Epimeric Alcohols of the cyclo*Hexane Series. Part X.** (±)-trans-3-*Methyl*cyclo*hexanecarboxylic Acid and* (±)-trans-3-*Methyl*cyclo*hexylamine.*

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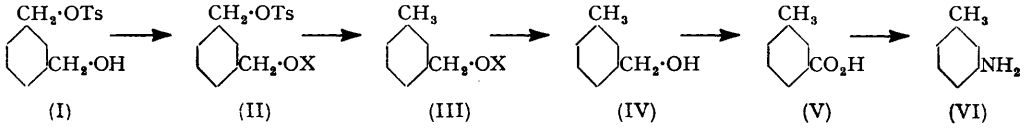
(±)-*trans*-3-Methyl*cyclo*hexanecarboxylic acid and (±)-*trans*-3-methyl*cyclo*hexylamine have been prepared by a series of stereochemically specific steps.

Frahn, Macbeth, and Shannon (unpublished work) prepared mixtures of the (±)-3-methyl*cyclo*hexylamines by hydrogenation with Raney nickel of aceto-*m*-toluidide under pressure, followed by hydrolysis, and by similar hydrogenation of *m*-toluidine. From the products a (±)-3-methyl*cyclo*hexylamine was obtained to which the *trans*-configuration would have been assigned on the basis of the Auwers–Skita rule, but the substance was shown to be the *cis*-amine (Macbeth, Aust. and N.Z. Assoc. for Advancement of Science, Sydney, August, 1952) by application of the stereochemically specific Schmidt reaction (Campbell and Kenyon, *J.*, 1946, 25; Dauben and Hoerger, *J. Amer. Chem. Soc.*, 1951, **73**, 1504) to (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid; the configuration of the acid follows from its relation to the corresponding methanol unequivocally synthesised by Owen and later described by Haggis and Owen (*J.*, 1953, 408). Noyce and Nagle (*J. Amer. Chem. Soc.*, 1953, **75**, 127) independently established the *cis*-configuration of the amine, and a detailed account of our work on the *trans*-amine only is now reported.

The literature on the preparation of the 3-methyl*cyclo*hexylamines need not be reviewed as only in a few cases were attempts made to separate the mixtures of epimers formed. In order to obtain stereochemically pure samples of the *trans*-acid and amine, and to provide a chemical proof of their configuration, we have used a synthesis which proceeds by stereochemically specific steps from *trans*-hexahydro*iso*phthalic acid, whose configuration has been rigorously established (Böeseken and Peek, *Rec. Trav. chim.*, 1925, **44**, 845). This acid was obtained by platinum-catalysed hydrogenation of *iso*phthalic acid under atmospheric conditions, followed by separation of the epimers through the calcium salts. The purity of the acetic acid employed as the solvent was found to be most critical in this hydrogenation. Reduction of the dimethyl ester with lithium aluminium hydride has been shown by Haggis and Owen (*J.*, 1953, 389) to proceed with retention of the configuration, and the diol so obtained was converted into the monotoluene-*p*-sulphonate (I) by the method described by these authors. The melting point and crystalline form of the *p*-nitrobenzoate of (I) differed from those of the sample prepared by Haggis and Owen.



(I) (II) (III) (IV) (V) (VI)

(Ts = *p*-$C_6H_4Me\cdot SO_2$; X = tetrahydro-2-pyranyl.)

Protection of the alcoholic group of (I) by formation of the tetrahydropyranyl ether (II) and reduction of the toluene-*p*-sulphonyl group with lithium aluminium hydride (Karrer, Asmis, Soreen, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022) gave (III), converted into *trans*-3-methyl*cyclo*hexylmethanol (IV) by acid hydrolysis (compare Goering and Serres, *J. Amer. Chem. Soc.*, 1952, **74**, 5908). This procedure gave a much better yield of (IV) than was obtained by Haggis and Owen (*J.*, 1953, 408). Oxidation of (IV) to *trans*-3-methyl*cyclo*hexanecarboxylic acid (V) was accomplished smoothly with the chromic acid reagent described by Curtis, Heilbron, Jones, and Woods (*J.*, 1953, 457). Conversion of the acid (V) into *trans*-3-methyl*cyclo*hexylamine was carried out by the

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stereochemically specific Schmidt reaction. The presence of a lower-boiling fraction in the crude amine might be attributed to the formation of methyl*cyclo*hexenes, since the amino-group might occupy a polar position and groups in polar positions are favourably situated for bimolecular elimination.

