyclohexanol and the epimers of 4-methylcyclohexanol, with lists of solid derivatives. A useful degree of separation of the epimers in mixtures of the 4-methylcyclohexanols, as well as the 2-methylcyclohexanols, may be effected by partial esterification with *o*-nitrobenzoyl chloride.

NEEDING pure samples of the geometrical isomers of the various methylcyclohexanols as reference compounds in another research, we have investigated the preparation of the epimeric forms of 2- and 4-methylcyclohexanol; the 3-methylcyclohexanols have been discussed recently (Macbeth and Mills, *J.*, 1945, 709).

Several investigators have reported the preparation of epimeric 2-methylcyclohexanols and their solid derivatives, and there is general agreement between the data of Skita and Faust (*Ber.*, 1931, **64**, 2878), Huckel and Hagenguth (*ibid.*, p. 2892), and Vavon, Perlin, and Horeau (*Bull. Soc. chim.*, 1932, **51**, 644). We have prepared the 2-methylcyclohexanols by somewhat different methods, and our results agree closely with those of Vavon, Perlin, and Horeau. The *cis*- and *trans*-3 : 5-dinitrobenzoates and the *trans*-*o*-nitrobenzoate are esters through which the alcohols may conveniently be purified. Attempts to separate the piperazine salts of the hydrogen phthalates, on the lines described by Macbeth and Mills (*loc. cit.*) for the 3-methylcyclohexanols, were unsuccessful.

The 4-methylcyclohexanols have been less thoroughly investigated than the 2-methylcyclohexanols, and the only papers describing purification of the epimers through solid esters are

those of Gough, Hunter, and Kenyon (*J.*, 1926, 2052) and of Skita and Faust (*loc. cit.*). Our results, which differ considerably from those of the above authors, indicate that the *cis*-epimer has not previously been obtained in a pure state. The *cis*-4-methylcyclohexanol of Skita and Faust apparently was impure *trans*-4-methylcyclohexanol, as the melting points of their solid esters are only slightly below that of the *trans*-esters. The *cis*-alcohol of Gough, Hunter, and Kenyon apparently was a mixture and gave a phenylurethane corresponding in melting point to our *trans*-phenylurethane, but a *p*-nitrobenzoate of melting point corresponding to our *cis*-*p*-nitrobenzoate; this is the behaviour to be expected of a mixture containing considerable amounts of each of the epimeric alcohols, in view of the melting points and solubilities of the esters concerned (cf. table).

Properties of the (±)-2-Methylcyclohexanols and the 4-Methylcyclohexanols.

	(±)-2-Methylcyclohexanols.		4-Methylcyclohexanols.	
	<i>cis.</i>	<i>trans.</i>	<i>cis.</i>	<i>trans.</i>
d_4^{20} of alcohol	0.9274	0.9174	0.9173	0.9040
n_D^{20} of alcohol	1.4649	1.4616	1.4614	1.4561
<i>o</i> -Nitrobenzoate, m. p.	oil	60—60.5°	oil	68—68.5°
<i>p</i> -Nitrobenzoate, m. p.	56—57°	64.5—65°	96°	64—65°
3 : 5-Dinitrobenzoate, m. p.	100—101°	117°	106—107°	142°
Hydrogen phthalate, m. p.	102—104°	124—125°	84—85°	120—121°
Phenylurethane, m. p.	92—93°	105°	103—104°	124—124.5°
α -Naphthylurethane, m. p.	112°	156°	106—107°	159.5—160°

The differences in physical properties of the *cis*- and *trans*-4-methylcyclohexanols, and in the melting points of their derivatives, were much greater than in the case of the 2- and 3-methylcyclohexanols, and the *p*-nitrobenzoate of *cis*-4-methylcyclohexanol showed an abnormally high melting point, but the purity of the epimeric alcohols was proved by regeneration of each epimer from two solid esters, the *cis*-*p*-nitrobenzoate and *cis*-hydrogen phthalate, the *trans*-3 : 5-dinitrobenzoate and *cis*-*o*-nitrobenzoate.

The physical constants of the epimeric alcohols and their derivatives are given in the table. They are in agreement with the configurations assigned, with the exception of *cis*-4-methylcyclohexyl *p*-nitrobenzoate.

