279. *Epimeric Alcohols of the* cyclo*Hexane Series. Part IX.** (±)-cis-3-*Methyl*cyclo*hexylmethanol and* (±)-cis-3-*Methyl*cyclo*hexanecarboxylic Acid.*

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Mixtures of varying proportions of the epimers of 3-methyl*cyclo*hexanecarboxylic acid have been prepared by the hydrogenation of *m*-toluic acid under different conditions, and by the catalytic hydrogenation of (±)-3-methyl*cyclo*hex-1-enecarboxylic acid. Purification through the piperazine salt gives pure (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid. Hydrogenolysis in the presence of copper chromite of the ethyl ester gives (±)-*cis*-3-methyl*cyclo*hexylmethanol, which was purified through the 3 : 5-dinitrobenzoate. Only one of the epimeric pairs of the acid, and of the alcohol, has been isolated, and the configuration rests on the unambiguous synthesis of the *cis*-alcohol which has recently been carried out by Haggis and Owen (*J.*, 1953, 408).

Systematic crystallisation of the l-menthylphthalamic ester led to the resolution of the (±)-carbinol, upwards of 20 per cent. of (+)-*cis*-3-methyl*cyclo*hexylmethanol being obtained.

THE 2-methyl*cyclo*hexanecarboxylic acids and the related carbinols have already been described by Macbeth, Mills, and Simmonds (*J.*, 1949, 1011), and the 4-methyl compounds by Cooke and Macbeth (*J.*, 1939, 1245). Both acids were prepared by catalytic hydrogenation of the corresponding toluic acids, the carbinols being derived by the hydrogenolysis of the esters of the alicyclic acids. The epimeric acids and alcohols were isolated, and the *cis*- and *trans*-configurations were assigned on the basis of the Auwers–Skita rule (Auwers, *Annalen*, 1919, **420**, 89; 1920, **421**, 1; Skita, *ibid.*, 1922, **427**, 255; *Ber.*, 1920, **53**, 1792; 1922, **55**, 144). Haggis and Owen (*loc. cit.*) have confirmed the configurations by their recent synthesis of the alcohols by a series of stereochemically specific steps.

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The study has now been extended to the 3-methyl*cyclo*hexanecarboxylic acids and the corresponding *cyclo*hexylmethanols. Several preparations of 3-methyl*cyclo*hexanecarboxylic acid have been recorded but in most cases the product was a mixture of the epimers and no effort was made to isolate either pure. A liquid acid was obtained by the sodium–*iso*amyl alcohol reduction of *m*-toluic acid (Markownikoff and Hagemann, *J. pr. Chem.*, 1894, **49**, 71; Perkin and Tattersall, *J.*, 1905, **87**, 1090). Similar products were obtained from 3-chloro- or 3-iodo-methyl*cyclo*hexane (Zelinsky, *Ber.*, 1902, **35**, 2689; Gutt, *ibid.*, 1907, **40**, 2061). Mousseron and Granger (*Bull. Soc. chim.*, 1946, 246) reported that the action of hydrochloric acid on (±)-*trans*-3-methyl*cyclo*hexanol gave (±)-*cis*-1-chloro-3-methyl*cyclo*hexane whereas the use of phosphorus pentachloride gave the *trans*-compound. When the magnesium derivatives of the halides were carbonated the so-called *cis*- and *trans*-3-methyl*cyclo*hexanecarboxylic acids were obtained. These were characterised by anilides. Later (*Bull. Soc. chim.*, 1947, 605), these workers prepared the (−)-*cis*- and the (+)-*trans*-acid from the active 1-chloro-3-methyl*cyclo*hexanes, the acids being purified by fractional distillation of their methyl esters.

