188. *Epimeric Alcohols of the* cyclo*Hexane Series. Part V. The Optically Inactive 3-Methyl*cyclo*hexanols.*

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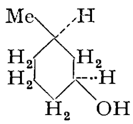
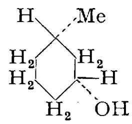
The *dl-cis-* and *dl-trans-*3-methyl*cyclo*hexanols have been prepared in the pure state and been characterised by a number of derivatives. The *trans*-compound is the main product when *m*-cresol is hydrogenated under pressure with Raney nickel catalyst; the *cis*-compound is conveniently prepared by pressure hydrogenation of *dl*-3-methyl*cyclo*hexanone with the same catalyst. The isomers may readily be separated by forming the piperazine salts of their hydrogen phthalates, as the physical characteristics of these salts are such as allow a mechanical separation by flotation to be effectively applied.

3-METHYL*cyclo*HEXANOL is a very suitable subject for a stereochemical investigation, as the spatial configurations of the epimers are related in a fundamental way to those of the naturally-occurring terpene alcohols. As the molecule presents the features involved in *cis–trans* isomerism, and as the carbon atoms 1 and 3 are both asymmetric, the full study of the isomerism involves the preparation and examination of the four isomers written below, namely *d*- and *l*-*cis*- and *trans*-3-methyl*cyclo*hexanol, and the corresponding *dl*-compounds.

The 3-methyl*cyclo*hexanols have been investigated previously, but the data available show some serious discrepancies, and in no case has the examination been complete. Methods for preparing the *dl*-*cis*- (I*a* and I*b*) and the *dl*-*trans*-(II*a* and II*b*) compounds in quantity in the pure state are now described, together


(I*a*.)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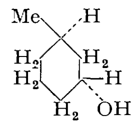
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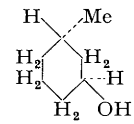
(II*b*.)

with the characterisation of the pure substances by physical constants and by suitable derivatives. Knoevenagel (*Annalen*, 1896, **289**, 142) first prepared *dl*-3-methyl*cyclo*hexanol by the reduction of *dl*-3-methyl*cyclo*hexanone and of *dl*-3-methyl-Δ^2-*cyclo*hexenone. He assigned the *trans*-configuration to the alcohol obtained by alkaline reduction, and assumed that the *cis*-form was the product of acid reduction. Present day views would support this classification but as his *trans*-form had the higher density and refractive index, at least one of his isomers was impure. Pickard and Littlebury (*J.*, 1912, **101**, 115) obtained a 3-methyl*cyclo*hexanol as a by-product from the catalytic hydrogenation of thymol, and this was probably mainly the *trans*-form. Auwers and Schmeltzer (*Chem. Zentr.*, 1927, II, 1562) and Skita and his co-workers (*Ber.*, 1931, **64**B, 2878; *Annalen*, 1923, **431**, 1) also isolated the 3-methyl*cyclo*hexanols as hydrogenation products, but their materials were not pure. The 3 : 5-dinitrobenzoates, for example, were used to purify the product of their hydrogenations of *m*-cresol, an unfortunate choice, as the *dl*-*cis*- and *dl*-*trans*-forms give 3 : 5-dinitrobenzoates which do not differ greatly either in melting point or solubility; and there is a difference of some 20° in m. p. between Skita and Faust's figure and that now recorded for *dl*-*cis*-3-methyl*cyclo*hexyl 3 : 5-dinitrobenzoate. Gough, Hunter, and Kenyon (*J.*, 1926, 2052) submitted the *p*-nitrobenzoates to fractional crystallisation in order to separate and purify the *dl*-*cis*- and *dl*-*trans*-alcohols which they described, but we have found this method also unsatisfactory. Incomplete separation of the epimers probably explains the conflicting m. p.s given for solid derivatives of the isomers in the literature. The figures for the derivatives now described are given in the table, and the occurrence of dimorphism in the case of two derivatives was noted.