As in the case of *m*-cresol (Macbeth and Mills, *loc. cit.*), rapid hydrogenation of *o*- and *p*-cresol over Raney nickel definitely favoured the formation of the corresponding *trans*-methylcyclohexanols, and hydrogenation of 2- and 4-methylcyclohexanone over Raney nickel at 120—130° gave mixture of alcohols in which the *cis*-epimer was in moderate excess (about 60%).

The separation of *cis*-2-methylcyclohexanol from large amounts of the *trans*-epimer involved very tedious fractional crystallisations, and an attempt was made to increase the percentage of *cis*-epimer by partial esterification of the mixture. Read and Grubb (*J.*, 1934, 1781) showed that with *p*-nitrobenzoyl chloride menthol (*trans*) reacts at 16.5 times the speed of neomenthol (*cis*), and that with *o*-nitrobenzoyl chloride the ratio of rates of reaction is 22.5; these differences were used to effect a separation of menthol and neomenthol. Read and co-workers have also used partial esterification to separate mixtures of isomenthols (*J.*, 1934, 313) and carvomenthols (*J.*, 1935, 1138). The data given for the separation of the carvomenthols show that the *trans*-configuration of methyl and hydroxyl groups increased the rate of reaction with *p*-nitrobenzoyl chloride about six-fold as compared with the *cis*-configuration. The configuration of methyl and hydroxyl groups found in carvomenthol is also present in 2-methylcyclohexanol, but for the latter the ratio of rates of reaction of *trans* and *cis* was only about 2 : 1, when using *o*-nitrobenzoyl chloride, which might be expected to show the largest ratio of reactivities. However, this difference in reactivity was sufficient to give a useful enrichment of *cis*-epimer in the mixture from the hydrogenation of 2-methylcyclohexanone, and its complete purification was then easily effected.

Purification of *cis*-4-methylcyclohexanol could be carried out without its enrichment in the mixture from hydrogenation, but a partial esterification was carried out on a mixture of *cis*- and *trans*-4-methylcyclohexanol, with the interesting result that for these two epimers with *o*-nitrobenzoyl chloride the ratio of reactivity of *trans* to that of *cis* is about 2.5 : 1, a ratio at least as great as that found for the 2-methylcyclohexanols. If the lower rate of reaction of the *cis*-epimer is due only to steric hindrance by the methyl group, the hindering effect is equally as great when the methyl group is in position 4 to the hydroxyl as when it is in position 2. The introduction of an *isopropyl* group at position 5, as in carvomenthol, accentuates the difference

in reactivity associated with the 2-methyl group. (For the method of calculating the ratios, see the article by Read and Grubb, *loc. cit.*)

3 : 5-Dinitrobenzoyl chloride was prepared by the use of pyridine and a molar proportion of thionyl chloride (cf. Human and Mills, *Nature*, 1946, 158, 877), and the solution so obtained was used directly for preparation of 3 : 5-dinitrobenzoates without isolation of the chloride.

EXPERIMENTAL.

(±)-*trans*-2-Methylcyclohexanol.—Purified *o*-cresol (187 g.) was hydrogenated over Raney nickel (3 g.), reaction commencing at 150°/2600 lb. and being complete after 3.5 hours at 180°. Removal of the catalyst, and distillation *in vacuo*, gave a mixture of 2-methylcyclohexanols (170 g.), d_4^{30} 0.9206 (68% *trans*).

Dry, powdered 3 : 5-dinitrobenzoic acid (50 g.) was mixed with anhydrous pyridine (40.5 g., 2.2 moles) and anhydrous benzene (100 ml.), and the suspension cooled. With thorough stirring and exclusion of moisture, pure thionyl chloride (25.6 g., 1.0 mole) in benzene (80 ml.) was dropped in during 30 minutes, the temperature being maintained below 30°. The solution was then boiled for 10 minutes. The mixture of 2-methylcyclohexanols (25.7 g., 1.0 mole) obtained above, dissolved in benzene (80 ml.), was added during a period of 40 minutes, with stirring and cooling to below 30°. The solution was then heated under reflux for an hour and kept at room temperature overnight. Removal of pyridine hydrochloride and free 3 : 5-dinitrobenzoic acid in the usual way was followed by steam-distillation of the benzene solution. The mixture of 3 : 5-dinitrobenzoates so obtained solidified readily on cooling; m. p. 70–80° (85% yield). A systematic three-stage crystallisation from 95% alcohol gave, after five crystallisations, a 43% recovery of pure (±)-*trans*-2-methylcyclohexyl 3 : 5-dinitrobenzoate, as fine pale yellow needles, m. p. 117°. The pure ester was hydrolysed by heating under reflux for 30 minutes with a 5% solution of potassium hydroxide (1.3 moles) in methyl alcohol. Working up in the usual way, followed by continuous extraction of the aqueous steam-distillate with light petroleum (b. p. 40–60°), gave pure (±)-*trans*-2-methylcyclohexanol, b. p. 53°/3.5 mm. (85%).

