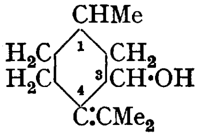
278. *Researches in the Menthone Series. Part XVI.* (d-neo)-iso*Pulegol.*

By Andrew G. Short and J. Hinton Read.

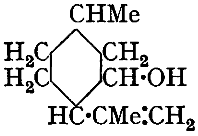
Selective reduction of *d*-pulegone by the Ponndorf reagent under stated conditions leads to the formation of a mixture of optically active pulegols (I) and *iso*pulegols (II), which undergo partial dehydration to yield terpenes. A pure dextrorotatory alcohol has been isolated by fractionally crystallising the derived 3 : 5-dinitrobenzoates. This is converted exclusively into *d-neo*menthol by catalytic hydrogenation, and thus possesses the molecular configuration (VI). The stereoisomerism and nomenclature of the pulegols and *iso*pulegols are discussed, and the new alcohol is named (d-neo)-iso*pulegol.*

In a recent communication (this vol., p. 1037) the molecular configuration of *l-trans*-Δ^4-menthen-3-ol was deduced by correlating this substance, through catalytic hydrogenation, with menthols of known relative molecular configurations. The method has now been applied successfully in the pulegol series.

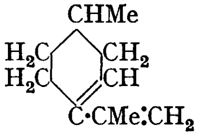
Read and Grubb (J., 1934, 242) were unable to isolate any secondary alcohol by applying the method of Ponndorf (*Z. angew. Chem.*, 1926, **39**, 138) to *d*-pulegone: the *d*-$\Delta^{3:8(9)}$-*p*-menthadiene (III) obtained was probably formed through the dehydration of intervening pulegols (I) or *iso*pulegols (II), by γ- or α-elimination, respectively:



(I.)



(II.)



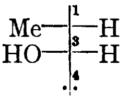
(III.)

Read and Grubb envisaged only the former method of dehydration, applicable to pulegols; but from the results now recorded it is evident that α-elimination of water from *iso*pulegols must also be taken into account as a possibility. The $\Delta^{2:4(8)}$-*p*-menthadiene reported by Dœuvre and Perret (see below) is presumably formed through α-elimination of water from pulegols.

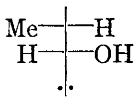
Read and Grubb used aluminium *iso*propoxide which had been purified beforehand by distillation under diminished pressure. In a later application of the Ponndorf reaction to *d*-pulegone, Dœuvre and Perret (*Bull. Soc. chim.*, 1935, **2**, 298) prepared this catalyst *in situ*: aluminium was dissolved in *iso*propyl alcohol to which the ketone was then added. Besides the two terpenes mentioned above, the product contained a so-called "*d*-pulegol," which was purified by treatment with sodium sulphite solution followed by fractional distillation. This was a viscid liquid, b. p. 91·5°/12 mm., $d_{4^\circ}^{18^\circ}$ 0·909, $n_{\mathrm{D}}^{18^\circ}$ 1·4714, $[\alpha]_{\mathrm{D}}^{18^\circ}$ $+70{\cdot}00^\circ$. No crystalline derivative was prepared.

The work now described indicates that the alcoholic product formed from *d*-pulegone in this variant of the Ponndorf method was a mixture of stereoisomeric pulegols and *iso*pulegols. From it, by fractional crystallisation of the mixed 3 : 5-dinitrobenzoates, was isolated in about 5% yield an alcohol having b. p. 95°/17 mm., $d_{4^\circ}^{25^\circ}$ 0·9107, $n_{\mathrm{D}}^{25^\circ}$ 1·4686, $\alpha_{\mathrm{D}}^{15^\circ}$ $+25{\cdot}30^\circ$ (*l* 1, homogeneous). *d*-$\Delta^{3:8(9)}$-*p*-Menthadiene was present in the accompanying terpene fraction (cf. Dœuvre and Perret, *loc. cit.*).