Derivatives of 3-*Methyl*cyclo*hexanols.*

	$n_D^{20°}$.	$d_{4°}^{30°}$.	Hydrogen phthalate.	*p*-Nitro-benzoate.	3 : 5-Dinitro-benzoate.	Phenyl-urethane.	α-Naphthyl-urethane.
dl-cis	1·4583	0·9137	72° 84	63°	111°	91° 103	118°
dl-trans	1·4573	0·9072	94	48	99	92	130

m-Cresol is the most convenient source of 3-methyl*cyclo*hexanol, but whereas previous workers generally used platinum catalysts or the less active forms of nickel it is now found that the phenol may be readily hydrogenated in large quantities in the homogeneous state by the use of Raney nickel and hydrogen under high pressure. The product is predominantly *trans*-3-methyl*cyclo*hexanol and, contrary to the statement of Gough, Hunter, and Kenyon (*loc. cit.*), it can be recovered as the hydrogen phthalate. This derivative solidified on standing and readily yielded pure *dl*-*trans*-3-methyl*cyclo*hexyl hydrogen phthalate on treatment with light petroleum.

The small quantity of the *cis*-compound could not be recovered economically from the residual material from the above preparation, but it was obtained (*ca.* 70%) by reduction of 3-methyl*cyclo*hexanone in acid media. Electrolytic reduction of alcoholic solutions containing sulphuric acid, and catalytic reduction using platinum oxide in glacial acetic acid, both gave yields rich in the *cis*-form, but optimum conditions were worked out for pressure hydrogenation of the ketone using Raney nickel, as this enabled work to be done conveniently and on a much larger scale. The rate of hydrogenation and the yield of the *cis*-isomer increase up to a temperature of about 140°; the rate of hydrogenation continues to increase with further rise of temperature, but the proportion of *cis*-form in the product becomes less. A reasonably exact method of assaying the relative proportion of the epimers in the hydrogenation products was based on density determinations after the preparation of pure specimens of the *cis*- and *trans*-compounds and determination of their physical constants. The difference in the refractive indices of the two forms is too small to be applied in this way, but the fraction x of the *cis*-form present in a mixture whose $d_{4°}^{30°}$ value is a, is given by the expression $\frac{a - 0{\cdot}9072}{x} = 0{\cdot}9137 - 0{\cdot}9072$.

A convenient method of separating mixtures of almost any proportions of the *cis*- and *trans*-forms consists in acting on the hydrogen phthalates with piperazine, in the ratio of one molecule of the base to two molecules of the acid phthalate. Acetone was found to be a suitable solvent, but traces of water must be present for satisfactory operation, as then the salts formed may be separated mechanically by flotation on account of their very different physical properties. As the salts are somewhat unstable it proved best to recover the hydrogen phthalates from the crude separated piperazine salts. The recovery of purified hydrogen phthalates was effective, only relatively small amounts of piperazine being required and the base itself being readily recovered for further use.

In the course of preparation of pure derivatives for the characterisation of the epimeric alcohols it was found that *dl-cis*-3-methyl*cyclo*hexanyl phenylurethane and *dl-cis*-3-methyl*cyclo*hexanyl hydrogen phthalate exist in two modifications, a lower-melting (β) form which could in each case be converted into a higher melting (α) form on heating. The α- and β-phenylurethanes can be reproduced at will, the α-form (m. p. 103°) separating from light petroleum, and the β-form (m. p. 91°) crystallising from alcohol–water mixture. Skita and Auwers (*loc. cit.*) described the *dl-cis*-phenylurethane as melting at 90° whereas Gough, Hunter, and Kenyon (*loc. cit.*) gave its m. p. as 103°. The proof of the existence of the two modifications reconciles these apparently conflicting reports.

Experimental.

