423. *The Configurations of Some* p-*Menthane Derivatives.*

By George H. Keats.

The object of this work was to relate menthol and *iso*menthol, and the two geometrically isomeric 8-hydroxy-*p*-menthanes, to the *cis*- and the *trans*-form of *p*-menthane, of which they are derivatives. Electrolytic reduction of *l*-menthone gave *trans-p*-menthane, and *dl-iso*menthone yielded the *cis*-isomer, the configurations of the *p*-menthanes being based on a comparison of their physical properties with application of the Auwers–Skita rule. Hence *l*-menthol belongs to the *trans-p*-menthane series and *dl-iso*menthol to the *cis*-series. *l*-Menthol was converted into the bromide, which was dehalogenated by various methods to give *trans-p*-menthane. *dl-iso*Menthol, however, by a similar series of reactions, gave a mixture of *cis*- and *trans-p*-menthane. A somewhat analogous isomerisation was observed in the conversion of the 8-hydroxy-*p*-menthanes into *p*-menthane *via* the 8-chloro-*p*-menthanes, the *trans*-carbinol yielding *trans-p*-menthane, and the *cis*-isomer a mixture of the *cis*- and the *trans*-hydrocarbon.

It is usually supposed that there is a *trans*-relationship between the methyl and the *iso*propyl group in menthone, whereas in *iso*menthone these groups occupy *cis*-positions. The evidence for this belief rests on a comparison of the physical properties of menthone and *iso*menthone. Zeitschel and Schmidt (*Ber.*, 1926, **59**, 2298) found that *d-iso*menthone has a slightly higher density and refractive index than *l*-menthone, and so, if these substances obey the Auwers–Skita rule (*Annalen*, 1915, **410**, 287; 1920, **420**, 91), the former is the *cis*-isomer. Again, Carter (J., 1927, 1278) has found that the parachors of menthones and *iso*menthones indicate a *cis*-configuration for the latter.

However, the small differences in the physical properties of menthone and *iso*menthone somewhat decrease the reliance to be placed on these deductions, and it was considered that, if menthol and *iso*menthol, or menthone and *iso*menthone, could be related to the two stereoisomeric forms of *p*-menthane, more definite evidence for the configurations of the former would be provided; for the Auwers–Skita rule could be applied with confidence to the *p*-menthanes, simple hydrocarbons differing considerably in physical properties.

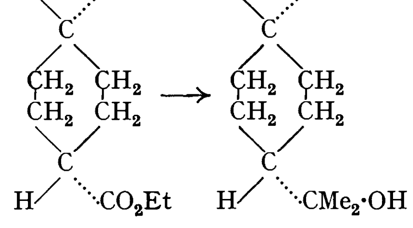
Schall and Kirst (*Z. Elektrochem.*, 1923, **29**, 537) found that menthone can be converted into *p*-menthane by electrolytic reduction at a cadmium cathode. On treating both *l*-menthone (II) and *dl-iso*menthone (VI) in this way, it was found that the *p*-menthane obtained from the latter had a considerably higher density ($d_{4°}^{20°}$ 0·8080) and refractive index ($n_D^{20°}$ 1·4414) than that from the former ($d_{4°}^{20°}$ 0·7964, $n_D^{20°}$ 1·4366). This clearly shows that menthone is derived from *trans-p*-menthane (III) and *iso*menthone from *cis-p*-menthane (VII). Since the ketones are made by the oxidation of *l*-menthol

(I) and *dl-iso*menthol (V), these substances also belong to the *trans*- and the *cis-p*-menthane series respectively.

Attempts to convert *l*-menthol and *dl-iso*menthol into the stereoisomeric *p*-menthanes by means of other reactions proved difficult. Menthyl and *iso*menthyl chlorides were not suitable intermediates from which the *p*-menthanes could be obtained by dehalogenation, for *iso*menthyl chloride is not accessible. The action of phosphorus pentachloride on *dl-iso*menthol results in the formation of equal amounts of a chloride and an unsaturated oil, presumably a menthene mixture, and it is evident that the intermediate formation of Δ^3-*p*-menthene will destroy the *cis-trans* isomerism which the experiments are designed to preserve. Thionyl chloride was no more suitable than phosphorus pentachloride, as it caused dehydration of *l*-menthol. However, by replacing the hydroxyl group by bromine and reducing the resulting menthyl and *iso*menthyl bromides, *l*-menthol and *dl-iso*menthol have been found to yield *p*-menthanes of differing densities and refractive indices. *l*-Menthol yielded a *p*-menthane of $d_{4^\circ}^{20^\circ}$ 0·7970; $n_D^{20^\circ}$ 1·4370 approx., whereas *dl-iso*menthol gave a product with $d_{4^\circ}^{20^\circ}$ 0·8020; $n_D^{20^\circ}$ 1·4395 approx. The *p*-menthane derived from *l*-menthol consists almost entirely of the *trans*-form, and that from *dl-iso*menthol is a mixture of the *cis*- and the *trans*-form. In *iso*menthol, then, replacement of groups on carbon atom number 3 appears to produce partial inversion of the configuration of the groups on the neighbouring carbon atom. This inversion probably occurs during the formation of the halides and not during their reduction, since the composition of the *p*-menthane mixture remains approximately the same when different methods of reduction are used.