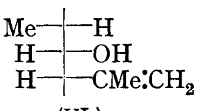
The chemical and stereochemical identity of the pure alcohol was deduced as follows. Any stereochemically homogeneous pulegol will yield two menthols (or corresponding products derived by dehydration, etc.) upon catalytic hydrogenation, owing to the creation of a new asymmetric carbon atom (4) in the process. Thus, the optically active *cis*-form of pulegol (IV) would yield *l*-menthol and d-*neoiso*menthol; and the *trans*-form (V) would yield *d*-*iso*menthol and *d*-*neo*menthol (J., 1934, 1781):



(IV.)



(V.)



(VI.)

The *iso*pulegol system, on the other hand, already contains the three asymmetric carbon atoms of the menthols; so that any stereochemically homogeneous *iso*pulegone will pass quantitatively into a stereochemically homogeneous menthol upon catalytic hydrogenation; *i.e.*, for each *iso*pulegol there is one, and only one, corresponding menthol. Thus, in the *iso*pulegol series the counterparts of the four typical menthols (*l*-, *d*-*neo*-, *d*-*iso*-, and *d*-*neoiso*-) may be designated as follows: (*l*)-*iso*pulegol, (*d*-*neo*)-*iso*pulegol, (*d*-*iso*)-*iso*pulegol, and (*d*-*neoiso*)-*iso*pulegol.

The new secondary alcohol isolated in the present research yielded exclusively *d*-*neo*menthol upon hydrogenation. It is therefore (d-neo)-iso*pulegol* (VI). It may be observed that *trans*-pulegol (V), besides giving the easily recognisable *iso*menthol, would probably furnish *p*-menthane in place of *d*-*neo*menthol (cf. this vol., p. 1037) upon catalytic hydrogenation.

From the condensation product of acetic anhydride and citronellal, Pickard, Hunter, Lewcock, and de Pennington (J., 1920, **117**, 1248) obtained the so-called "*l*-*iso*pulegol" and "*d*-α-*iso*pulegol." The former, since it was hydrogenated exclusively to *l*-menthol, may be designated (*l*)-*iso*pulegol. The latter yielded impure *d*-*neo*menthol when hydrogenated, and apparently consisted mainly of the (*d*-*neo*)-*iso*pulegol now described. The oxidation of pulegols or *iso*pulegols with Beckmann's chromic acid reagent at 50° yields mixtures of pulegone and *iso*pulegone, and this method is therefore not diagnostic.

Dœuvre and Perret (*loc. cit.*) mention the recovery of unchanged *d*-pulegone from the Ponndorf reduction. The ketone recovered in the present investigation, however, invariably had a much higher optical rotation than the original *d*-pulegone, and appeared to consist of a mixture of *d*-pulegone and *d*-*iso*pulegone. Owing to the ready interconversion of these two ketones there can be little doubt that the reduction in question yields a mixture of pulegols and *iso*pulegols. The value $\alpha_{\mathrm{D}}^{17^\circ}$ $+42{\cdot}7^\circ$ (*l* 1) observed for the recovered ketone appears to be the highest yet recorded for any mixture of the two ketones concerned (cf. Simonsen, "The Terpenes," Cambridge, 1931, I, 342).

The method described in this communication is being applied in a further study of the piperitols (J., 1934, 308).

EXPERIMENTAL.

Reduction of d-*Pulegone.*—*iso*Propyl alcohol (1000 c.c.) was boiled under reflux for 5 hours with mercuric chloride (2·5 g.), clean magnesium ribbon (0·3 g.), and a few pieces of porous plate, and then distilled under somewhat diminished pressure. To the dry alcohol (50 c.c.), kept at the b. p. under reflux, was added mercuric chloride (2 g.), followed by a little coarse aluminium powder (2 g.). If the reaction failed to start, a little iodine, copper acetate, or *sec.*-butyl alcohol was added as catalyst, but this was rarely necessary (cf. *Ber.*, 1937, **70**, 1522). When the reaction set in, the remainder of the aluminium powder (10 g.) was added at intervals. Later, more dry *iso*propyl alcohol (350 c.c.), previously heated to boiling, was added in several portions. If necessary, the reaction was checked occasionally at this stage by cooling. Finally, the mixture was heated under reflux on the water-bath until the reaction ceased (8 hours).

