222. *Researches in the Menthone Series. Part XV.*
l-trans-Δ^4-*Menthen-3-ol.*

By David Malcolm and John Read.

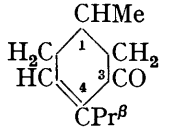
This paper initiates the stereochemical characterisation of a series of *p*-menthenols. One of the two epimeric Δ^4-menthen-3-ols (II) formed in the reduction of *l*-Δ^4-menthen-3-one (I) has been isolated and identified as the *trans*-isomeride (IV). A method has been devised for the conversion of *l*-menthol into *d-iso*menthol, thus supplementing earlier work on the conversion of *l*-menthol into *d-neo*menthol.

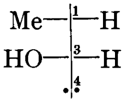
Although many *p*-menthenols have been described, these substances have not usually been obtained in a state of stereochemical purity; moreover, little definite has been established concerning their relative molecular configurations. The present communication records the results of the first of a series of investigations in which it is proposed to deal with such problems.

When selectively reduced by Ponndorf's method, *l*-Δ^4-menthen-3-one (I) yields a mixture of two stereoisomeric Δ^4-menthen-3-ols (II), of which one has been isolated as a stereochemically pure substance, through fractional crystallisation of the derived 3 : 5-dinitrobenzoates.

Because of the stereochemical relationship existing between *l*-Δ^4-menthen-3-one and *l*-menthone (Read and Robertson, J., 1926, 2211), it follows that these two Δ^4-menthen-3-ols must possess the respective molecular configurations (III) and (IV). Further, the information available for the relative molecular configurations of the menthols (J., 1934, 1781) enables a specific configuration to be assigned to each of the Δ^4-menthen-3-ols under notice : upon hydrogenation, the substance (III) would yield a mixture of *l*-menthol

(VII) and *d-neoiso*menthol, and (IV) would give a mixture of *d-iso*menthol (V) and *d-neo*menthol (VI).


(I.)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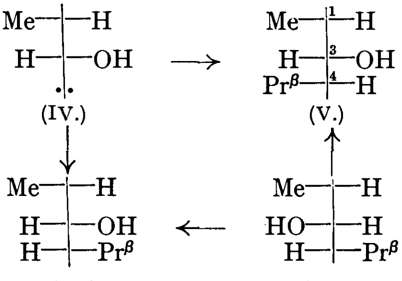
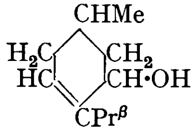

(IV.) (V.) (VI.) (VII.)


(II.)

The pure Δ^4-menthen-3-ol obtained from the less soluble 3 : 5-dinitrobenzoate yielded, in fact, a hydrogenation product consisting chiefly of *d-iso*menthol (V), and containing also some *trans-p*-menthane, formed evidently as a consequence of the ready dehydration of *d-neo*menthol (J., 1934, 1781), followed by hydrogenation of the *d*-Δ^3-menthene thus produced. The substance is thus revealed as l-trans-Δ^4-*menthen*-3-*ol* (IV).

This menthenol, in common with other αβ-unsaturated alcohols, undergoes partial racemisation in presence of acids (J., 1937, 239).

The processes now described provide a method for the conversion of *l*-menthol (VII) into *d-iso*menthol (V), leading to the inversion of the asymmetry of carbon atoms (3) and (4). The conversion of *l*-menthol into *d-neo*menthol (VI), through the inversion of the asymmetry of carbon atom (3), has already been detailed (*J. Soc. Chem. Ind.*, 1934, **53**, 52T).

The purest specimen of *l-cis*-Δ^4-menthen-3-ol obtained in this work was still contaminated with some of the *trans*-epimer. The refractive index and density observed for a mixture of these *cis*- and *trans*-forms were markedly higher than for the pure *trans*-compound, so that the relative molecular configurations now assigned to these two menthenols conform to the Auwers–Skita rule (*Annalen*, 1915, **410**, 287; 1920, **420**, 91). Independent confirmation is thus obtained of the relative configurations assigned earlier (J., 1934, 1781) to the corresponding menthols, in so far as the 1 : 3-positions are concerned. Moreover, as anticipated, *l-trans*-Δ^4-menthen-3-ol reacted more rapidly than *l-cis*-Δ^4-menthen-3-ol with *p*-nitrobenzoyl chloride (J., 1934, 1780). Upon catalytic hydrogenation, the impure specimen of the *cis*-menthenol yielded a product in which *l*-menthol (VII), *l*-menthone, and *trans-p*-menthane were identified, a result which is in keeping with the configuration (III) for *l-cis*-Δ^4-menthen-3-ol.