Hydrogenation of m-*Cresol*.—In a typical reduction *m*-cresol (90 g.) with Raney nickel (*ca.* 4 g. in 20 c.c. abs. alcohol) was shaken with hydrogen at an initial temperature of 150° and pressure 2,000 lb./sq. in. The reaction started immediately and the temperature soon rose to 200° at which the hydrogenation was allowed to proceed, the pressure being maintained above 1,000 lb. by passing in hydrogen as required. Reaction was complete in about 1·5 hours. After filtration from the catalyst, the product was stirred with dilute alkali to remove traces of phenol and then continuously extracted with ether. After drying the ethereal extract over anhydrous magnesium sulphate and removing the solvent, crude, pale-yellow 3-methyl*cyclo*hexanol (85 g.) was recovered. After distillation this had $d_{4°}^{30°}$ 0·9082 indicating *ca.* 85% *trans*-epimer.

The crude material from such hydrogenations was esterified by heating overnight at 110—115° with 1·1 mol. phthalic anhydride, the syrupy product was stirred whilst hot into sodium carbonate solution (1·5 mols.; 5%) and agitated till dissolved. Traces of oil (possibly methyl*cyclo*hexene) were removed by ether, the carbonate solution acidified with conc. HCl, and the precipitated syrup dissolved in chloroform to separate traces of phthalic acid. After removal of the chloroform (under reduced pressure at the end) the hydrogen phthalate was left standing with occasional stirring and, after some days, became semi-solid. The sticky solid was stirred with twice its volume of ligroin (b. p. 60—90°), filtered, and washed with the same solvent. Recrystallised four times from the ligroin it formed transparent prisms of *dl-trans*-3-methyl*cyclo*hexyl hydrogen phthalate, m. p. 94° (Found: C, 69·1; H, 7·1. Calc.: C, 68·7; H, 6·9%). Further quantities were recovered from the mother-liquors.

Attempts were made to separate the liquid hydrogen phthalate recovered from the light petroleum trituration by formation of metallic salts (Pickard and Littlebury, *loc. cit.*) but, although on the small scale the *trans*-compound could be recovered by fractional crystallisation of the calcium salt, no salt suitable for isolating the *cis*-form was discovered.

dl-3-*Methyl*cyclo*hexanone*.—The conditions prescribed by Beckmann (*Annalen*, 1889, **250**, 325) for the oxidation of *l*-menthol did not give good yields when applied to 3-methyl*cyclo*hexanol. Yields approaching 90% were obtained by the modified procedure described in a typical case, and never more than traces of unchanged alcohol were present. *dl*-3-Methyl*cyclo*hexanol (70 g.) recovered from the above hydrogen phthalates was mixed with water (500 c.c.) and potassium dichromate (66·0 g., 10% excess) in a three-necked 2-l. flask fitted with a mechanical stirrer, thermometer and dropping funnel. Sulphuric acid (93%, 57 c.c.; 20% excess) was dropped in to maintain the temperature at 50—60°. Towards the end, the temperature fell and, after addition of all the acid and cooling, the mixture was extracted with ether, the extract washed thrice with sodium hydroxide (5%), then with water and dried over magnesium sulphate. After removal of the solvent the ketone was distilled, b. p. 64—65°/30 mm.