We do not regard preparation through the halogen compounds as an altogether reliable method as we found that the methyl*cyclo*hexanecarboxylic acid, obtained from 3-methyl*cyclo*hexanol through the chloride (prepared by the action of hydrochloric acid), contains considerable quantities of 4-methyl*cyclo*hexanecarboxylic acid, identical with the *trans*-acid, prepared by Cooke and Macbeth (*loc. cit.*); migration evidently takes place during the formation of the chloro-compound. Palfray and Rothstein (*Compt. rend.*, 1929, **189**, 701; **190**, 942) also experienced migration when *cyclo*hexane-1 : 3-diol was heated with hydrochloric acid, as 1 : 4-dichloro*cyclo*hexane and 4-chloro*cyclo*hexanol were isolated. Other preparations of the 3-methyl acid have been described by Wallach (*Annalen*, 1912, **389**, 194) and by Mousseron and Granger (*Compt. rend.*, 1944, **218**, 358). In only a few cases have crystalline derivatives of the acid been prepared. These derivatives therefore appear to be of no great value in the characterisation of the acid.

Samples of the mixed epimers of (±)-3-methyl*cyclo*hexanecarboxylic acid were obtained, with d_4^{30} varying from 0·9951 to 0·9971, by the catalytic hydrogenation of *m*-toluic acid under different conditions. In other experiments, hydrogenation of (±)-3-methyl*cyclo*hex-1-enecarboxylic acid in the presence of Raney nickel gave a mixture (d_4^{30} 0·9988) of the epimeric acids, and hydrogenation with platinum oxide in glacial acetic acid gave a mixture (d_4^{30} 0·9977).

Repeated crystallisation of the piperazine salt was found to be the most satisfactory method for the purification of the mixed acids, but some 10 recrystallisations from anhydrous acetone were necessary before a salt of constant m. p. was obtained. The purified piperazine salt on hydrolysis gave (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid, which was further characterised by the preparation of an amide, an anilide, and a *p*-bromophenacyl ester. Only the one epimer could be isolated from the various mixtures, and all attempts to obtain the acid of higher density, from the mother-liquors obtained during the purification of the piperazine salt, were unsuccessful. The amide and some metallic salts were also fractionally crystallised without success.

Little attention has been directed to the 3-methyl*cyclo*hexylmethanols and no solid ester appears to have been prepared. Skita (*loc. cit.*) prepared a mixture of the inactive alcohols in 28% yield by the sodium–ethanol reduction of the ethyl 3-methyl*cyclo*hexanecarboxylate, and Mousseron and Granger reduced the methyl esters of the so-called (−)-*cis*- and (+)-*trans*-acids mentioned above to get the corresponding carbinols. The purity of these alcohols is in doubt as no attempt was made at purification through crystalline derivatives. In the present work the mixed acids obtained by the hydrogenation methods were esterfied with ethanol and sulphuric acid and the resulting ester was, after purification, hydrogenolysed in the presence of a copper chromite catalyst. Attempts to purify the resulting alcohol through its hydrogen phthalate were unsuccessful, but crystallisation of the crude 3 : 5-dinitrobenzoate gave an ester m. p. 81·5—82° which on hydrolysis gave pure (±)-*cis*-3-methyl*cyclo*hexylmethanol, which was characterised by the preparation of a number of esters. We did not succeed in separating the epimeric alcohol from any of our mixtures.

The application of the Auwers–Skita rule appears to find favour generally in the case of 1 : 2- and 1 : 4-disubstituted *cyclo*hexanes : and other workers also associate higher energy content and higher entropy with the *cis*-compound. Haggis and Owen (*loc. cit.*) have synthesised *cis*- and *trans*-2- and *trans*-4-methyl*cyclo*hexylmethanols by a series of stereochemically specific steps, and the identity of their products with those previously prepared has shown the validity of the application of the Auwers–Skita rule in assigning these configurations (Cooke and Macbeth; Macbeth, Mills, and Simmonds, *locc. cit.*).