EXPERIMENTAL.

d-Δ^3-*Menthene*.—The use of toluene in the preparation of methyl *l*-menthylxanthate (Tschugaev, *Ber.*, 1899, **32**, 3333) was obviated by dissolving sodium (23 g.) in molten *l*-menthol (250 g.) at 160—180°, most of the unchanged *l*-menthol being then distilled off under diminished pressure. Carbon disulphide (63·5 c.c.) was added slowly to the ice-cooled solution of the residual sodium *l*-menthoxide in dry ether (375 c.c.). The mixture was then warmed under reflux for 30 minutes. Methyl iodide (64·9 c.c.) was added slowly to the ice-cooled liquid, the reaction being completed by an hour's heating under reflux. The ethereal solution, when shaken with water, dried, and distilled, yielded a heavy oil. Dissolution in hot alcohol yielded crystalline methyl *l*-menthylxanthate (86% yield) upon cooling. When distilled at 200° under ordinary pressure (cf. Tschugaev, *loc. cit.*), 890 g. of the once recrystallised xanthate gave 498 g. of crude *d*-Δ^3-menthene. After being heated with sodium wire under reflux for several hours, this yielded *d*-Δ^3-menthene (439 g.), b. p. 60—62°/15 mm., $d_{12^\circ}^{12^\circ}$ 0·8210, $n_D^{12^\circ}$ 1·4540, $\alpha_D^{12^\circ}$ +93·4° (*l* 1), $[\alpha]_D^{12^\circ}$ +113·8° (homogeneous), $[\alpha]_D^{14^\circ}$ +114·1° (*c* 2·0, alcohol).

l-Δ^4-*Menthen*-3-*one*.—*d*-Δ^3-Menthene nitrosochloride (Richtmann, *Amer. Chem. J.*, 1896, **18**, 762; Read and Robertson, J., 1926, 2217) was converted into the oxime of *l*-Δ^4-menthen-3-one (*loc. cit.*). When purified by distillation in superheated steam, this had $[\alpha]_D^{16^\circ}$ −55·0° (*c* 2·0, alcohol), m. p. 60—61·5°. Owing to the loss in this process it is preferable to do no more than wash the ethereal solution of the crude oxime with water. The pale yellow syrup thus obtained had $[\alpha]_{\mathrm{D}}^{12^\circ}$ $-42{\cdot}6^\circ$ (*c* 2·0, alcohol), and when hydrolysed with boiling hydrochloric acid (1 : 1) it yielded *l*-Δ^4-menthen-3-one having $n_{\mathrm{D}}^{19^\circ}$ 1·4723, $\alpha_{\mathrm{D}}^{16^\circ}$ $-70{\cdot}52^\circ$ (*l* 1).

Reduction of l-Δ^4-*Menthen*-3-*one*.—1. A solution of the ketone (15 g.) in dry *iso*propyl alcohol (50 c.c.) containing aluminium *iso*propoxide (3 g.) was submitted to a slow constant-volume distillation through a 30-cm. Vigreux column from an oil-bath at 110°, according to the method of Ponndorf (*Z. angew. Chem.*, 1926, **39**, 138), fresh quantities of aluminium *iso*propoxide (1·5 g.) being added at intervals of 8 hours. After 24 hours' treatment, most of the *iso*propyl alcohol was distilled away through the column, and the residue was steam-distilled. No menthenol was found.