Hydrogenation of dl-3-*Methyl*cyclo*hexanone*.—(*a*) The ketone (25 g.) in glacial acetic acid (100 c.c.) in a 250 c.c. flask was shaken at laboratory temperature and pressure with Adams (platinum oxide) catalyst (0·3 g.) after removal of air and introduction of hydrogen. Hydrogen uptake was slow and the catalyst had frequently to be reactivated. After 10 hours reaction had ceased and *ca.* 87% of the theoretical amount of hydrogen had been absorbed. After removal of the catalyst and dilution, the acetic acid was neutralised with strong cooling and the mixture continuously extracted with ether. Unchanged ketone was removed from the extract by sodium bisulphite, and the extract washed, dried and distilled under reduced pressure gave *dl*-3-methyl*cyclo*hexanol (14 g.), $d_{4°}^{30°}$ 0·9117, indicating about 69% of the *cis*-epimer. (*b*) The method used by Gillespie, Macbeth, and Swanson (*J.*, 1938, 1820) for the electrolytic reduction of cryptone to dihydrocryptol was used. Each reduction was carried out with 25 g. of the ketone, and was complete in 2 hours at a temperature of 30—35°. The alcoholic solution was diluted with water and continuously extracted with ether, and the extract worked up as above. 3-Methyl*cyclo*hexanol (16 g.) with $d_{4°}^{30°}$ 0·9119, indicating about 72% of the *cis*-epimer, was usually obtained. (*c*) Cooke, Gillespie, and Macbeth (*J.*, 1939, 518) obtained a good yield of *cis*-dihydrocryptol by hydrogenation of cryptone over Raney nickel, and the preparation of 3-methyl*cyclo*hexanol rich in the *cis*-epimer by hydrogenation at a temperature of about 140° was satisfactory. This method was adopted in all preparations of the *cis*-alcohol on account of its convenience and good yields. The ketone (50—60 g.) mixed with Raney nickel (3 g.) in abs. alcohol (20 c.c.) was hydrogenated in a glass-lined bomb at 140° the initial hydrogen pressure being 1,700—1,800 lb./sq. in. The hydrogen uptake extended over about 2 hours. After working up in the usual way 3-methyl*cyclo*hexanol, $d_{4°}^{30°}$ 0·9122 (indicating 77% *cis*-epimer), was obtained in 85—90% yields.

The *dl-trans*-piperazine salt separated in masses of white needles when pure *dl-trans*-3-methyl*cyclo*hexyl hydrogen phthalate (1 g.) and piperazine hydrate (0·35 g.) were dissolved separately in warm acetone and the solutions mixed. Recrystallisation from boiling acetone (100 c.c.) yielded white needles, m. p. 135—136°, which separated slowly. The salt is insoluble in ether and paraffin hydrocarbons, moderately soluble in alcohol, ethyl acetate and hot benzene. The *dl-cis*-salt was prepared similarly and recrystallised from hot acetone, in which it is easily soluble and from which it separates in shining granules having m. p. 122—123·5°. It is insoluble in ether, and more soluble than the *trans*-salt in other solvents, being readily soluble in cold alcohol and in chloroform. The salts are considered to be the neutral piperazine salts, $C_4H_8(NH)_2,2C_7H_{13}O_2C{\cdot}C_6H_4CO_2H$, although it was impossible to get exact analytical figures for this formula as the salts appear to contain variable amounts of water.

The *cis*- and *trans*-salts could be separated when prepared from a mixture of the hydrogen phthalates by using about six times the weight of acetone. The following examples are typical. (*a*) The hydrogen phthalate (92 g.) formed from the alcohol prepared by the hydrogenation of 3-methyl*cyclo*hexanone was added to a solution of piperazine (36·5 g.) in warm acetone (600 c.c.). The reaction was exothermic and the acetone boiled. The hot solution was seeded with crystals of both the pure salts and left two days undisturbed at room temperature. A mixture of fine white needles and glistening prisms separated and after breaking up the crusts the whole mixture was agitated with a turbine stirrer. The suspension of needles could then be poured from the sedimented heavy granules on to a filter. Both lots of crystals were separately stirred again with the filtrates and eventually a clean separation was effected into heavy crystals (53 g.) and needles of the *trans*-salt (18 g.). (*b*) Occasionally, particularly with mixtures containing predominantly *trans*-epimer, seeding of the hot acetone solution with the *trans*-salt alone caused the crystallisation of needles of the *trans*-salt without any *cis*-salt: the latter could be obtained after separating the precipitate and seeding the filtrate with the *cis*-salt. For example, the hydrogen phthalate (138 g.) obtained from the hydrogenation product of *m*-cresol was mixed with piperazine hydrate (55 g.) in hot acetone (900 c.c.). On seeding the hot solution, crystallisation started immediately and only needles appeared when left overnight. These were separated (79 g.) and the filtrate, when seeded with the *cis*-salt and left for two days, deposited a mixture of needles (6 g.) and prisms (24 g.) which were separated as above. On strong cooling a low-melting product (18 g.) of mixed *cis*- and *trans*-forms separated. Its formation during large scale separations is avoided by slow crystallisation without disturbance in a stoppered flask at room temperature.

