214. *Epimeric Alcohols of the* cyclo*Hexane Series. Part VII. The 2-Methyl*cyclo*hexylcarbinols.*

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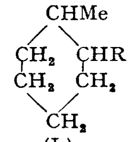
The epimeric forms of the racemic 2-methyl*cyclo*hexanecarboxylic acids and 2-methyl*cyclo*hexylcarbinols have been purified through and characterised by solid derivatives. Resolution of (±)-*trans*-2-methyl*cyclo*hexylcarbinol has been achieved through the (—)-*N*-menthylphthalamate.

In continuance of the study of simple derivatives of *cyclo*hexane, the epimeric 2-methyl*cyclo*hexylcarbinols (I; R = CH_2·OH) have been prepared by the general methods used for 4-methyl*cyclo*hexylcarbinols (Cooke and Macbeth, *J.*, 1939, 1245). Reduction of *o*-toluic acid by catalytic hydrogenation over platinum in acetic acid, or over nickel in neutral aqueous solution, gave a liquid and a solid 2-methyl*cyclo*hexanecarboxylic acid (I; R = CO_2H), probably *cis*- and *trans*-, respectively. After purification these acids were converted into the ethyl esters which were converted into the epimeric carbinols (I; R = CH_2·OH) by hydrogenolysis over copper chromite.



(I.)

Compounds in the above series have been described previously, but without satisfactory evidence of purity for the liquids, as there has been no attempt at purification through solid derivatives. Markownikoff and Sernoff (*J. pr. Chem.*, 1894, **49**, 65), Goodwin and Perkin (*J.*, 1895, **67**, 119), Einhorn (*Annalen*, 1898, **300**, 156), Goldschmidt (*Chem.-Ztg.*, 1902, **26**, 335), and Skita (*Annalen*, 1923, **431**, 1) prepared a solid 2-methyl*cyclo*hexanecarboxylic acid, usually by reduction of *o*-toluic acid, and their results in general agree with ours, the m. p.s of the solid acid, its anilide, and its amide being 52°, 149°, and 183°, respectively.

For the liquid, or *cis*-, acid previously published results are unsatisfactory. The anilide has been most often used for characterisation, and recorded m. p.s of this derivative are 68° by Goodwin and Perkin (*loc. cit.*)for an acid prepared from acyclic intermediates, 66° by Goldschmidt (*loc. cit.*), preparation from *o*-toluic acid, and 106° by Skita (*loc. cit.*), preparation from *cis*-2-methyl*cyclo*hexyl iodide. In the present research the liquid acid was purified through its solid *piperazine* salt, and the pure acid gave an anilide of m. p. 127°, depressed by the *trans*-anilide, but only to 105°. The amide of the pure *cis*-acid melted at 156°, agreeing closely with the data of Skita (*loc. cit.*) and Zelinsky (*Ber.*, 1908, **41**, 2680).

Skita (*loc. cit.*) described the preparation of the carbinols (I; R = CH_2·OH) by reduction of the methyl esters of the epimeric acids (I), but gave no evidence of homogeneity in the products. We found that esterification of the acids (I) and hydrogenolysis of the ester over copper chromite caused some inversion of configuration, and the crude carbinols needed extensive purification, which was rather difficult, as there was a marked tendency for solid derivatives to form mixed crystals with small amounts of the epimeric derivatives. Each of the crude hydrogen phthalates, and the 3 : 5-dinitrobenzoate of the crude *trans*-carbinol, resisted purification by crystallisation. Even after purification of the carbinols, several of their derivatives did not give very sharp m. p.s, and they showed the property of separating in different crystalline forms, apparently of slightly different m. p., depending on whether light petroleum or aqueous methyl alcohol was the solvent.

Attempts to resolve the acids (I; R = CO_2H) and the hydrogen phthalates of the carbinols (I; R = CH_2·OH) with several alkaloids were unsuccessful, for in no case was any separation of the diastereoisomeric mixtures observed. Eventually, the *trans*-carbinol was resolved as its (−)-*N*-menthylphthalamate, by the method of Human and Mills (*J.*, **1948**, 1457), but the *cis*-carbinol was only partly resolved by this method.

EXPERIMENTAL.