Of the derivatives listed in the table, the *p*-nitrobenzoate (plates) was recrystallised from aqueous methyl alcohol, the hydrogen phthalate (granules), phenylurethane (rosettes), and α -naphthylurethane (fine needles) from light petroleum. The melting points of these derivatives, and all others for which no analyses are given, agree closely with values in the literature.

(±)-*cis*-2-Methylcyclohexanol.—The mixture of 2-methylcyclohexanols resulting from the hydrogenation of *o*-cresol was oxidised by the method used by Macbeth and Mills (*loc. cit.*) for 3-methylcyclohexanol, giving (±)-2-methylcyclohexanone, d_4^{30} 0.9160, in 80% yield.

This ketone (50 g.) was hydrogenated over Raney nickel (3 g.) at 130°/2300 lb., the reduction requiring 2.5 hours. From the product, (±)-2-methylcyclohexanol, free of ketone, was recovered in 92% yield; it had d_4^{30} 0.9231 (57% *cis*).

The following procedure doubled the ratio of *cis*- to *trans*-epimer in the mixture. Pure *o*-nitrobenzoic acid was converted into the chloride by thionyl chloride under the conditions recommended by Bonner and Hurd (*J. Amer. Chem. Soc.*, 1946, 68, 344). The (±)-2-methylcyclohexanol (57% *cis*) (49 g.) was dissolved in anhydrous pyridine (200 ml., 5.7 moles) and stirred vigorously while a solution of *o*-nitrobenzoyl chloride (from 50 g. of acid, 0.7 mole) in benzene (40 ml.) was added during 1.5 hours at <25°. The solution of *o*-nitrobenzoyl chloride gave a dark-blue insoluble solid if allowed to react with pyridine in the absence of excess of alcohol and must thus be dropped into the pyridine solution without splashing on the walls of the flask. After the mixture had been kept at 25–30° overnight, pyridine was removed by pouring it into hydrochloric acid containing crushed ice, the acidic solution was extracted with ether, and the extracts were washed with dilute alkali, followed by water. The ether, benzene, and unesterified alcohol were steam-distilled from the mixed *o*-nitrobenzoates, and from the distillate (±)-2-methylcyclohexanol was recovered (12.5 g., 77%), d_4^{30} 0.9251 (77% *cis*).

This alcohol was esterified with 3 : 5-dinitrobenzoic acid by the method described above, giving a crude ester with m. p. 70–75° (88% yield). A six-fold systematic recrystallisation from 95% alcohol gave (±)-*cis*-2-methylcyclohexyl 3 : 5-dinitrobenzoate as fine, pale yellow needles, m. p. 100–101° (55% recovery). Hydrolysis of this ester gave pure (±)-*cis*-2-methylcyclohexanol, b. p. 50.5°/2.9 mm. (80%).

Physical properties are listed in the table. The *p*-nitrobenzoate (pale needles) was recrystallised from aqueous methyl alcohol, the hydrogen phthalate (rosettes) and the phenylurethane (fine needles) from light petroleum. The α -naphthylurethane was obtained as felted white needles from light petroleum (Found: N, 5.0. $C_{18}H_{21}O_2N$ requires N, 5.0%).

The mixed *o*-nitrobenzoates obtained in the partial esterification were placed in a refrigerator, where they slowly became partly solid. Washing out of oil by ice-cold light petroleum (b. p. 40–60°), followed by several recrystallisations of the solid from light petroleum, gave pure (±)-*trans*-2-methylcyclohexyl *o*-nitrobenzoate (19 g.) as large yellow rhombs, m. p. 60–60.5° (Found: N, 5.4. $C_{14}H_{17}O_2N$ requires N, 5.3%). Hydrolysis of this ester with methanolic potassium hydroxide gave (±)-*trans*-2-methylcyclohexanol with the same density, d_4^{30} 0.9174, as the product from the 3 : 5-dinitrobenzoate.

trans-4-Methylcyclohexanol.—Pure *p*-cresol was hydrogenated under conditions similar to those used for *o*-cresol and gave a 91% yield of 4-methylcyclohexanol, d_4^{30} 0.9069 (82% *trans*).