Freshly distilled *d*-pulegone (200 g.), obtained from oil of pennyroyal (*Mentha pulegium*) and having $\alpha_D^{20°}$ + 19·97° (*l* 1), $n_D^{20°}$ 1·4859, was then added to the solution, and a slow constant-volume distillation was conducted through a 30-cm. Vigreux column, dry *iso*propyl alcohol being added at intervals to replace the distillate (*ca.* 40 c.c. per hour). The temperature of the oil-bath was kept at about 120° for several hours, and was then raised gradually to 170° in order to maintain the rate of distillation during an intermediate phase of the reaction in which the mixture thickened and gelatinised. Later, the gel broke down, the mixture became more fluid, and the temperature was allowed to fall to 125—130°.

At intervals 5 drops of the distillate were tested by Legal's sodium nitroprusside test. After 20 hours' heating, the purple colour in the test became very faint, and most of the *iso*propyl alcohol was then removed by distillation.

The products of two such experiments were united and steam-distilled. The dried ethereal extract of the distillate gave the following fractions when distilled: (1) b. p. 55—82°/17 mm. (34 g.); (2) b. p. 82—107°/17 mm., $\alpha_D^{13·5°}$ + 58·03° (*l* 1), $n_D^{13·5°}$ 1·4836 (255 g.). The undistilled residue was negligible.

Esterification of the Reduction Product.—To the ice-cooled solution of the above second fraction (50 g.) in dry pyridine (100 c.c.) was added gradually powdered 3 : 5-dinitrobenzoyl chloride (33 g.) with vigorous shaking. After 16 hours the ice-cooled product was treated carefully with an ice-cooled solution of concentrated hydrochloric acid (100 c.c.) in water (100 c.c.). The ethereal extract of the resulting solution was washed with 2N-sodium hydroxide until the washings were colourless, and then with water. The ether was distilled from the extract, and unesterified material (153 g. from 250 g. of the above second fraction, see below) was removed from the residue by steam-distillation.

The non-volatile residue contained some 3 : 5-dinitrobenzoic acid, formed through dehydration of part of the ester in the steam-distillation; this acid was removed by washing the ethereal solution of the residue with 2N-sodium hydroxide. When the ether was distilled away from the dried solution, the residual reddish-brown oil soon crystallised to a brown pasty solid. The total material obtained in this way from 250 g. of the above second fraction was recrystallised once from methyl alcohol and twice from methyl alcohol–chloroform. The product (11·5 g.) had m. p. 138—139°, $[\alpha]_D^{16°}$ + 45·0° (*c* 1·0, chloroform), and these values remained unaltered after further recrystallisation. The (d-neo)-iso*pulegyl* 3 : 5-*dinitrobenzoate* thus obtained crystallised in long, fine, colourless needles (Found: C, 58·8; H, 6·0. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·8%).

(d-neo)-iso*Pulegol.*—The above ester (9 g.) was heated under reflux for 30 minutes with 5% methyl-alcoholic potassium hydroxide (51 c.c.; 1·2 mols.). The resulting (*d-neo*)-*iso*pulegol, isolated by steam-distillation followed by extraction with ether, was a fairly mobile, colourless liquid, with a characteristic fresh odour: b. p. 95°/17 mm., $d_{4°}^{25°}$ 0·9107, $n_D^{25°}$ 1·4686, $\alpha_D^{15°}$ + 25·30° (*l* 1, homogeneous), $[\alpha]_D^{15°}$ + 39·3° (*c* 1·0, alcohol), $[R_L]_D$ 47·13 (Calc.: 47·24). The yield was almost theoretical.

