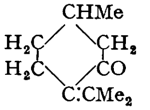
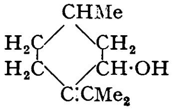
927. *Reactions of* $\alpha\beta$*-Unsaturated Cyclic Aldehydes and Ketones. Part X.** (+)-trans-*Pulegol and a* (−)-*Pulegol from* (+)-*Pulegone.*

By A. Killen Macbeth and J. S. Shannon.

The difficulty hitherto experienced in preparing pulegols by the reduction of pulegone has been overcome by using lithium aluminium hydride. In this way (+)-pulegone readily gives a high yield of mixed alcohols. From this, (+)-*trans*-pulegol was isolated, the configuration being established by its hydrogenation to *iso*menthol. The alcohol is considered to be stereochemically pure, and a number of derivatives are described. A (−)-pulegol which is a stereochemical mixture containing mainly (−)-*cis*-pulegol was also isolated. Infra-red absorption measurements support the pulegol, as opposed to the *iso*pulegol, structure.

Pulegone (I) can, on reduction, give rise to a pair of epimeric alcohols (II), but dehydration to unsaturated hydrocarbons, particularly *p*-mentha-3 : 8-diene (III) and *p*-mentha-2 : 4(8)-diene (IV), has hitherto prevented the isolation of the alcohols in other than small yields; and the purity of the alcohols is open to doubt.


(I)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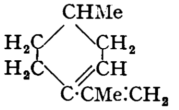
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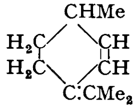
(IV)

Tiemann and Schmidt (*Ber.*, 1896, **29**, 914) claimed to have prepared a pulegol by the reduction of (+)-pulegone by sodium and ethanol, but could not isolate it from the menthol mixture produced. The reaction was further examined by Paolini (*Atti R. Accad. Lincei*, 1919, **28**, II, 190, 236) who by fractional crystallisation of what he claimed was the strychnine salt of pulegyl hydrogen phthalate and subsequent hydrolysis isolated an oil, $[\alpha]_D$ −54°, which he concluded was a pulegol. The claim is doubtful as we have never succeeded in preparing a hydrogen phthalate of pulegol on account of the ready dehydration to dienes : and it is very unlikely that a pulegol would survive the conditions of acid hydrolysis which Paolini employed.

The Meerwein–Ponndorf reduction method has also proved unsatisfactory. Read and Grubb (*J.*, 1934, 242) did not succeed in isolating any secondary alcohol by the reduction of (+)-pulegone by aluminium *iso*propoxide, as dehydration to the menthadiene (III) occurred. Using the same reagent under different conditions Doeuvre and Perret (*Bull. Soc. chim.*, 1935, **2**, 298) obtained the two menthadienes (III, IV) and a viscid liquid which they claimed to be "*d*-pulegol" : but no crystalline derivatives were prepared. Later Short, Hinton, and Read (*J.*, 1939, 1306) using aluminium *iso*propoxide under stated conditions claimed to have obtained from (+)-pulegone a mixture of optically active pulegols and *iso*pulegols which underwent partial dehydration to yield terpenes. From the reaction mixture they prepared a 3 : 5-dinitrobenzoate, m. p. 138—139°, $[\alpha]_D^{16}$ +45° (*c*, 1 in chloroform), which on hydrolysis gave an alcohol, b. p. 95°/17 mm., $[\alpha]_D^{15}$ +39·3° (*c*, 1 in alcohol). The alcohol was obtained in a yield of less than 1·5% of the (+)-pulegone used in the reductions, and was considered to be an *iso*pulegol.

Macbeth and Shannon (*J.*, 1952, 2852) obtained excellent yields of the secondary alcohols when (−)-piperitone was reduced by lithium aluminium hydride, and the two epimeric piperitols were isolated stereochemically pure. It was thought that, in the case of (+)-pulegone, similar techniques would lead to equally good yields of the related secondary alcohols, and to the characterisation of the epimeric pulegols. Expectations of high yields of the pulegols have been realised and stereochemically pure (+)-*trans*-pulegol has been obtained. A lævorotatory alcohol which appears to contain a high proportion of (−)-*cis*-pulegol has also been prepared, but so far it has not been possible to obtain it stereochemically pure.

