cyclo*Hexane Derivatives. Part I. Preparation of* cis- *and* trans-3 : 3 : 5-*Trimethyl*cyclo*hexanol and Proof of Configuration.*

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The *cis*- and the *trans*-isomer of 3 : 3 : 5-trimethyl*cyclo*hexanol have been isolated in the pure state and several of their derivatives prepared; the melting point–composition relation of the isomeric alcohols has been studied, and configurations have been assigned to them on the basis of their relative stability and infrared spectra; the isomer of m. p. 57·3° is considered to be the *trans*-, and that of m. p. 37·3 to be the *cis*-form.

CONSIDERABLE confusion exists as to the identity and configuration of *cis*- and *trans*-3 : 3 : 5-trimethyl*cyclo*hexanol (see Table 1). Pure isomers were required for work on the mechanism of reductions of cyclic compounds, also unassailable assignment of configurations.

TABLE 1. *Summary of previous methods of preparation and properties of* 3 : 3 : 5-*trimethyl*cyclo*hexanol,*

Starting material	Reagent	M. p. of product	Configuration assigned	Yield (%)
(*a*) *iso*Phorone	Moist Et_2O–Na	37°	*trans* [b]	—
(*b*) *iso*Phorone	Na–EtOH	34·5	*trans*	70—75
(*c*) Dihydro*iso*phorone	H_2–Pt in AcOH	52	—	—
(*d*) *iso*Phorone	H_2–Adkins' catalyst	58·5	*	—
(*e*) *iso*Phorone	H_2–Pt	58·5—59·0	—	—
(*f*) *iso*Phorone	H_2–Ni	—	—	~100%
(*g*) *iso*Phorone	H_2–catalyst	—	—	98
(*h*) Dihydro*iso*phorone	$LiAlH_4$ in Et_2O	Oil	*cis*	85
(*i*) 3 : 3 : 5-Trimethyl*cyclo*hexanol (m. p. 34·5°)	Isomerisation with Zn–HCl–AcOH	Oil	*cis*	—

* Considered to be identical with products from (*a*) and (*b*).

[a] Kerp, *Annalen*, 1896, **290**, 139. [b] Knoevenagel and Fischer, *ibid.*, 1897, **297**, 194. [c] Skita and Meyer, *Ber.*, 1912, **45**, 3593. [d] Morgan and Hardy, *Chem. and Ind.*, 1933, 518. [e] Dodge and Kremers, *J. Amer. Pharm. Assoc.*, 1942, **31**, 527. [f] Birch and Johnson, *J.*, 1951, 1493. [g] Ipatiev, Germain, and Pines, *Bull. Soc. chim. France*, 1951, 259. [h] Braude and Evans, *J.*, 1954, 607. [i] As (*b*).

This led us to re-investigate the hydrogenation of *iso*phorone. By a combination of fractional distillation and crystallisation of the mixtures resulting after the use of a reduced nickel catalyst, we have obtained isomers of 3 : 3 : 5-trimethyl*cyclo*hexanol of m. p. 57·3°, b. p. 76°/10 mm., and m. p. 37·3°, b. p. 85°/10 mm., and characterised them by a number of derivatives (see Table 2); a melting point–composition diagram of the two isomers has

TABLE 2. *M.p.s of* cis- *and* trans-3 : 3 : 5-*trimethyl*cyclo*hexanol and its derivatives.*

	cis	*trans*		*cis*	*trans*
Alcohol	37·3°	57·3°	Hydrogen phthalate ...	129°	122·5°
α-Naphthylurethane	71	132	Phthalate	93	57
3 : 5-Dinitrobenzoate † ...	71	98			

† Dodge and Kremers (*loc. cit.*) described a 3 : 5-dinitrobenzoate, m. p. 98·5—99°, prepared from their alcohol of m. p. 58·5—59°; no analysis was reported. From their commercial "*iso*phoronyl alcohols" they prepared another two products described as 3 : 5-dinitrobenzoates, again without analytical figures, of m. p. 61·5—63° and 71·5—72·5°. Braude and Evans (*loc. cit.*) isolated from their liquid product a 3 : 5-dinitrobenzoate, m. p. 71°, which may have been a stereochemically pure ester.

been used to analyse the products obtained in this work. The isomer of higher m. p. is much less soluble in all the usual organic solvents than the other isomer, which is extremely soluble; mixtures containing not less than 30% of the other form are

difficult to separate by crystallisation or simple distillation. It seems that earlier workers have, in general, isolated the higher-melting isomer admixed with varying amounts of the other.