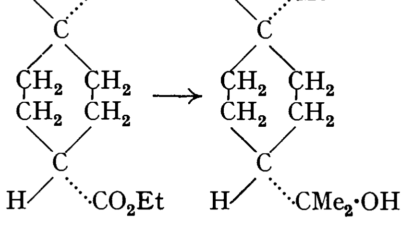
A somewhat similar phenomenon was observed when the two stereoisomeric 8-hydroxy-*p*-menthanes were converted into the 8-chloro-*p*-menthanes and these were reduced to the *p*-menthanes. The 8-hydroxy-*p*-menthane of m. p. 35° (IV), prepared from the ethyl ester of solid hexahydro-*p*-toluic acid as described by Perkin and Pickles (J., 1905, **87**, 650), yielded practically pure *trans-p*-menthane. The stereoisomeric 8-hydroxy-*p*-menthane of m. p. 25° (VIII), now for the first time prepared in the pure state by treating the ethyl ester of "liquid" hexahydro-*p*-toluic acid with methylmagnesium iodide, gave a mixture of *cis*- and *trans-p*-menthanes having $d_{4^\circ}^{20^\circ}$ 0·8017; $n_D^{20^\circ}$ 1·4390. Experiments on the reduction of the 8-bromo-*p*-menthanes (obtained by the action of fuming hydrobromic acid on the 8-hydroxy-*p*-menthanes) gave unexpected results. Both bromo-compounds, when reduced by zinc dust in methyl alcohol, gave *trans-p*-menthane, whereas decomposition of the corresponding Grignard compounds derived from them gave a mixture of *cis*- and *trans-p*-menthane of the same composition in both cases. Here, then, the nature of the *p*-menthane produced depends on the method of debromination and is independent of the 8-hydroxy-*p*-menthane used as starting material.

In view of these complications, the evidence for the configurations of the 8-hydroxy-*p*-menthanes must be obtained mainly by a comparison of their physical properties and those of the hexahydro-*p*-toluic acids and esters from which they are derived.



Ethyl ester of acid, m. p. 111°; $d_{4^\circ}^{20^\circ}$ 0·9361, n_D^{20} 1·4392.

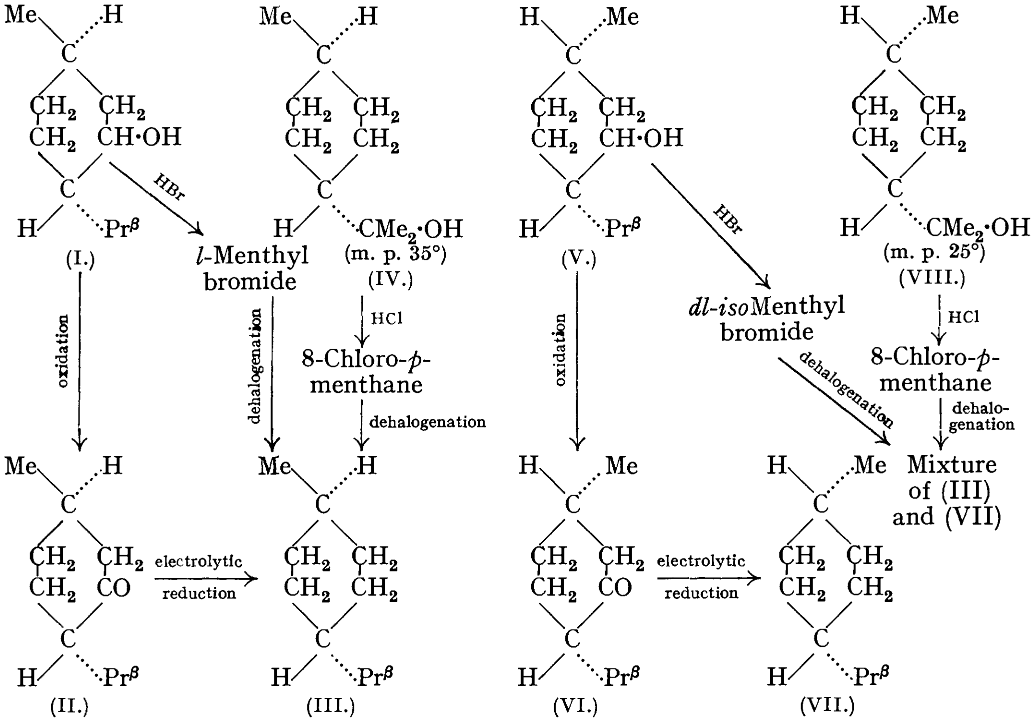
8-Hydroxy-*p*-menthane, m. p. 35°; $d_{4^\circ}^{45^\circ}$ 0·8962.