The Racemic Epimeric Acids (I; R = CO_2H).—(*a*) Purified *o*-toluic acid (40 g.) was made up to a neutral solution in 9% aqueous sodium hydroxide (125 ml.), mixed with Raney nickel catalyst (4 ml.), and hydrogenated at 230—240° and 2500 lb. pressure, requiring 3—8 hours for complete hydrogenation. The crude *trans*-acid, recovered by filtration, acidification, ether extraction, and distillation under reduced pressure, was a pasty solid very soluble in all organic solvents. Contrary to the statement of Markownikoff and Sernoff (*loc. cit.*), it could not be recrystallised satisfactorily from benzene.

The crude acid (20·7 g.) was mixed with anhydrous piperazine (6·5 g., 1 equiv.) in dry acetone (65 ml.), and the solution boiled and cooled, yielding a crude salt (8·5 g.), m. p. 128—131°. The mother-liquors were used to convert more acid (24·9 g.) into the salt (36·3 g.), which was less pure, m. p. 112—125°. Recrystallisation from dry acetone in four fractions, the first fraction being recrystallised twice, the others four or five times, gave the pure *piperazine* salt (17 g.) as fine white needles, m. p. 135—136°, very soluble in alcohol and chloroform, sparingly in dry acetone, readily in moist acetone. Benzene and ethyl acetate were unsatisfactory solvents (Found : N, 7·5. $C_{20}H_{38}O_4N_2$ requires N, 7·6%).

The purified piperazine salt (16·5 g.) was shaken with 5% hydrochloric acid (60 ml.) and ether (50 ml.) for a short time, and the aqueous layer was separated and extracted with ether (20 ml.). The combined ethereal extracts were washed with water and dried, and the (±)-*trans*-2-methyl*cyclo*hexanecarboxylic acid recovered by distillation had b. p. 99°/2 mm., m. p. 51—52° (92% yield). This acid gave an anilide, fine scales from light petroleum, m. p. 148—149°; an amide, needles from light petroleum, m. p. 182—183°; and a p-*bromophenacyl* ester, needles from aqueous alcohol, m. p. 103—104° (Found : Br, 23·3. $C_{16}H_{19}O_3Br$ requires Br, 23·6%).

A sample of crude *trans*-acid was purified through the anilide, and the pure anilide was hydrolysed by refluxing with 70% sulphuric acid in an apparatus with a Dean and Stark attachment. The organic acid, which is volatile in steam, is thus recovered as fast as it is formed. The yield and purity (m. p. 47—51°) of the recovered acid were inferior to those from the purification as piperazine salt.

(*b*) Pure *o*-toluic acid (15 g.) was dissolved in glacial acetic acid (100 ml.) and hydrogenated over platinum oxide (0·5 g.) during 10 hours at 100° and atmospheric pressure. The hydrogenated acid, recovered by distilling the filtered solution under reduced pressure, was a liquid, which was combined with piperazine, giving a salt, m. p. 80—90°, in 75% yield. Recrystallisation from hot acetone (2 ml./g.) gave the pure *piperazine* salt in 88% recovery, as a crystalline powder, m. p. 96°, more soluble in all solvents than the corresponding *trans*-salt (Found : N, 7·6%). Decomposition of the pure salt yielded (±)-*cis*-2-methyl*cyclo*hexanecarboxylic acid, as a viscous liquid of mild, oily smell, b. p. 119/°11 mm., $d_{4°}^{30°}$ 1·0159, $n_D^{20°}$ 1·4644.

To minimise the danger of epimerisation when preparing the anilide, the pure *cis*-acid was converted into the chloride by treating it in cold benzene solution with exactly one mole each of thionyl chloride and pyridine, and after 5 hours excess of aniline was added to the solution. The product recovered from the reaction was deep orange, but recrystallisation from dilute alcohol readily gave the pure *anilide* as white pearly plates, m. p. 126·5—127·5° (Found : C, 77·3; H, 8·9. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%). A mixed m. p. with the *trans*-anilide was observed under the microscope; there was no change at 66—68°, and the mixture melted at 105—115°. It was found that preparation of the *cis*-anilide by the method of Goodwin and Perkin (*loc. cit.*), involving a prolonged refluxing of the acid with aniline, gave a product, m. p. 112—115°, from which only a very small quantity of crude *cis*-anilide, m. p. 123—125° (identity shown by mixed m. p.), could be isolated. Evidently extensive epimerisation takes place.