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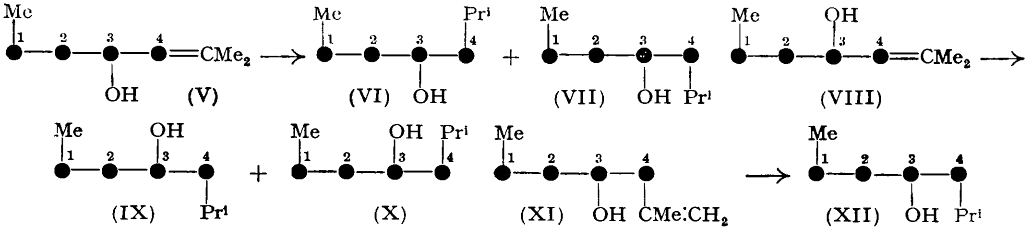
* Part IX, *J.*, 1952, 2852.

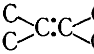
In the work now described the reduction of (+)-pulegone (α_D +20°) with lithium aluminium hydride gave a 90% yield of mixed pulegols (they can usually be distilled without dehydration, but on occasions traces of water were formed during distillation through a column). Esterification and a few recrystallisations of the product gave (+)-*trans*-pulegyl 3 : 5-dinitrobenzoate of constant m. p. (103°) and rotation {$[\alpha]_D^{20}$ +105° (*c*, 1 in chloroform)}. A special technique (see p. 4750) is necessary for these recrystallisations owing to the ease of dehydration. Hydrolysis of the ester by the usual methods gave only hydrocarbons, but the alcohol was obtained in excellent yield by a simple modification (p. 4750). (+)-*trans*-Pulegol, m. p. 76°, $[\alpha]_D^{20}$ +100° (*c*, 2 in alcohol), which is thus obtained, readily sublimes under reduced pressure, and when pure is quite stable. The sublimate may be crystallised from aqueous methanol, but crystallisation before sublimation usually results in dehydration. It was further characterised as phenylurethane and α-naphthylurethane; these are formed in excellent yield and only require one crystallisation to attain maximum melting point and rotation, which is indicative of the stereochemical purity of the pulegol. The *trans*-configuration of the alcohol is established by its hydrogenation to (+)-*iso*menthol (see below).

The mixed pulegols give a *p*-nitrobenzoate in good yield which attains a steady m. p. 58° and maximum rotation −104° (*c*, 1 in chloroform) after several crystallisations. A small amount of ester isolated from the mother-liquors had a maximum rotation of +55° and m. p. 82°. Both esters are readily hydrolysed by the special method mentioned above, the (−)-ester giving a (−)-pulegol, m. p. 25°, $[\alpha]_D^{18}$ −85° (*c*, 2 in alcohol). Catalytic hydrogenation of this alcohol gives a menthol mixture from which (−)-menthyl 3 : 5-dinitrobenzoate was isolated. The alcohol therefore contains a fair proportion of (−)-*cis*-pulegol. It also contains an isomeric alcohol as dextrorotatory phenyl- and α-naphthyl-urethanes were prepared from it, although in poor yield. We are of the opinion that (−)-*cis*-pulegol should have a specific rotation of the order of −150°, and further work is being carried out with a view to isolating a stereochemically pure sample.

It is of interest that the difficulty experienced in the separation of the pulegols from their esters owing to dehydration was first overcome by cleavage of the (−)-pulegyl *p*-nitrobenzoate by lithium aluminium hydride. In this way the pulegol mixture having $[\alpha]_D^{18}$ −85° was obtained in 35% yield. The last traces of the "azo-alcohol" which is formed together with the pulegol are difficult to remove and the method was abandoned when the modified alkaline hydrolysis method already mentioned was devised and found to give much better yields. The hydride may, however, be useful in the case of alcohols which are very readily dehydrated during the hydrolysis of their esters. The azo-alcohol is being further examined.

Malcolm and Read (*J.*, 1939, 1037) deduced the molecular configuration of (−)-*trans*-menth-4-en-3-ol by correlation of the alcohol with the methols obtained on catalytic hydrogenation : and a general method of establishing the configuration of the menthen-3-ols in this way was envisaged. (+)-*trans*-Pulegol (V) can give rise to a mixture of (+)-*iso*-menthol (VI) and (+)-*neo*menthol (VII), as a new asymmetric centre at $C_{(4)}$ is produced on saturation of the ethylene linkage. Similarly (−)-*cis*-pulegol (VIII) may be expected to yield (−)-menthol (IX) and (+)-*neoiso*menthol (X). The *iso*pulegols (cf. XI) can yield only one menthol (cf. XII), the product being determined by the existing configuration of the particular *iso*pulegol examined.