On the other hand several significant cases have been recorded in which the Auwers–Skita rule is undoubtedly reversed for 1 : 3-disubstituted *cyclo*hexanes. von Auwers and Schmelzer (*Chem. Zentr.*, 1927, II, 1562) queried the validity of the rule for 3-methyl*cyclo*hexylamines; Skita and Rossler (*Ber.*, 1939, **72**, 265) found that the resolvable hexahydro*iso*phthalic acid (*trans*; the *cis*-acid has a plane of symmetry) had in fact the higher density and refractive index. Skita and Faust (*Ber.*, 1939, **72**, 1127) showed that *trans*-3 : 5-dimethyl*cyclo*hexanol, which was also capable of resolution, had a higher refractive index than the inactive isomer : and Mousseron and Granger (*Compt. rend.*, 1938, **207**, 367; *Bull. Soc. chim.*, 1938, 1618; 1946, 218) provided similar arguments in the case of the 1 : 3-dimethyl*cyclo*hexanes.

A more critical approach to the question of isomerism must therefore be made in the case of the 1 : 3-disubstituted *cyclo*hexanes. Consideration of the substitution of the equatorial and polar hydrogen atoms in the more stable, chair form of *cyclo*hexanes (Pitzer *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 977, 2488; Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929; Hassel and Furberg, *ibid.*, 1950, **4**, 597) indicates that of the pairs of geometrical isomers the one possessing lower density, lower refractive index, etc., has the lesser steric hindrance : and the lower physical constants are associated with *trans*-1 : 2- and -1 : 4- but *cis*-1 : 3-disubstituted *cyclo*hexanes. Rossini and Pitzer (*Science*, 1947, **105**, 647) accordingly proposed the relabelling of the 1 : 3-dimethyl*cyclo*hexanes, and it is likely that a similar step should be taken for the 3-methyl*cyclo*hexanols (Macbeth and Mills, *J.*, 1945, 709; 1947, 205). On this basis the *cis*-configuration should be assigned to the (±)-3-methyl*cyclo*hexanecarboxylic acid now described, as it has a much lower density than that of any of the mixtures of the epimers obtained in the hydrogenations : and the related alcohol should also be regarded as being the *cis*-form. The matter has been placed beyond doubt by Haggis and Owen's (*loc. cit.*) unambiguous synthesis of *cis*-3-methyl*cyclo*hexylmethanol and its identity with the alcohol now described.

The resolution of the *cis*-alcohol was attempted so that comparison could be made with the optically active alcohols described by Mousseron and Granger (*loc. cit.*). Crystallisations of the alkaloidal salts of the hydrogen phthalate of the racemic alcohol did not provide a method, but resolution was successfully carried out by recrystallisation of the (—)-menthylphthalamate. In this way more than 20% of (+)-*cis*-3-methyl*cyclo*hexylmethanol was isolated, but we failed to obtain the (—)-*cis*-alcohol.

EXPERIMENTAL

Hydrogenation of m-*Toluic Acid over Raney Nickel.*—The sample was purified by treating an alkaline solution of *m*-toluic acid with charcoal and crystallising the acid liberated on acidification. The acid [from ethanol–water (1 : 4)] had m. p. 111—112°. The Raney nickel used was prepared according to Pavlic and Adkins (*J. Amer. Chem. Soc.*, 1946, **68**, 1471). (a) *Alkaline hydrogenation.* In a typical experiment *m*-toluic acid (40 g.) in sodium hydroxide (9%; 140 ml.) containing Raney nickel (4 g.) was shaken with hydrogen at 1840 lbs./sq. in. at an initial temperature of 18°. The temperature was raised to 165° during 50 minutes, and this temperature was maintained until the hydrogenation was completed (2 hours in all). After removal of the catalyst, the solution was poured into an excess of 10% hydrochloric acid, and the separated oil was extracted with ether. After drying ($MgSO_4$) and removal of the solvent the 3-methyl*cyclo*hexanecarboxylic acid was distilled; it had b. p. 139—143°/20 mm., d_4^{30} 0·9971 (yield 38·5 g., 92%). When less pure *m*-toluic acid or less active catalyst was used the time of hydrogenation was increased and the yields were not so good, but the density of the product was substantially the same.

(b) *Neutral solution.* Pure *m*-toluic acid (40 g.) with an equivalent of sodium hydroxide

(9%; 131 ml.) and Raney nickel (4 g.) was hydrogenated (3 hours) at 190°. The product (38 g.) had b. p. 91—94°/0·75 mm., d_4^{30} 0·9992.