Hydrogenation of (d-neo)-iso*Pulegol.*—The alcohol readily underwent hydrogenation in ethereal solution, in presence of a palladium sol stabilised with gum arabic (cf. J., 1934, 240). The product was a colourless liquid with the faint mentholic odour of *neo*menthol: b. p. 97·5°/17·5 mm., $n_D^{18°}$ 1·4614, $\alpha_D^{16·5°}$ + 16·56° (*l* 1, homogeneous). These constants are closely similar to those quoted by Read and Grubb (*J. Soc. Chem. Ind.*, 1934, **53**, 53T) for *d-neo*menthol. No other substance was found in the hydrogenation product, which appeared to be homogeneous.

When esterified in dry pyridine (5 c.c.) with *p*-nitrobenzoyl chloride (1·4 g.), the hydrogenation product (1 g.) yielded a crude ester having $[\alpha]_D^{14°}$ + 18·1° (*c* 1·1, chloroform). Recrystallisation from alcohol yielded fine, colourless needles, m. p. 95°, $[\alpha]_D^{14°}$ + 18·0° (*c* 1·0, chloroform). The substance was therefore *d-neo*menthyl *p*-nitrobenzoate (Read and Grubb, *loc. cit.*).

Examination of the Unesterifiable Material from the Reduction of d-*Pulegone.*—The unesterified material (153 g.) recovered by steam-distillation (see above) was separated by repeated fractional distillation under diminished pressure into two main fractions. The first, b. p. 79—81°/16 mm., $n_D^{17·5°}$ 1·4935, $\alpha_D^{17·5°}$ + 110·2° (*l* 1), consisted essentially of *d*-$\Delta^{3:8(9)}$-*p*-menthadiene (Read and Grubb, J., 1934, 242). The second had b. p. 100—105°/17 mm., $\alpha_D^{17°}$ + 42·7° (*l* 1); when treated with semicarbazide acetate in aqueous alcohol in the cold it yielded *d*-pulegonesemicarbazone, m. p. 172°, $[\alpha]_D^{21°}$ + 68·2° (*c* 1·0, chloroform) (Found: C, 63·4; H, 9·2. Calc.: C, 63·2; H, 9·1%) (*Ber.*, 1895, **28**, 653). It was not α-pulegone, however, for its 2 : 4-*dinitrophenylhydrazone*, obtained by Brady's method (J., 1931, 756), crystallised from methyl alcohol in bright red needles, m. p. 149—150°, $[\alpha]_D^{19°}$ + 116·0° (*c* 0·5, chloroform) (Found: C, 57·6; H, 6·0. $C_{16}H_{20}O_4N_4$ requires C, 57·8; H, 6·1%), whereas the original *d*-pulegone, when treated similarly, yielded a thick syrup which solidified slowly and separated from light petroleum (b. p. 60—80°) in dark crimson leaflets, m. p. 141°, $[\alpha]_D^{19°}$ + 130·0° (*c* 0·5, chloroform) (cf. J., 1931, 758), the m. p. being depressed by admixture with the derivative of m. p. 149—150°.

When hydrogenated in presence of a palladium sol, this ketonic fraction yielded a product with the odour of menthone, b. p. 96°/20 mm., $n_D^{21°}$ 1·4521, $\alpha_D^{18°}$ + 24·04° (*l* 1) (cf. Read and Robertson, J., 1926, 2216). This product readily furnished *l*-menthone-2 : 4-dinitrophenylhydrazone, crystallising from methyl alcohol–chloroform in orange needles, m. p. 146°, $[\alpha]_D^{15°}$ −26·0° (*c* 1·0, chloroform) (cf. *J. Amer. Chem. Soc.*, 1930, **52**, 2216; this vol., p. 1040).

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