Reductions with sodium and alcohol in this laboratory have given total products of m. p. 26°, containing 37% of high- and 63% of low-melting isomer;* thus, the products isolated by Kerp, and by Knoevenagel and Fischer, must have been mixtures containing about 65% of high- and 35% of low-melting isomer.

An experiment by Morgan and Hardy's method gave a mixture containing about 70% of the low-melting isomer although the other form was the isomer isolated after extensive recrystallisation. The product isolated by Dodge and Kremers was the pure high-melting isomer; Skita and Meyer's was mainly the high- containing about 15% of the low-melting isomer. Since all the mixtures melt at not below 20°, the liquid product isolated by Braude and Evans cannot have been a pure isomer. Work in these laboratories has shown that reduction of dihydro*iso*phorone by lithium aluminium hydride gives a 1 : 1 mixture of *cis*- and *trans*-isomers.*

The isomer of m. p. 37·3° which we have isolated therefore does not appear to have been described previously. It is suitably prepared (*ca.* 70% of the total product) by hydrogenation of *iso*phorone with nickel catalyst at about 130°/100 lb. per sq. in. On the other hand similar hydrogenation at room temperature gives a crude product containing up to 90% of the high-melting isomer. We found that in the presence of nickel catalyst and hydrogen either isomer can be epimerised to a mixture of the two; at equilibrium the isomer of lower m. p. preponderates and it would therefore be expected, from the work of Hassel and Ottar (*Acta Chem. Scand.*, 1947, **1**, 929), of Beckett, Pitzer, and Spitzer, (*J. Amer. Chem. Soc.*, 1947, **69**, 2488), and of many later workers, that this, the more stable isomer, is the *cis*-form. In *cis*-1 : 3-disubstituted *cyclo*hexanes the two substituents are both in relatively unhindered equatorial positions and, when one of these is a hydroxyl group, the tendency for intermolecular hydrogen bonding would be expected to be much greater than in the corresponding *trans*-compound. We prepared pure *cis*- and *trans*-3-methyl*cyclo*hexanol as reference compounds since their configuration has been unequivocally established (Goering and Serres, *ibid.*, 1952, **74**, 5908; Noyce and Denney, *ibid.*, p. 5912). The infrared spectra (Table 3) show that, as postulated, the intensity of

TABLE 3. *Optical density of two infrared bands of* cis- *and* trans-*isomers.*

		3-Methyl*cyclo*hexanol				3 : 3 : 5-Trimethyl*cyclo*hexanol			
Concn.	Cell	*cis*		*trans*		M. p. 37·3°		M. p. 57·3°	
(%)	(mm.)	2·75 μ	2·9 μ	2·75 μ	2·9 μ	2·75 μ	2·9 μ	2·75 μ	2·9 μ
5	0·5	0·099	0·984	0·130	0·640	0·096	0·795	0·154	0·361
1	10	0·286	0·602	0·324	0·434	0·350	0·480	0·380	0·288
0·25	10	0·195	0·030	0·203	0·018	0·208	0·027	0·213	0·012

absorption at 2·9 (hydrogen-bonded hydroxyl) relative to that at 2·75 μ (unassociated hydroxyl) is markedly greater in the *cis*- than in the *trans*-compound; a similar difference exists in the spectra of the isomers of 3 : 3 : 5-trimethyl*cyclo*hexanol; here, owing to the proximity of the associated and unassociated hydroxyl bands and their consequent interaction, it proved impossible to measure optical densities with a high absolute accuracy, but relative values at any one concentration illustrate the stronger association in the *cis*-compounds and we conclude that the isomers of m. p. 37·3° and 57·3° are respectively *cis*- and *trans*-3 : 3 : 5-trimethylcyclohexanol.† No relation appears to exist between configuration and m. p. of these alcohols and their derivatives (see Table 2).

* These and other non-catalytic reductions will be described in a later paper.

† Pickett and Ungnade (*J. Amer. Chem. Soc.*, 1949, **71**, 1311) showed that the intensity of infrared absorption due to the associated hydroxyl group is greater in the *trans*- than in the *cis*-isomer of 4-phenyl- and 4-*cyclo*hexyl-*cyclo*hexanol and attributed this to some form of steric inhibition; the reason for this inhibition is undoubtedly the same as that given for the compounds described above, except, of course, that in the case of 2- and 4-substituted *cyclo*hexanols it is the *cis*-, and not the *trans*-isomers in which the hydroxyl group occupies the hindered axial position. The infrared method thus appears capable of differentiating *cis*- and *trans*-isomers of substituted *cyclo*hexanols.