Short and Hinton Read (*loc. cit.*) found that catalytic reduction of their alcohol yielded exclusively (+)-*neo*menthol (XII) and so considered it to be (+)-*neoiso*pulegol (XI). It would seem, however, that this test is not rigidly diagnostic since Macbeth and Shannon (*loc. cit.*) have shown that (+)-*trans*-piperitol yields only (+)-*iso*menthol on catalytic hydrogenation over Raney nickel: and it is now found that the (+)-*trans*-pulegol described in this paper also yields exclusively (+)-*iso*menthol under the same conditions. Since the lævorotatory alcohol on similar hydrogenation gives a good yield of (−)-menthol it is considered to consist essentially of (−)-*cis*-pulegol. As both the pulegols now described are solids, and as their 3 : 5-dinitrobenzoates differ markedly from that obtained by Short and Hinton Read (*loc. cit.*), it may well be that their alcohol is in fact (+)-*neoiso*pulegol. In view of the doubt about the correlation of the menthols as a diagnostic principle in establishing configuration, further support was sought from the study of the infra-red spectra of the alcohols. Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland (*J.*, 1950, 916) have shown that the out-of-plane deformational modes of vibration of the olefinic hydrogens of the *iso*propenyl group result in a strong band at or very near to 890 cm.$^{-1}$, while the C=C stretching frequency of the same group appears near 1645 cm.$^{-1}$. In close agreement with these figures a sample of *iso*pulegol kindly examined for us by Mr. J. B. Willis and Mr. R. Werner was found to have a strong band at 889 cm.$^{-1}$, its C=C stretching frequency occurring at 1641 cm.$^{-1}$. The spectrum of the pure sample of (+)-*trans*-pulegol showed no band at 885—890 cm.$^{-1}$, so that the presence of an *iso*propenyl group is precluded. It showed no band between 1600 and 1700 cm.$^{-1}$ which is expected for the C=C bond, but this is very weak in the grouping  $(C)_2C{:}C(C)_2$ (Kletz and Sumner, *J.*, 1948, 1456).

EXPERIMENTAL

Reduction of (+)-*Pulegone*.—(+)-Pulegone (100 g.), b. p. 70°/2 mm., α_D^{20} +20·6° (homogeneous), obtained from oil of pennyroyal (*Mentha pulegium*) by fractional distillation, was dropped in anhydrous ether (200 ml.) into a stirred suspension of lithium aluminium hydride (9 g.) in ether (250 ml.) during 1 hour, and the mixture was boiled for a further 2 hours, then decomposed by the addition of water (10 ml.), followed by 5% sodium hydroxide solution (100 ml.). The aluminium hydroxide was filtered off on a sintered-glass funnel, and the filtrate washed with water. The ethereal solution was dried ($MgSO_4$–K_2CO_3) after addition of a few drops of dimethyl*cyclo*hexylamine, and subsequent removal of the solvent and distillation of the residue gave a mixture of pulegols (92 g., 90%), b. p. 50°/0·2 mm., $[\alpha]_D^{20}$ −70° (*c*, 2 in alcohol), which soon crystallised as a camphoraceous mass, m. p. *ca.* 20°.

This mixture (80 g.) was dissolved in light petroleum (1100 ml.; b. p. 60—80°) and dried ($MgSO_4$–K_2CO_3). Pyridine (40 g.) was added and then 3 : 5-dinitrobenzoyl chloride (115 g.) in dry benzene (200 ml.), with shaking, at such a rate that the temperature did not rise above 35° After 3 hours the mixture was washed successively with water, 5% sodium hydroxide solution, and water. Removal of the solvent after drying ($MgSO_4$–K_2CO_3) left the crude ester (50 g.) as yellow crystals (27% based on pulegol). These were purified as follows. Their suspension in light petroleum (b. p. 40—60°) was treated at <60° with benzene until dissolution occurred. Crystals separated as the solution cooled. Three such crystallisations gave (+)-trans-*pulegyl* 3 : 5-*dinitrobenzoate* (36 g.) as long yellow needles, m. p. 103°, $[\alpha]_D^{20}$ +105° (*c*, 1 in chloroform) (Found: C, 59·2; H, 5·7. $C_{17}H_{20}O_6N_2$ requires C, 58·95; H, 5·5%).