Ethyl ester of acid, m. p. 13°; $d_{4^\circ}^{20^\circ}$ 0·9448, $n_D^{20^\circ}$ 1·4429.

8-Hydroxy-*p*-menthane, m. p. 25°; $d_{4^\circ}^{45^\circ}$ 0·9025.

The above two pairs of geometrical isomers differ considerably in physical properties, and the Auwers–Skita rule indicates that the substances of higher melting point are the *trans*-isomers.



EXPERIMENTAL.

The Electrolytic Reduction of l-*Menthone and* dl-iso*Menthone*.—The *l*-menthone and *dl*-*iso*menthone were made by the oxidation of natural *l*-menthol and of *dl*-*iso*menthol. The experimental conditions were as described by Schall and Kirst (*loc. cit.*) with slight modifications. The cathode consisted of pure sheet cadmium, the total area of metal immersed being 120 sq. cm.; the anode was of pure lead sheet. The anolyte, contained inside a porous pot, consisted of dilute sulphuric acid kept cool by a cooling coil. The catholyte was a mixture of 20 g. of *l*-menthone (or *dl*-*iso*menthone), 300 c.c. of ethyl alcohol, 70 c.c. of water, and 15 c.c. of concentrated sulphuric acid. The catholyte was stirred mechanically and was surrounded by a vessel of iced water. A current of 3—3·3 amps. was passed for 8 hours, and after 2 hours from the start 10 g. of menthone (or *iso*menthone) were gradually added to the catholyte. During the electrolysis the temperature of the catholyte remained between 10° and 15°, and at the end of the experiment the liquid had separated into two layers.

The *p*-menthane was isolated as described by Schall and Kirst, and purified as described below; yield 20 g., b. p. 167—168·5°.

The Action of Phosphorus Pentachloride on dl-iso*Menthol*.—60 G. of phosphorus pentachloride were covered with low-boiling petrol and cooled to 0°. 40 G. of *dl*-*iso*menthol were slowly added, and after 1 hour the mixture was poured on ice. The oil was washed with water and sodium hydroxide solution, dried over calcium chloride, and distilled under reduced pressure; yield, 16 g. of an unsaturated oil, b. p. 75—85°/18 mm., and 18 g. of a chloride, b. p. 97°/18 mm. 40 G. of *l*-menthol, treated in a similar way, gave 38 g. of menthyl chloride, b. p. 97°/18 mm.

The Action of Thionyl Chloride on l-*Menthol*.—20 G. of *l*-menthol were slowly added with shaking to 40 g. of thionyl chloride at 0°, and the mixture left for 2 hours, some hydrogen chloride being evolved during this period. The product was poured on ice and stirred well, and the oil was extracted with ether. The extract was washed with sodium hydroxide solution, dried over calcium chloride, and fractionated under reduced pressure; yield, 6 g. of menthene, b. p. 65—70°/15 mm., and 10 g. of unchanged menthol, b. p. 103—105°/15 mm.

The Preparation of l-*Menthyl and* dl-iso*Menthyl Bromide.*—These halides are best prepared by the action of fuming hydrobromic acid on the menthols. 20 G. of *l*-menthol or *dl-iso*menthol were shaken in a pressure bottle with 100 c.c. of fuming hydrobromic acid, saturated at 0°. After 36 hours the oil was separated, washed with dilute sodium hydroxide solution, and fractionated under reduced pressure; yield, 15 g., b. p. 114°/22 mm.