The amide of the *cis*-acid was obtained as small scales from light petroleum, m. p. 155—156°, and the p-*bromophenacyl* ester as plates from aqueous alcohol, m. p. 81—82° (Found : Br, 23·6%).

The Racemic trans-*Carbinol* (I; R = CH_2·OH).—The pure *trans*-acid (52 g.) was dissolved in absolute alcohol (500 ml.) with concentrated sulphuric acid (18 g.) and the mixture was slowly distilled through a column during 13 hours, water and alcohol (200 ml.) being collected. From the residual solution the ethyl ester was obtained in 97% yield as a liquid of rank and very persistent smell, b. p. 74°/11 mm., $d_{4^\circ}^{30^\circ}$ 0·9272, $n_{\mathrm{D}}^{16^\circ}$ 1·4426.

The ester (20 g.) was mixed with copper chromite catalyst (2 g.) and shaken with hydrogen for 4 hours at 250° and 3000 lb. pressure. After removal of the catalyst, the crude carbinol was distilled; b. p. 80—81°/10 mm. (12·9 g., 90%).

The carbinol thus obtained was not stereochemically pure, and after unsuccessful attempts at purification through the hydrogen phthalate and 3 : 5-dinitrobenzoate, it was converted into the *p*-nitrobenzoate. The crude product obtained in 68% yield, had m. p. 42—44°, but four recrystallisations from 90—95% methyl alcohol gave half its weight as pure (±)-trans-2-*methyl*cyclo*hexylcarbinyl* p-*nitrobenzoate*, pale yellow plates, m. p. 59—60° (Found: C, 65·0; H, 6·9. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·9%). Hydrolysis of this ester with 4% methyl-alcoholic caustic potash (1·25 moles) during one hour, and working up in the usual way, yielded (±)-*trans*-2-methyl*cyclo*hexylcarbinol, a viscous liquid, b. p. 80°/10 mm., $d_{4^\circ}^{30^\circ}$ 0·9134, $n_{\mathrm{D}}^{20^\circ}$ 1·4633 (75% yield).

The pure *trans*-carbinol was converted into several esters : 3 : 5-*dinitrobenzoate*, small needles from light petroleum, m. p. 68·5—69·5° (Found: N, 8·7. $C_{15}H_{18}O_6N_2$ requires N, 8·7%); *phenylurethane*, triangular plates from light petroleum, m. p. 64—65°, or long needles from aqueous methyl alcohol, m. p. (partly) 59—60°, with second m. p. 63—64° (Found : N, 5·8. $C_{15}H_{21}O_2N$ requires N, 5·7%); *α-naphthylurethane*, needles from light petroleum, m. p. 87—88° (Found : C, 76·9; H, 8·1. $C_{19}H_{23}O_2N$ requires C, 76·7; H, 7·8%); *hydrogen phthalate*, crystalline powder from light petroleum, m. p. 98·5—99·5° (Found : C, 69·6; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%).

The Racemic cis-*Carbinol* (I; R = $CH_2{\cdot}OH$).—The pure *cis*-acid was esterified by the method used for the *trans*-acid but with only two-thirds the quantity of sulphuric acid catalyst. The ethyl ester, obtained in 93% yield after distillation, had b. p. 76°/11 mm., $d_{4^\circ}^{30^\circ}$ 0·9422, $n_{\mathrm{D}}^{20^\circ}$ 1·4472. Hydrogenation–hydrogenolysis was carried out as for the *trans*-ester. The crude *cis*-carbinol, which could not be purified through its hydrogen phthalate, was converted in 98% yield into a crude 3 : 5-dinitrobenzoate, m. p. 79—81°, and after three recrystallisations of this from methyl alcohol (10 ml./g.), three-fifths of it was recovered as pure (±)-cis-2-*methyl*cyclo*hexylcarbinyl* 3 : 5-*dinitrobenzoate*, small flat needles, m. p. 92—93° (Found: N, 8·7%). Hydrolysis with 4% methyl-alcoholic potash (1·5 moles) yielded (±)-*cis*-2-methyl*cyclo*hexylcarbinol, b. p. 83°/10 mm., $d_{4^\circ}^{30^\circ}$ 0·9286, $n_{\mathrm{D}}^{20^\circ}$ 1·4690 (80% yield).