2. A solution of the ketone (50 g.) in dry *iso*butyl alcohol (100 c.c.) containing aluminium *iso*propoxide (12 g.) in solution was treated as above for 20 hours at 160—165°. Dry *iso*butyl alcohol was added periodically to replace loss, and every 5 hours a solution of aluminium *iso*propoxide (6 g.) in dry *iso*butyl alcohol (25 c.c.) was added. After 20 hours the last part of the distillate (total, 350 c.c.) still gave a faint positive reaction for acetone by the sodium nitroprusside test. The steam distillate obtained as in (1) above was extracted with ether. The residue from the dried extract yielded upon distillation a fraction (42 g.), b. p. 90—97°/13 mm., $n_{\mathrm{D}}^{14^\circ}$ 1·4748, $\alpha_{\mathrm{D}}^{14^\circ}$ $-114{\cdot}73^\circ$ (*l* 1, homogeneous), consisting of a mixture of Δ^4-menthen-3-ols.

l-trans-Δ^4-*Menthen*-3-*ol*.—The above mixture of Δ^4-menthen-3-ols (78·8 g.) was esterified in dry pyridine with 3 : 5-dinitrobenzoyl chloride. The product was poured into water and a chloroform extract of the resulting mixture was washed with dilute acid, dilute alkali, and water. The chloroform was removed, and steam distillation of part of the solid residue showed that it contained no unchanged ketone or alcohol. The crude ester, obtained in almost quantitative yield, had m. p. 139—140°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ $-109{\cdot}0^\circ$ (*c* 2·0, chloroform). After two recrystallisations from alcohol containing a little chloroform the ester had $[\alpha]_{\mathrm{D}}^{15^\circ}$ $-128{\cdot}0^\circ$, and after one more recrystallisation from this solvent, followed by two from acetone, it had $[\alpha]_{\mathrm{D}}^{17^\circ}$ $-172{\cdot}4^\circ$ (52·5 g.). A sixth recrystallisation, from acetone, gave colourless needles of pure l-trans-Δ^4-*menthen*-3-*yl* 3 : 5-*dinitrobenzoate* (42·5 g.), m. p. 164—165°, $[\alpha]_{\mathrm{D}}^{16^\circ}$ $-175{\cdot}0^\circ$ (*c* 2·0, chloroform) (Found : C, 58·4; H, 5·7. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·8%).

When hydrolysed with alcoholic potassium hydroxide, this ester yielded l-trans-Δ^4-*menthen*-3-*ol* (Found : C, 77·6; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%). This was a colourless, viscid liquid with a somewhat sharp odour, b. p. 102—104°/18 mm., $d_{4^\circ}^{25^\circ}$ 0·9109, $n_{\mathrm{D}}^{25^\circ}$ 1·4712, $[R_L]_{\mathrm{D}}$ 47·28 (calc. for $C_{10}H_{18}O\,|\overline{1}$, 47·16), $\alpha_{\mathrm{D}}^{20^\circ}$ $-176{\cdot}74^\circ$ (*l* 1, homogeneous), $[\alpha]_{\mathrm{D}}^{25^\circ}$ $-165{\cdot}7^\circ$ (*c* 2·3, alcohol). The *p*-nitrobenzoate crystallised from aqueous methyl alcohol in needles, m. p. 55°, $[\alpha]_{\mathrm{D}}^{18^\circ}$ $-210{\cdot}0^\circ$ (*c* 1·0, chloroform). When a specimen of this menthenol was heated on the water-bath for 30 minutes with 16% hydrochloric acid, the rotatory power declined to $[\alpha]_{\mathrm{D}}^{14^\circ}$ $-2{\cdot}2^\circ$ (*c* 2·7, alcohol); the recovered menthenol gave no terpene fraction when redistilled.

Hydrogenation of l-trans-Δ^4-*menthen*-3-*ol*.—When hydrogenated in presence of colloidal palladium stabilised by gum arabic (J., 1934, 240), the above menthenol having $\alpha_{\mathrm{D}}^{17^\circ}$ $-172{\cdot}0^\circ$ (*l* 1, homogeneous) gave a product which crystallised in part and had $[\alpha]_{\mathrm{D}}^{17^\circ}$ $+18{\cdot}20^\circ$ (*c* 2·0, alcohol). Distillation yielded a first fraction, b. p. 51°/10·5 mm., $n_{\mathrm{D}}^{15^\circ}$ 1·4410. This was optically inactive, and consisted of *trans-p*-menthane (*Ber.*, 1922, **55**, 148). The second fraction, b. p. 92—93°/10 mm., which formed the bulk of the hydrogenation product, had the odour of *iso*menthol and crystallised almost completely in the receiver, forming long needles, the m. p. of which (69—70°) was not depressed by pure *d-iso*menthol (m. p. 82·5°). The derived *p*-nitrobenzoate had m. p. 54°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ $+25{\cdot}0^\circ$ (*c* 1·0, chloroform), and was identical with *d-iso*menthyl *p*-nitrobenzoate (J., 1933, 170).