*dl-iso*Menthyl bromide was also made by the following method. *dl-iso*Menthyl acetate was prepared by the action of acetyl chloride on *dl-iso*menthol, and was isolated as a pleasant-smelling liquid, b. p. 111°/20 mm., $d_{4^\circ}^{20^\circ}$ 0·9369. It was mixed with twice its volume of light petroleum (b. p. 60—80°), and the solution saturated with dry hydrogen bromide at − 10°; the reaction bottle was then stoppered and left for 4 days. The mixture was shaken with water, and the petroleum layer separated, shaken with sodium hydroxide solution, and dried over calcium chloride. It was fractionated under reduced pressure, and the portion, b. p. 116°/25 mm., collected; $d_{4^\circ}^{20^\circ}$ 1·130; the yield equalled the weight of *iso*menthyl acetate taken. *l*-Menthyl acetate is only partly converted into the bromide by this treatment. Estimations (by the Stepanow method) of the bromine contents of the above bromides gave values varying from 36·0% to 36·5% (Calc. for $C_{10}H_{19}Br$: Br, 36·5%).

The Dehalogenation of l-*Menthyl and* dl-iso*Menthyl Bromide.*—(a) The bromides were treated in glacial acetic acid solution with zinc dust (freed from oxide) with gentle warming and shaking. (b) The bromides were treated with magnesium in ether, and the resulting Grignard compounds were decomposed by iced water, followed by dilute acid (cf. Hesse, *Ber.*, 1906, **39**, 1132, 1151). (c) Solutions of the bromides in methyl alcohol (4 vols.) were shaken with zinc dust (3 parts) for a week at room temperature (cf. Harries and Stirm, *Ber.*, 1901, **34**, 1924).

In each case the *p*-menthane was isolated and purified as follows. The reduction product was extracted with ether, and the extract was washed, and dried over calcium chloride. After removal of the ether the residue was distilled, and the portion, b. p. 165—170°, was shaken with an equal volume of cold concentrated sulphuric acid for 15 minutes. This treatment removed any menthene, the acid becoming orange-coloured in the process. The *p*-menthane layer was separated, washed, and dried over calcium chloride. It was then twice distilled over sodium, and twice fractionated in a small flask with sealed-on glass Dufton column; b. p. 168°/760 mm. The physical properties of the *p*-menthanes after such treatment were not altered by further fractionation. The products contained no trace of halide, as shown by negative Beilstein and Lassaigne tests. Furthermore, refluxing with alcoholic potash, followed by re-isolation and purification, caused no change in physical properties.

Results: (1) 20 G. of menthyl bromide (from *l*-menthol and hydrobromic acid), reduced *via* the Grignard compound, gave 2 g. of *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·7971, $n_D^{20^\circ}$ 1·4373.

(2) 15 G. of menthyl bromide (from *l*-menthol and hydrobromic acid), reduced by zinc in methyl alcohol, gave 1·5 g. of *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·7973, $n_D^{20^\circ}$ 1·4367.

(3) 15 G. of *iso*menthyl bromide (from *dl-iso*menthol and hydrobromic acid), reduced *via* the Grignard compound, gave 2 g. of *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·8024, $n_D^{20^\circ}$ 1·4398.

(4) 10 G. of *iso*menthyl bromide (from *dl-iso*menthol and hydrobromic acid), reduced by zinc in methyl alcohol, gave 1·5 g. of *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·8020, $n_D^{20^\circ}$ 1·4390.

(5) 60 G. of *iso*menthyl bromide (from *dl-iso*menthyl acetate and hydrobromic acid), reduced *via* the Grignard compound or by zinc in acetic acid, gave 5·5 g. of *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·8022, $n_D^{20^\circ}$ 1·4396.

The Hydrogenation of p-*Toluic Acid.*—A solution of 10 g. of *p*-toluic acid in 60 c.c. of glacial acetic acid was shaken with hydrogen at atmospheric pressure in the presence of 0·5 g. of Adams's platinum oxide catalyst. The hydrogenation flask was kept warm by means of a steam jet, and with occasional aeration of the catalyst the reduction was complete in 4—5 hours, 3 mols. of hydrogen having been absorbed. The product was filtered, the acetic acid removed, and the residue fractionated under reduced pressure; yield, 8 g., b. p. 135°/20 mm. When kept in a freezing mixture, it slowly solidified to a mass of colourless needles, m. p. 13°. The ethyl ester of *p*-toluic acid was not hydrogenated so readily as the acid itself.