Experimental

M. p.s of the isomeric alcohols and mixtures of them were determined by a standard cooling-curve method and are corrected, those of the derivatives of the alcohols by the usual capillary-tube method and are uncorrected. Unless otherwise stated, light petroleum had b. p. 60—80°.

*iso*Phorone was obtained by fractionally distilling commercial material through a column packed with 4-mm. Fenske glass helices (approx. 15 theoretical plates); fractions of constant n_D^{20} (1·478) were collected.

Preparation of trans-3 : 3 : 5-*Trimethyl*cyclo*hexanol*.—*iso*Phorone (138 g.) in methanol (100 ml.) was hydrogenated at room temperature and 100 lb. per sq. in. with a commercial reduced nickel catalyst (7 g.) for 16 hr.; the catalyst was filtered off and washed with methanol. Methanol was distilled off, finally under a vacuum. A colourless crystalline product, m. p. 53—54° (132 g., 93%), was obtained; the m. p. indicated a composition of 86—88% of *trans*-isomer. Analysis by the hydroxylamine method showed less than 1% of ketone calculated as *iso*phorone. This product was recrystallised from light petroleum and then from ethylene dichloride several times until a product of high purity, as indicated by cooling-curve determination, was obtained. The purest sample obtained by this means had m. p. 57·3°, b. p. 76°/10 mm., and gave an *α-naphthylurethane* [from light petroleum (b. p. 80—100°)] (Found : C, 77·1; H, 8·2; N, 4·8. $C_{20}H_{25}O_2N$ requires C, 77·1; H, 8·1; N, 4·5%), *hydrogen phthalate* (from absolute alcohol) (Found : C, 70·6; H, 7·7. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%), *phthalate* (from aqueous alcohol) (Found : C, 75·4; H, 9·4. $C_{26}H_{38}O_4$ requires C, 75·3; H, 9·2%), and 3 : 5-*dinitrobenzoate* (from 95% alcohol) (Found : C, 56·9; H, 6·0; N, 7·9. $C_{16}H_{20}O_6N_2$ requires C, 57·1; H, 6·0; N, 8·3%) (for m. p.s see Table 2).

Preparation of cis-3 : 3 : 5-*Trimethyl*cyclo*hexanol*.—*iso*Phorone (138 g.) was hydrogenated at 130°/100 lb. per sq. in. with a commercial reduced nickel catalyst (7 g.) and, after the absorption of hydrogen ceased (5 hr.), stirring and heating were continued for a further 9 hr. The catalyst was filtered off; the filtrate solidified to a crystalline solid, m. p. 27° (133 g., 94%), containing 70% of *cis*-isomer and less than 0·5% of ketone. This product was fractionally distilled through a packed column (Fenske helices, 15 theoretical plates) with a reflux ratio of 25 : 1.1 Fractions were tested at intervals and those with a cooling curve indicating high purity were combined. The purest material so obtained had m. p. 37·3°, b. p. 86°/10 mm., and gave an *α-naphthylurethane* [from light petroleum (b. p. 80—100°)] (Found : C, 76·8; H, 8·5; N, 4·7%), *hydrogen phthalate* (from acetic acid) (Found : C, 69·9; H, 7·7%), *phthalate* (from absolute alcohol) (Found : C, 75·3; H, 9·2%), and 3 : 5-*dinitrobenzoate* (from 95% alcohol) (Found : C, 57·1; H, 6·3; N, 8·35%) (m. p.s in Table 2).

Melting Point–Composition Curve.—This was constructed from m. p.s determined by the cooling-curve method, using known mixtures of the above two pure isomers. Table 4 illustrates the figures.

TABLE 4. *Melting points of mixtures of* cis- *and* trans-3 : 3 : 5-*trimethyl*cyclo*hexanol*.

Trans (%)	100	95	90	80	70	60	55	50	47·5	40	30	20	10	5	0
M. p.	57·3°	56·8°	55·0°	49·0°	41·5°	32·5°	27·0°	20·0°	21·0°	24·0°	26·8°	30·5°	33·5°	35·5°	37·3°

Isomerisation of 3 : 3 : 5-*Trimethyl*cyclo*hexanol*.—(*a*) 3 : 3 : 5-Trimethyl*cyclo*hexanol (m. p. 54°; 10 g.), containing 88% of *trans*-isomer, and commercial reduced nickel catalyst (0·5 g.) were shaken in an autoclave under hydrogen at 130°/100 lb. per sq. in. for 9 hr. The catalyst was removed. The product had m. p. 27° and contained 70% of *cis*-isomer. Analysis by the hydroxylamine method showed that less than 0·5% of ketone was present.