It will be observed that the physical constants of the *trans*-epimers obtained are without exception higher than those of the corresponding *cis*-compounds, although in one or two cases allowances for temperature differences must be made. In addition, the melting points of all the (±)-*trans*-epimers are lower than those of the corresponding (±)-*cis*-derivatives. As well as providing further justification for the reversal of the Auwers–Skita rule for the 1 : 3-disubstituted *cyclo*hexanes (von Auwers and Schmelzer, *Chem. Zentr.*, 1927, II, 1562) these results are in accord with the recent work of Pitzer *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 977, 2488), Hassel and Ottar (*Acta Chem. Scand.*, 1947, **1**, 929), and Hassel and Furberg (*ibid.*, 1950, **4**, 597) indicating that of pairs of geometrical isomers the one possessing the greater steric hindrance will also have higher physical constants, *i.e.*, the *cis*-1 : 2-, the *trans*-1 : 3-, and the *cis*-1 : 4-disubstituted *cyclo*hexanes.

Experimental

Dimethyl trans-*Hexahydro*iso*phthalate.*—*iso*Phthalic acid, twice recrystallised from 95% ethanol, was quantitatively hydrogenated in suspension in carefully fractionated glacial acetic acid, over Adams platinum oxide at room temperature and atmospheric pressure. The *cis*-+*trans*-hexahydro*iso*phthalic acids so obtained (m. p. 117—126°) were separated through their calcium salts, and the *cis*-acid partially isomerised (Skita and Rössler, *Ber.*, 1939, **72**, 265). From 60 g. of mixed isomers, several repetitions of this isomerisation and separation afforded 28 g. of *trans*-acid, which was again purified through the calcium salt and twice recrystallised from water.

The *trans*-acid (m. p. 150—151°) was esterified with methyl iodide through its silver salt (Skita and Rössler, *loc. cit.*).

trans-1 : 3-*Bishydroxymethyl*cyclo*hexane.*—The *trans*-dimethyl ester was reduced with lithium aluminium hydride in high yield by a method essentially similar to that of Haggis and Owen (*loc. cit.*). The ditoluene-*p*-sulphonate of the diol had m. p. 91—92°, and the di-*p*-nitrobenzoate, m. p. 122—123°. Haggis and Owen give 86—87° and 122—123° respectively.

The monotoluene-*p*-sulphonate of the diol was prepared under conditions identical with those described by Haggis and Owen (*loc. cit.*) in 57% yield, and the p-*nitrobenzoate* thereof crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 85° (Found: C, 59·4; H, 5·7; N, 3·3. $C_{22}H_{25}O_7NS$ requires C, 59·1; H, 5·6; N, 3·1%). Haggis and Owen report this to be a microcrystalline powder, m. p. 97—98°.