The ethyl esters of the two hexahydro-*p*-toluic acids, made by the Fischer–Speier method, were liquids, b. p. 97°/22 mm. A persistent and unpleasant smell was produced during their preparation.

The ethyl ester of hexahydro-*p*-toluic acid (m. p. 13°) had $d_{4^\circ}^{20^\circ}$ 0·9448, $d_{4^\circ}^{25^\circ}$ 0·9423, and $n_D^{20^\circ}$ 1·4429. The ethyl ester of hexahydro-*p*-toluic acid (m. p. 111°) had $d_{4^\circ}^{20^\circ}$ 0·9361, $d_{4^\circ}^{25^\circ}$ 0·9340, and $n_D^{20^\circ}$ 1·4392.

The Preparation of cis-*8-Hydroxy*-p-*menthane*.—This was made in good yield by the action of methylmagnesium iodide on the ethyl ester of the hexahydro-*p*-toluic acid of lower m. p., exactly as Perkin and Pickles (*loc. cit.*) made the *trans*-isomer from the ester of the acid of higher m. p. It was isolated by distillation under reduced pressure, and had b. p. 110°/30 mm.; it solidified to a mass of fine long needles, m. p. 25°. This carbinol had a fainter smell than its isomer of m. p. 35° and had $d_{4^\circ}^{45^\circ}$ 0·9025, whereas the *trans*-isomer had $d_{4^\circ}^{45^\circ}$ 0·8962 (Found: C, 76·8; H, 13·0. Calc. for $C_{10}H_{20}O$: C, 77·0; H, 12·8%). Its phenylurethane crystallised from light petroleum in clumps of short needles, m. p. 114°, depressed by the phenylurethane of the *trans*-carbinol, which crystallised from petroleum in long needles, m. p. 115°.

Zeitschel and Schmidt (*Ber.*, 1927, **60**, 1372) claimed to have isolated this *cis*-8-hydroxy-*p*-menthane from the mixture resulting from the hydrogenation of α-terpineol, but their product was an oil and so it cannot have been pure.

The Preparation and Dehalogenation of the 8-Bromo-p-*menthanes*.—18 G. of 8-hydroxy-*p*-menthane were shaken at room temperature for 2 days in a pressure bottle with 120 c.c. of hydrobromic acid (saturated at − 10°). The heavy oil was separated and extracted with ether, the extract washed and dried over calcium chloride, and the ether removed. The bromo-compounds were not distilled. Conversion into the Grignard compounds, followed by decomposition with water, gave approx. 1 g. of *p*-menthane. 8-Hydroxy-*p*-menthane (m. p. 25°) gave *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·8015, $n_D^{20^\circ}$ 1·4384. 8-Hydroxy-*p*-menthane (m. p. 35°) gave *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·8015, $n_D^{20^\circ}$ 1·4389.

Reduction of the bromo-compounds by zinc dust in methyl alcohol gave 1 g. of *p*-menthane having the following properties: 8-hydroxy-*p*-menthane (m. p. 25°) gave *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·7970, $n_D^{20^\circ}$ 1·4370; 8-hydroxy-*p*-menthane (m. p. 35°) gave *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·7966, $n_D^{20^\circ}$ 1·4366.

The Preparation and Dehalogenation of the 8-Chloro-p-*menthanes*.—The 8-hydroxy-*p*-menthanes were dissolved in 10 times their weight of dry ether saturated with dry hydrogen chloride at − 5°, and the solutions were left in pressure bottles at 0° for a day, and then at room temperature one day longer. The resulting chloro-compounds could be distilled under reduced pressure without decomposition; b. p. 59°/0·15 mm. (This method cannot be used for the preparation of menthyl chloride, since ethereal hydrogen chloride is without action on *l*-menthol.) The 8-chloro-*p*-menthanes were dehalogenated by decomposing the Grignard compounds with water. From 15 g. of 8-hydroxy-*p*-menthane, 3—4 g. of *p*-menthane were obtained: 8-hydroxy-*p*-menthane (m. p. 25°) gave *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·8017, $n_D^{20^\circ}$ 1·4390; 8-hydroxy-*p*-menthane (m. p. 35°) gave *p*-menthane, $d_{4^\circ}^{20^\circ}$ 0·7970, $n_D^{20^\circ}$ 1·4373.

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