The salts remaining in the mother-liquors, after removal of the crystalline piperazine salts, are decomposed to the hydrogen phthalates for treatment again with piperazine. This is more satisfactory than attempted recovery by further concentration. For example, in the two separations described above, the mother-liquors, containing the low-melting mixture of salts (18 g.), were evaporated to small bulk and run into dilute hydrochloric acid. The hydrogen phthalate (105 g.) recovered as a brownish syrup after extraction with ether was again converted into the piperazine salt, and crystallisation and separation as above yielded the crude *cis*- (51·5 g.) and *trans*- (31·5 g.) salts. From the total crude hydrogen phthalates (230 g.) employed in (*a*) and (*b*) above these relatively simple operations gave good recoveries of the crude *cis*- (128·5 g.) and *trans*- (134·5 g.) salts. The fact that the separation of *cis*- and *trans*-salts was effected from mixtures rich in either form is also of interest.

It was found more convenient and effective not to attempt to purify the piperazine salts but to decompose them to hydrogen phthalates and purify the latter. (*a*) Crude *dl-trans*-piperazine salt (110 g.) was dissolved in boiling methanol (250 c.c.) and the hot solution stirred into cold HCl (600 c.c.; 5%). The hydrogen phthalate separated as an oil and was recovered by ether extraction (thrice). After removal of the solvent the crude hydrogen phthalate (92 g.; 95% recovery) was recrystallised thrice from light petroleum (b. p. 60—90°) giving the pure product (51 g.). The mother-liquors were used for crystallising further batches of the crude material. (*b*) The crude *cis*-salt (85 g.) when similarly decomposed gave the crude hydrogen phthalate (66 g.; 91% recovery) which yielded the pure product (26 g.) after three crystallisations from light petroleum (b. p. 40—90°).

The purified hydrogen phthalates were hydrolysed and the liberated alcohol separated by steam distillation of the solution containing aqueous sodium hydroxide (3 mols., 10%). The distillate was continuously extracted with ether, the extract dried with anhydrous magnesium sulphate and, after removal of the solvent, the alcohol was distilled under reduced pressure. This gave (93% yield) *dl-trans*-3-methyl*cyclo*hexanol, b. p. 60°/2 mm.; $n_D^{20°}$ 1·4573; $d_{4°}^{20°}$ 0·9072. Similarly *dl-cis*-3-methyl*cyclo*hexanol was obtained having b. p. 72—73°/20 mm.; $n_D^{20°}$ 1·4583; $d_{4°}^{20°}$ 0·9137.