trans-3-*Methyl*cyclo*hexylmethanol.*—A solution of the monotoluene-*p*-sulphonate (13·5 g.) in freshly purified dihydropyran (25 ml.) was shaken for 20 min. with three drops of concentrated hydrochloric acid and then set aside for 15 hr. The excess of dihydropyran was removed *in vacuo* and the residual sweet-smelling tetrahydropyranyl ether (17·3 g.) in dry ether (50 ml.) was added to a mechanically stirred suspension of lithium aluminium hydride (6 g.) in dry ether (300 ml.). The mixture was boiled under reflux for 30 hr. with occasional stirring, and, when cool, the excess of hydride was decomposed with ethyl acetate, followed by aqueous sodium hydroxide (200 ml. of 10%). The ethereal layer was separated, the aqueous suspension of aluminium hydroxide was filtered, and both the filtrate and precipitate were extracted with ether. Evaporation of the combined ethereal extracts gave a residue (11·5 g.) which was boiled in methanol (200 ml.) under reflux for 2 hr. after addition of 5N-hydrochloric acid (40 ml.). The resultant liquid was diluted with water, and the methanol removed through a short column. Extraction of the aqueous residue with light petroleum (b. p. 60—70°) and evaporation of the dried extract gave an oil, which was fractionally distilled at 15 mm., yielding materials (*a*) (2·4 g.), b. p. 94—96°, n_D^{22} 1·4628, d_4^{22} 0·9252, $[R_L]_D$ 38·17 (calc. 38·47), and (*b*) (1·0 g.), b. p. 96—130° (residue 2·5 g.).

A portion of fraction (*a*) was converted into *trans*-3-methyl*cyclo*hexylmethyl 3 : 5-dinitrobenzoate, m. p. 78—79°. Haggis and Owen (*loc. cit.*) give m. p. 77—78°. A further quantity of this ester was obtained by esterification of fraction (*b*). Chromatography of the crude product on acid-washed alumina and elution with light petroleum (b. p. 50—70°)–benzene (8 : 1) gave the ester (1·0 g.), m. p. and mixed m. p. 78—79°.

trans-3-*Methyl*cyclo*hexanecarboxylic Acid.*—*trans*-3-Methyl*cyclo*hexylmethanol (2·1 g.) in

pure acetone (20 ml.) was titrated at 20° with an acid solution of chromium trioxide (8N with respect to oxygen). To produce a persistent orange-brown colour 8·4 ml. of the reagent were required (theory, 8·2 ml.). The mixture was diluted with water, and the crude acid extracted with ether. After removal of the solvent from the dried ($MgSO_4$) extract, the residue was distilled, yielding the *acid* (1·5 g.), b. p. 92°/1·3 mm., n_D^{20} 1·4618, d_4^{30} 1·0051, $[R_L]_D$ 38·58 (calc. 38·48) (Found : C, 68·1; H, 10·2. $C_8H_{14}O_2$ requires C, 67·6; H, 10·0%). It gave an *anilide*, plates, m. p. 123° [from light petroleum (b. p. 60—70°)], depressed to 107—113° on admixture with the anilide derived from the *cis*-acid (Found : C, 77·6; H, 8·7. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%), and a p-*bromophenacyl* ester, plates, m. p. 56—57° (from aqueous methanol) (Found : C, 56·6; H, 5·8; Br, 23·7. $C_{16}H_{19}O_3Br$ requires C, 56·7; H, 5·7; Br, 23·6%).

trans-3-*Methyl*cyclo*hexylamine*.—Powdered sodium azide (0·75 g.) was added in portions during 30 min. to a well-stirred solution of *trans*-3-methyl*cyclo*hexanecarboxylic acid (1·1 g.) in chloroform (25 ml.) and concentrated sulphuric acid (15 ml.) kept at 40°. The temperature was raised to 50° and stirring continued for a further 30 min. When cool, the mixture was poured on crushed ice and separated. Evaporation of the chloroform gave a negligible residue. The aqueous layer was made alkaline with 10% sodium hydroxide solution, the amine extracted with ether, and the extract washed with water and dried (KOH). The ether was removed through a fractionating column, and the crude residue (0·7 g.) distilled. Redistillation of the higher-boiling fraction gave *trans*-3-methyl*cyclo*hexylamine (0·3 g.), b. p. 150·5—151°/767 mm., n_D^{16} 1·4610, d_4^{15} 0·8760, $[R_L]_D$ 35·46 (calc. 35·75). It gave a p-*nitrobenzoyl* derivative, plates, m. p. 104—105°, from aqueous methanol (Found : C, 64·3; H, 6·8; N, 10·8. $C_{14}H_{18}O_3N_2$ requires C, 64·2; H, 6·9; N, 10·7%). The carbonate (needles) had m. p. 81—83° (sealed tube).

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