l-cis-Δ^4-*Menthen*-3-*ol*.—The first mother-liquor obtained in the recrystallisation of the above crude 3 : 5-dinitrobenzoate, $[\alpha]_{\mathrm{D}}^{17^\circ}$ $-109{\cdot}0^\circ$, gave a residue having $[\alpha]_{\mathrm{D}}^{18^\circ}$ $-61{\cdot}3^\circ$ (*c* 2·0, chloroform); upon hydrolysis, this yielded impure *l-cis*-Δ^4-menthen-3-ol having $\alpha_{\mathrm{D}}^{15^\circ}$ $-69{\cdot}4^\circ$ (*l* 1, homogeneous). The separation of stereochemically pure *l-cis*-Δ^4-menthen-3-ol from such residues has not yet been accomplished. Another specimen of the impure *cis*-compound had $d_{4^\circ}^{25^\circ}$ 0·9141, $n_{\mathrm{D}}^{25^\circ}$ 1·4723, $[R_L]_{\mathrm{D}}$ 47·19 (calc., 47·16), $\alpha_{\mathrm{D}}^{19^\circ}$ $-95{\cdot}56^\circ$ (*l* 1, homogeneous).

Complete esterification with *p*-nitrobenzoyl chloride of the above mixture of *l-cis*- and *l-trans*-Δ^4-menthen-3-ol, having $\alpha_{\mathrm{D}}^{19^\circ}$ $-95{\cdot}56^\circ$, gave a partly crystalline mass with $[\alpha]_{\mathrm{D}}^{25^\circ}$ $-87{\cdot}9^\circ$ (*c* 1·2, chloroform). Partial esterification of some of the same specimen with *p*-nitrobenzoyl chloride (0·67 mol.) (J., 1934, 1782) gave a more fully crystalline product with $[\alpha]_{\mathrm{D}}^{25^\circ}$ $-91{\cdot}0^\circ$. Thus, the *trans*-compound reacted more rapidly than the *cis*-compound with this reagent.

When submitted to catalytic hydrogenation, as described above, the mixture of the two epimeric menthenols, having $\alpha_{\mathrm{D}}^{19^\circ}$ $-95{\cdot}56^\circ$, yielded a small amount of *trans-p*-menthane, together with *d-iso*menthol and *l*-menthol (identified by the *p*-nitrobenzoates; J., 1933, 170), and *l*-menthone (2 : 4-dinitrophenylhydrazone, m. p. 146°, $[\alpha]_D^{20°}$ $-26{\cdot}0°$, *c* 1·0 in chloroform).

dl-Δ^3-*Menthene and* dl-Δ^4-*Menthen*-3-*one*.—*dl*-Δ^3-Menthene (J., 1928, 1492) gave a low yield of crystalline nitrosochloride (7 g. from 36 g.). The derived *dl*-Δ^4-menthen-3-one oxime, when distilled under diminished pressure, crystallised in rosettes of feathery needles, m. p. 66—67°. It dissolved readily in organic solvents, but was insoluble in cold dilute mineral acids. Upon hydrolysis it yielded *dl*-Δ^4-menthen-3-one, b. p. 92—94°/18 mm. The semicarbazone was a crystalline powder, m. p. 142° (Wallach, *Annalen*, 1908, **362**, 276). Reduction of this ketone, according to Ponndorf's method, as described above, furnished a product, b. p. 113—117°/35 mm., $n_D^{15°}$ 1·4703, which gave a dl-Δ^4-*menthen*-3-*yl* 3 : 5-*dinitrobenzoate* separating after two recrystallisations from alcohol containing a little acetone in needles, m. p. 135° (Found: C, 58·9; H, 5·9. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·8%).

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