From the pure *cis*-carbinol the following esters were made : p-*nitrobenzoate*, small plates from aqueous methyl alcohol, m. p. 43—44° (Found : C, 64·9; H, 6·8%); *phenylurethane*, stout rods from aqueous methyl alcohol, m. p. 47—48° (Found : N, 5·8%); *α-naphthylurethane*, small stout needles from light petroleum, m. p. 66—68° (Found : C, 76·9; H, 7·6%); *hydrogen phthalate*, minute needles from light petroleum, m. p. 112·5—114° (Found : C, 69·3; H, 7·1%).

Optical Resolution of (±)-trans-2-*Methyl*cyclo*hexylcarbinol*.—The hydrogen phthalate (50 g.) of this carbinol was dissolved in dry ether (600 ml.) and dry pyridine (14·3 g., 1 mole) was added; then to the refluxing solution thionyl chloride (13·0 ml., 1 mole) dissolved in ether (50 ml.) was added during one hour, with stirring. Refluxing was maintained for one hour longer, then a solution of (—)menthylamine (29·2 g., 1 mole) and pyridine (14·3 g.) in ether (100 ml.) was added during one hour. After a further 30 minutes' heating under reflux, the whole was set aside overnight. The crystalline precipitate of pyridine hydrochloride was dissolved in water, and the ethereal solution washed in turn with dilute hydrochloric acid, sodium carbonate solution, and water, and dried ($MgSO_4$). Removal of the ether left the diastereoisomeric mixture of esters as a yellow pasty solid (71 g., 95%).

Treatment of the crude product with light petroleum (b. p. 60—90°) left part of it undissolved as white needles, m. p. 102° (12·9 g.), and careful concentration of the light petroleum washings gave a further amount of similar material (15 g.). The two lots were mixed and recrystallised systematically in five fractions from aqueous methyl alcohol (80%, 25 ml./g.), and after five or six series of crystallisations pure (—)trans-2-*methyl*cyclo*hexylcarbinyl* (—)-N-*menthylphthalamate* (11 g.) was obtained as long needles, m. p. 109·5—110·5°, $[\alpha]_{\mathrm{D}}^{16.5^\circ}$ —39·7° (chloroform, *c* 5) (Found : N, 3·3. $C_{26}H_{29}O_3N$ requires N, 3·4%).

Hydrolysis of this ester was effected by refluxing for ½ hour with 8% methyl-alcoholic potash (1·3 moles), and after distillation of the bulk of the methyl alcohol, the residue was steam-distilled, and the steam-distillate submitted to continuous ether extraction. Removal of the ether left (—)*trans*-2-methyl*cyclo*hexylcarbinol, b. p. 73°/8 mm., $\alpha_{\mathrm{D}}^{15.5^\circ}$ —26·37° (homogeneous, l = 1), in 90% recovery, and 22% overall yield fron the (±)-carbinol.

The active carbinol was characterised by the preparation of the 3 : 5-*dinitrobenzoate*, fine needles from aqueous methyl alcohol, m. p. 48—50° (Found : N, 8·7%), and the *α-naphthylurethane*, fine needles from aqueous methyl alcohol, m. p. 104—104·5° (Found : N, 4·8%).

Attempted Resolution of (±)-cis-2-*Methyl*cyclo*hexylcarbinol*.—The (±)-*cis*-carbinol was converted into the (—)-*N*-methylphthalamic ester by the method used for the (±)-*trans*-carbinol. After a little oily material had been washed out with light petroleum (b. p. 40—60°), the diastereoisomeric mixture had m. p. 94—97°, $[\alpha]_{\mathrm{D}}^{15.5^\circ}$ —27·2° (chloroform, c = 5) (Found : N, 3·4%). Repeated recrystallisation from aqueous methyl alcohol altered these constants very little, so it is improbable that any appreciable resolution was achieved. Hydrolysis of the recrystallised ester yielded a carbinol with $\alpha_{\mathrm{D}}^{14^\circ}$ —1·66° (homogeneous, l = 1), a value which is much lower than is to be expected. This slightly active carbinol gave an α-naphthylurethane and a 3 : 5-dinitrobenzoate identical with those of the (±)-*cis*-carbinol.

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