Derivatives of the 3-*Methyl*cyclo*hexanols*.—*dl-trans*-3-Methyl*cyclo*hexyl *p*-nitrobenzoate crystallised from methanol–water in pale-yellow feathery crystals, m. p. 47·8° (Found: C, 63·9; H, 6·4. Calc.: C, 63·85; H, 6·5%). *dl-cis*-3-Methyl-*cyclo*hexyl *p*-nitrobenzoate crystallised from the same solvent had m. p. 62—63°. *dl-trans*-3-Methyl*cyclo*hexyl 3:5-dinitrobenzoate separated from ligroin or methanol–water in almost colourless granules, m. p. 99° (Found: C, 54·5; H, 5·2; N, 9·15. Calc.: C, 54·6; H, 5·4; N, 9·1%). The *α-naphthylamine complex* was precipitated by adding a 5% ethereal solution of the dinitrobenzoate to a slight excess of α-naphthylamine in 85% alcohol. It recrystallised from light petroleum in long, brick-red needles having m. p. 142—143° (Found: C, 63·9; H, 5·5. $C_{14}H_{16}O_6N_2,C_{10}H_9N$ requires C, 63·8; H, 5·6%). *dl-cis*-3-Methyl*cyclo*hexyl 3:5-dinitrobenzoate separated from methanol in long, colourless needles having m. p. 110—111° (Found: C, 54·5; H, 5·2. Calc.: C, 54·5; H, 5·2%). The *α-naphthylamine complex*, made as above, separated from ligroin in fine, brick-red needles, m. p. 129·5—130·5° (decomp.) (Found: C, 63·75; H, 5·65. $C_{24}H_{25}O_6N_3$ requires C, 63·8; H, 5·6%). *dl-trans*-3-Methyl*cyclo*hexanyl α-naphthylurethane was prepared by mixing the alcohol and α-naphthyl *iso*cyanate in equimolecular quantities in a little light petroleum. The solid which separated was recrystallised from light petroleum and had m. p. 128·5—129·5° (Found: C, 76·5; H, 7·5. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5%). dl-cis-3-*Methyl*cyclo*hexanyl α-naphthylurethane* crystallised from light petroleum as brilliant slender needles having m. p. 117·5—118·5° (Found: C, 76·25; H, 7·4. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5%). *dl-trans*-3-Methyl*cyclo*hexanyl phenylurethane was prepared in a similar way and purified by recrystallisation from light petroleum (charcoal); but there was some difficulty in obtaining it with a constant and definite m. p. It crystallised in small pearly plates, m. p. 91—92° (Found: C, 71·9; H, 8·2; N, 6·05. Calc.: C, 72·05; H, 8·2; N, 6·0%). *dl-cis*-3-Methyl*cyclo*hexanyl phenylurethane, recrystallised from light petroleum, separated in flat hexagonal prisms, melting at 101—103° with some softening *ca.* 80—90° (Found: C, 72·15; H, 8·2. Calc. for $C_{14}H_{19}O_2N$: C, 72·05; H, 8·2%). The compound is dimorphic and can be obtained as the α-form when crystallised from light petroleum or as the unstable β-form from dilute alcohol from which it separates as white needles which melt at 90—91° but quickly solidify to melt again at 100—102° on continued heating (Found: C, 71·95; H, 8·25. Calc. for $C_{14}H_{19}O_2N$: C, 72·05; H, 8·2%).

dl-cis-3-Methyl*cyclo*hexyl hydrogen phthalate is also dimorphic. The *cis*-alcohol was heated with 10% excess of phthalic anhydride in pyridine at 50—60° for several hours, the mixture poured into dilute acid, and the hydrogen phthalate extracted with ether. On working up in the usual way the hydrogen phthalate was obtained as a white solid melting from 60—65°. It was recrystallised from light petroleum and separated on slow crystallisation as hard nodules and after three crystallisations the m. p. was 68—71°. This was the lower-melting or β-form (Found: C, 68·75; H, 7·05. Calc. for $C_{15}H_{18}O_4$: C, 68·7; H, 6·9%). When finely powdered the substance described above was found to melt at 82—83·5°. The melt of this, and also of the uncrushed nodules having m. p. 68—71°, was found to have m. p. 81—83°. On dissolving the nodular crystals in light petroleum and seeding with some of the solid which had been melted and cooled the higher-melting, α, form of hydrogen phthalate quickly separated in transparent irregular crystals having m. p. 82—83°. This form is identical with the *dl-cis*-hydrogen phthalate obtained from the piperazine salt separations described above (Found: C, 69·2; H, 7·0%).

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