Hydrogenation of m-*Toluic Acid over Platinum Oxide*.—The catalyst was prepared according to Adams, Voorhees, and Shriner (*Org. Synth.*, Coll. Vol. I, 1941, 463). Pure *m*-toluic acid (10 g.), in redistilled acetic acid (100 ml.), and catalyst (0·5 g.), were shaken with hydrogen at room temperature and atmospheric pressure. After nearly 6 hours almost the theoretical amount (5 l.) of hydrogen had been absorbed. After filtration and washing of the catalyst with light petroleum (60—90°), the solvent was removed from the combined filtrates, and the crude acid distilled. The product (9·6 g., 92%) had b. p. 98—99°/1·2 mm., d_4^{30} 0·9950.

Hydrogenation of 3-*Methyl*cyclo*hex*-1-*enecarboxylic Acid*.—The acid was prepared *via* the nitrile from 3-methyl*cyclo*hexanone cyanohydrin, and was characterised as the *piperazine* salt, flat, white crystals (from acetone), m. p. 157·5—159° (decomp.) (Found: N, 7·55. $C_{20}H_{34}O_4N_2$ requires N, 7·6%), and as the p-*bromophenacyl* ester, m. p. 86—87° (from aqueous methyl alcohol) (Found: Br, 23·3, 23·5. $C_{16}H_{17}O_3Br$ requires Br, 23·7%).

(a) *Raney nickel catalyst.* The acid (13 g.) in sodium hydroxide solution (9%; 42 ml.) and water (30 ml.) was hydrogenated in the presence of Raney nickel (3 g.) as described above for *m*-toluic acid; 3-methyl*cyclo*hexanecarboxylic acid (12 g., 92%), d_4^{30} 0·9988, was obtained.

(b) *Platinum oxide catalyst.* The unsaturated acid (6·2 g.) in glacial acetic acid (70 ml.) was hydrogenated in the presence of platinum oxide catalyst (0·3 g.) as described above for *m*-toluic acid. The product (5·2 g.) had b. p. 91—92°/0·5 mm., d_4^{30} 0·9977.

Piperazine Salt of (±)-cis-3-*Methyl*cyclo*hexanecarboxylic Acid*.—The mixture of the epimeric acids (20 g.) from the hydrogenation in alkaline solution in the presence of Raney nickel was dissolved in dry acetone (15 ml.), and anhydrous piperazine (6·1 g.) in dry acetone (25 ml.) was added, the mixture being heated on the water-bath under reflux for 5 minutes. After cooling, the salt was filtered off, washed with dry acetone (10 ml.), and dried at about 70°. The salt (25·2 g., 92%), m. p. 92—98°, was repeatedly recrystallised from dry acetone and ultimately gave the pure *piperazine* salt of (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid (7·9 g., 30%), m. p. 113—114° (Found: C, 65·0; H, 10·35; N, 7·65. $C_{20}H_{38}O_4N_2$ requires C, 64·85; H, 10·05; N, 7·6%).

Similar preparations were carried out with the mixed acids obtained in the other hydrogenations, and in all cases the salt was identical with that described above.

(±)-cis-3-*Methyl*cyclo*hexanecarboxylic Acid*.—The piperazine salt (7·8 g.) was decomposed by shaking it with hydrochloric acid (3%; 180 ml.) and ether (50 ml.). (±)-*cis*-3-Methyl*cyclo*hexanecarboxylic acid (5·4 g., 90%) had b. p. 93°/0·8 mm., d_4^{30} 0·9921, $n_D^{20°}$ 1·4570; it was characterised by the following derivatives: p-*bromophenacyl* ester, plates (from aqueous methanol), m. p. 93—94° (Found: Br, 23·3. $C_{16}H_{19}O_3Br$ requires Br, 23·55%); *amide*, pearly plates (from benzene), m. p. 160° (Found: N, 9·95. $C_8H_{15}ON$ requires N, 9·95%); and *anilide*, clusters of fine needles [from petroleum (b. p. 100—120°)], m. p. 128—129° (Found: N, 6·4. $C_{14}H_{19}ON$ requires N, 6·45%).