(*b*) 3 : 3 : 5-Trimethyl*cyclo*hexanol (m. p. 35·2°; 5 g.), containing 95% of *cis*-isomer, and commercial reduced nickel catalyst (0·25 g.) were treated as in (*a*) at 140° for 9 hr. The resulting product had m. p. 28° and contained 73% of *cis*-isomer; its ketone content was less than 0·5%.

Hydrogenation of iso*Phorone by Morgan and Hardy's Method* (loc. cit.).—*iso*Phorone (276 g.) was hydrogenated at 160°/1500 lb. per sq. in. with Adkins's copper–barium chromite catalyst (*J. Amer. Chem. Soc.*, 1932, **54**, 1139) (10 g.) for 10 hr. The catalyst was filtered off; the filtrate solidified, had m. p. 27° (268 g., 94%), and contained 70% of *cis*-isomer. Analysis by the hydroxylamine method showed that less than 0·5% of ketone was present.

Preparation of trans-3-*Methyl*cyclo*hexanol*.—3-Methyl*cyclo*hexanone (50 g.) was hydrogenated with commercial nickel catalyst (2·5 g.) at room temperature and 100 lb. per sq. in. until hydrogen absorption ceased (2 hr.). The catalyst was filtered off; the resultant 3-methyl-*cyclo*hexanol had d_4^{30} 0·9122 and thus contained 77% of *trans*-isomer, according to the figures

given by Macbeth and Mills (*J.*, 1945, 709), transposed to allow for the later reversal of the configuration there assigned to the two isomers.

This 3-methyl*cyclo*hexanol (26 g.) was heated with 3 : 5-dinitrobenzoyl chloride (54 g.) at 130° for 30 min. and the product recrystallised from light petroleum several times, to give the 3 : 5-dinitrobenzoate, m. p. 99°, of the *cis*-alcohol. The mother-liquors gave a residue which, recrystallised four times from methanol, gave impure *cis*-3 : 5-dinitrobenzoate, m. p. 94—98° (mixed m. p. with the *trans*-dinitrobenzoate, 80°). The mother-liquors from the methanol recrystallisations were evaporated and the residue was recrystallised four times from light petroleum, to give the 3 : 5-dinitrobenzoate, m. p. 108—111°, of the *trans*-alcohol.

The *trans*-ester (10 g.) was refluxed with potassium hydroxide (3 g.) in water (25 ml.) and ethanol (250 ml.) for 24 hr. Dilution with water, extraction with ether, evaporation of the extract, steam-distillation of the residue, and extraction of the distillate with light petroleum (b. p. 40—60°) gave *trans*-3-methyl*cyclo*hexanol, b. p. 170—171°/772 mm., n_D^{20} 1·4581 (Macbeth and Mills, *loc. cit.*, give n_D^{20} 1·4583).

Preparation of cis-3-*Methyl*cyclo*hexanol.*—*m*-Cresol (100 g.) was hydrogenated with commercial nickel catalyst (5 g.) at 160°/100 lb. per sq. in. The resultant 3-methyl*cyclo*hexanol had d_4^{30} 0·9101 and thus contained 55% of *cis*-isomer. This material (62 g.) was heated with phthalic anhydride (74 g.) on the steam-bath for 24 hr. The product was poured into an excess of 10% aqueous sodium carbonate solution and stirred until dissolved. The aqueous solution was extracted twice with benzene and then aerated until no smell of benzene remained. The aqueous phase was then acidified and extracted with chloroform; after removal of chloroform, the crude product (100 g.) was treated with light petroleum and cooled in acetone–solid carbon dioxide; the precipitated solid, recrystallised from light petroleum, gave pure *cis*-3-methyl-*cyclo*hexyl hydrogen phthalate, m. p. 94°.

This ester (10 g.) was refluxed with potassium hydroxide (3 g.) in water (25 ml.) and ethanol (250 ml.) for 48 hr. The ethanol was distilled off *in vacuo* from the steam-bath, and the 3-methyl*cyclo*hexanol steam-distilled. The distillate was extracted with light petroleum and the final product distilled, giving *cis*-3-methyl*cyclo*hexanol, b. p. 175°/777 mm., n_D^{20} 1·4579 (Macbeth and Mills, *loc. cit.*, report n_D^{20} 1·4573). Hydrolysis of the ester was later found to proceed satisfactorily in the absence of ethanol and the product could then be directly steam-distilled.

Measurement of Infrared Spectra.—These were determined in CCl_4 solution with a Hilger D. 209 infrared spectrometer with a modified double-beam system (Hales, *J. Sci. Instr.*, 1953, **30**, 52).

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