The alcohol was esterified with pure 3 : 5-dinitrobenzoyl chloride, giving a nearly theoretical yield of ester, m. p. 103–120°, which after five crystallisations from light petroleum (b. p. 80–140°, 8 ml./g.) was obtained as pure *trans*-4-methylcyclohexyl 3 : 5-dinitrobenzoate, fine pale yellow needles, m. p. 142° (47% recovery). Hydrolysis of the 3 : 5-dinitrobenzoate in the usual way gave an 85% yield of *trans*-4-methylcyclohexanol, b. p. 54°/3 mm.

The *p*-nitrobenzoate (plates) was recrystallised from aqueous methanol, the hydrogen phthalate (rectangular prisms) and the phenylurethane (flat plates) from light petroleum. The α -naphthylurethane was obtained after crystallisation from light petroleum as white felted crystals (Found: N, 5.0%).

cis-4-Methylcyclohexanol.—Oxidation of 4-methylcyclohexanol by the method used for 2-methyl-

cyclohexanol gave 4-methylcyclohexanone, d_4^{30} 0.9072, in 86% yield. Hydrogenation of this ketone over Raney nickel at 125—130° gave in 93% yield a 4-methylcyclohexanol, d_4^{30} 0.9118 (59% cis).

Esterification of the alcohol with a slight excess of *p*-nitrobenzoyl chloride gave a crude *p*-nitrobenzoate, m. p. 60—68° (95%). Fractional crystallisation five times from methyl alcohol (95%, 5 ml./g.) yielded pure *cis*-4-methylcyclohexyl *p*-nitrobenzoate, thin pale yellow laths, m. p. 96° (34% recovery) (Found: N, 5.2. Calc. for $C_{14}H_{17}O_4N$: N, 5.3%), hydrolysis of which gave pure *cis*-4-methylcyclohexanol, b. p. 52°/2 mm., d_4^{30} 0.9173, n_D^{30} 1.4614 (87% yield).

The pure *cis*-alcohol was characterised by the preparation of the 3 : 5-dinitrobenzoate, large yellow needles from light petroleum (Found: N, 8.8. $C_{14}H_{16}O_6N_2$ requires N, 9.1%), the phenylurethane, fine white needles from light petroleum (Found: N, 6.1. $C_{14}H_{19}O_2N$ requires N, 6.0%), and the α -naphthylurethane, white granules from light petroleum (Found: N, 5.0%).

The hydrogen phthalate was made in 93% yield from the *cis*-4-methylcyclohexanol obtained above, by heating it with phthalic anhydride (1.1 moles) in pyridine (2.5 moles) for four hours at 50—60°. One crystallisation of the crude ester from light petroleum (b. p. 60—90°) gave white, chunky crystals, m. p. 84—85° (Found: neut. equiv., 261. $C_{15}H_{18}O_4$ requires neut. equiv., 262). Three more recrystallisations from the same solvent caused no change in melting point, and hydrolysis at this stage regenerated an alcohol with d_4^{30} 0.9174, which was converted into a *p*-nitrobenzoate, m. p. 96°.

Separation of 4-Methylcyclohexanols by Partial Esterification.—A mixture of *cis*- and *trans*-4-methylcyclohexanol (91 g.), d_4^{30} 0.9084 (33% *cis*), was esterified with the acid chloride prepared from *o*-nitrobenzoic acid (100 g., 0.75 mole), by the method used for the partial esterification of 2-methylcyclohexanol. Unesterified alcohol was recovered (16.5 g., 72%), d_4^{30} 0.9116 (57% *cis*). The mixture of *o*-nitrobenzoates obtained was set aside until partial solidification occurred, and worked up by the method used for the 2-methylcyclohexyl esters, yielding pure *trans*-4-methylcyclohexyl *o*-nitrobenzoate (56 g., 49%) as large pale yellow rhombs, m. p. 68°, from light petroleum (Found: N, 5.2%). Hydrolysis of this ester gave *trans*-4-methylcyclohexanol, d_4^{30} 0.9041.

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