Halogenation of 3-*Methyl*cyclo*hexanol and Preparation of the Carboxylic Acid*.—*Migration to* trans-4-*methyl*cyclo*hexanecarboxylic acid.* A sample (46 g.) of 3-methyl*cyclo*hexanol rich in the *trans*-epimer was heated with fuming hydrochloric acid (Borsche and Lange, *Ber.*, 1907, **40**, 2222) (300 ml.) with stirring under reflux on a boiling-water bath. After 5 hours the solution was cooled, and the chloride extracted with ether and distilled under reduced pressure. Part of the chloride (27 g.) was converted into a Grignard reagent which was carbonated (Gilman and Kirby, *Org. Synth.*, Coll. Vol. I, 1932, 353) to the carboxylic acid (23 g., 70%), b. p. 143—145°/14·8 mm., d_4^{30} 0·9926, n_D^{20} 1·4572. The piperazine salt was prepared as described above and after 10 crystallisations reached a constant m. p., 162—163°, which was not depressed when the salt was mixed with the piperazine salt prepared from *trans*-4-methyl*cyclo*hexanecarboxylic acid [Cooke and Macbeth (*loc. cit.*)] (Found: N, 7·65, 7·3. Calc. for $C_{20}H_{38}O_4N_2$: N, 7·6%). The piperazine salt gave *trans*-4-methyl*cyclo*hexanecarboxylic acid, m. p. 110—111° not depressed on admixture with an authentic sample.

(±)-cis-3-*Methyl*cyclo*hexylmethanol*.—(a) *Preparation of ethyl* (±)-cis-3-*methyl*cyclo*hexanecarboxylate.* The ethyl ester (43 g., 95%) was prepared by refluxing the acid (37·5 g.) with ethanol (380 ml.) and sulphuric acid (3·5 ml.) for 1 hour. The mixture was slowly fractionated [more ethanol being added dropwise during the fractionation], then concentrated (to 100 ml.) and extracted with ether.

(b) *Hydrogenolysis of the ester.* Copper chromite catalyst (6·5 g.) was suspended in the ester (63 g.) and the mixture shaken with hydrogen at 1720 lbs./sq. inch, the temperature being gradually increased to 250° during 2 hours, then maintained at 250° for 3·5 hours. The alcohol was recovered in the usual way and distilled under reduced pressure. The hydrogen phthalate was unsatisfactory for purification, but the 3 : 5-dinitrobenzoate proved suitable. This was prepared from the alcohol (49 g.), in pyridine (34 ml.) and dry benzene (80 ml.), and 3 : 5-dinitrobenzoyl chloride (106 g.) in dry benzene (340 ml.). The crude dinitrobenzoate (118 g., m. p. 54—68°) was systematically crystallised from ethanol, giving pale yellow well-defined orthorhombic crystals of (±)-cis-3-*methyl*cyclo*hexylmethyl* 3 : 5-*dinitrobenzoate* (51 g.), m. p. 81·5—82° (Found : N, 8·6. $C_{15}H_{18}O_6N_2$ requires N, 8·7%).

(c) *Hydrolysis of* (±)-cis-3-*methyl*cyclo*hexylmethyl* 3 : 5-*dinitrobenzoate*. The pure 3 : 5-dinitrobenzoate (30 g.) was dissolved in methanol (150 ml.) and refluxed for 30 minutes with potassium hydroxide (7 g.), dissolved in the minimum amount of water. Water (100 ml.) was then added and most of the methanol was removed by distillation. The residue was distilled with steam, and the alcohol obtained by extraction with light petroleum (b. p. 40—50°). (±)-*cis*-3-Methyl*cyclo*hexylmethanol (10·5 g., 88%) had b. p. 47—48°/0·4 mm., d_4^{30} 0·8896, n_D^{20} 1·4585. It was characterised by the following derivatives : *phenylurethane*, lustrous plates (from aqueous methanol), m. p. 73·5—74·5° (Found : N, 5·75. $C_{15}H_{21}O_2N$ requires N, 5·65%) ; α-*naphthylurethane*, needles (from aqueous methanol), m. p. 81—81·5° (Found : N, 4·9. $C_{19}H_{23}O_2N$ requires N, 4·7%) ; *hydrogen phthalate*, prismatic crystals (from carbon tetrachloride), m. p. 120—121° (Found : C, 69·4; H, 7·05. $C_{16}H_{20}O_4$ requires C, 69·55; H, 7·3%) ; p-*nitrobenzoate*, m. p. 35—36° (Found : N, 7·05. $C_{15}H_{19}O_4N$ requires N, 5·05%) ; and allophanate, fine needles (from acetone), m. p. 177—178°.

Ethyl 3-methyl*cyclo*hex-1-enecarboxylate was subjected to simultaneous hydrogenation and hydrogenolysis in the presence of copper chromite catalyst. Only the *cis*-alcohol was obtained on purification through the 3 : 5-dinitrobenzoate.

Resolution of (±)-cis-3-*Methyl*cyclo*hexylmethanol*.—(a) The inactive alcohol (8 g.) was heated with stirring at 50—60° with phthalic anhydride (10·2 g.) and pyridine (A.R.; 15 ml.) for 4·5 hours. The cooled mixture was poured into hydrochloric acid (10%; 40 ml.) and water (100 ml.), and the solution extracted with benzene. The hydrogen phthalate was transferred from the washed benzene solution into sodium carbonate solution (5% ; 200 ml.), and this was acidified with hydrochloric acid (10%; 27 ml.) and the liberated ester taken up in chloroform. The solvent was removed from the washed and dried extract, and the residue was crystallised from carbon tetrachloride, giving the hydrogen phthalate (16·5 g.), m. p. 120—121°. Brucine, strychnine, and quinine salts of the ester were prepared, but repeated crystallisation failed to achieve any resolution.

(b) Thionyl chloride (2·1 ml.) in ether (15 ml.) was added with stirring to (−)-menthylphthalamic acid (8·7 g.) in anhydrous ether (70 ml.) and pyridine (2·3 ml.) during 30 minutes, and stirring continued for a further hour. The inactive alcohol (3·7 g.) was then added, followed during 30 minutes by pyridine (2·3 ml.) in anhydrous ether (25 ml.). The mixture was stirred for another hour and kept overnight. Removal of the solvent from the washed, dried ethereal solution gave the crude ester (9·9 g., 84%, m. p. 80—100°). Yields up to 97% were obtained in larger scale experiments. Fifteen crystallisations of the crude ester from light petroleum (b. p. 60—90°) gave pure (+)-*cis*-3-methyl*cyclo*hexylmenthyl (−)-methylphthalamate, m. p. 140—141° (yield 23%, based on the inactive alcohol).

The ester (8·8 g.) in methanol (25 ml.) was heated under reflux for 30 minutes after the addition of potassium hydroxide (1·6 g., in water 2 ml.). Most of the methanol was removed under reduced pressure and the residue distilled with steam. The distillate was extracted with light petroleum (b. p. 50—60°) and, after removal of the solvent, the alcohol was distilled under reduced pressure. (+)-*cis*-3-Methyl*cyclo*hexylmethanol (2·3 g., 85%), had b. p. 84°/7·5 mm., d_4^{30} 0·8997, n_D^{20} 1·4585, $[\alpha]_D^{14}$ +4·94° (homogeneous).

It was characterised by the following derivatives: *phenylurethane*, fine needles (from aqueous methanol), m. p. 78—79° (Found: C, 72·9, 73·05; H, 8·4, 8·6; N, 5·8%); α-*naphthylurethane*, needles (from aqueous methanol), m. p. 101·5—102° (Found : C, 76·5; H, 7·9; N, 4·85%); 3 : 5-*dinitrobenzoate*, white, pearly plates (from ethanol), m. p. 75—76° (Found : C, 55·95; H, 5·55; N, 8·95%) ; and *hydrogen phthalate*, m. p. 127—128° (Found : C, 69·2; H, 7·3%).

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