(+)-trans-*Pulegol*.—Potassium hydroxide (10 g.), dissolved in the minimum amount of absolute methanol (near the b. p. on the hot plate), was added to a solution of (+)-*trans*-pulegyl 3 : 5-dinitrobenzoate (30 g.) in anhydrous ether (250 ml.). Potassium 3 : 5-dinitrobenzoate was precipitated immediately and after a few minutes' shaking the mixture was set aside for an hour. After filtration of the potassium salt the ethereal solution was washed and dried ($MgSO_4$–K_2CO_3), and on removal of the solvent (+)-trans-*pulegol* was obtained as colourless crystals which sublimed when distillation under reduced pressure was attempted. The pure crystals obtained by sublimation had m. p. 76°, $[\alpha]_D^{20}$ +100° (*c*, 1 in alcohol), unaltered on recrystallisation from aqueous methanol (Found: C, 77·9; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%).

Phenyl *iso*cyanate (0·7 g.) was added to the pulegol (0·8 g.) in the absence of a solvent and the mixture left overnight. One crystallisation from light petroleum (b. p. 60—80°) gave pure (+)-trans-*pulegylphenylurethane* (1·35 g., 90%), needles, m.p. 101°, $[\alpha]_D^{18}$ +55° (*c*, 1 in chloroform) (Found: C, 75·0; H, 8·2; N, 5·4. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·4; N, 5·15%). (+)-trans-*Pulegyl-α-naphthylurethane*, similarly prepared and once crystallised from light petroleum

(b. p. 60—80°), formed needles, m. p. 111°, $[\alpha]_D^{18}$ +97° (*c*, 1 in chloroform) (Found: C, 78·0; H, 8·0; N, 4·2. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·75; N, 4·35%).

Hydrogenation of (+)-trans-*Pulegol.*—The alcohol (0·5 g.) in ethanol (8 ml.) containing Raney nickel catalyst (0·3 g.) was hydrogenated at 130°/800 lbs. for an hour. After filtration and removal of most of the ethanol under reduced pressure, addition of water (25 ml.) precipitated a solid with a menthol-like odour. This was extracted with light petroleum (b. p. 60—80°) and after drying and removal of the solvent the residual solid, $[\alpha]_D^{20}$ +28° (*c* 1 in alcohol), was converted into the 3 : 5-dinitrobenzoate. One crystallisation from light petroleum (b. p. 60—80°) gave an ester (1·1 g., 95% based on pulegol), m. p. 147° alone or mixed with (+)-*iso*menthyl 3 : 5-dinitrobenzoate.

(−)-*Pulegyl* p-*Nitrobenzoate.*—The crude alcohol (22 g.), m. p. *ca.* 20°, $[\alpha]_D^{20}$ −70°, was esterified by adding *p*-nitrobenzoyl chloride (28 g.) in dry benzene (50 ml.) to its stirred solution in light petroleum (b. p. 60—80°; 100 ml.) at <35°. After 3 hours the mixture was washed successively with water, 5% sodium hydroxide solution, and water. After drying ($MgSO_4$–K_2CO_3) the solvent was removed. The resulting *ester* (37 g., 84% based on pulegol), m. p. 42—45°, $[\alpha]_D^{18}$ −85° (*c*, 1 in chloroform), recrystallised from light petroleum (b. p. <40°) in which it is very soluble, as large prismatic rods (after four crystallisations), m. p. 58°, $[\alpha]_D^{20}$ −104° (*c*, 1 in chloroform) (Found: C, 67·65; H, 7·1; N, 4·95. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·95; N, 4·6%).

(+)-*Pulegol.*—(i) Attempts to hydrolyse the *p*-nitrobenzoate by alcoholic alkali yielded only hydrocarbons by the usual methods.

(ii) *Lithium aluminium hydride cleavage.* The ester (5 g.) in anhydrous ether (25 ml.) was dropped during 20 minutes into a stirred suspension of the hydride (3 g.) in ether (50 ml.). A scarlet-red colour was produced when the two solutions mixed, the solution as a whole being greenish-yellow. The mixture was refluxed for a further 2 hours. After decomposition by 5% sodium hydroxide solution, the aluminium hydroxide was filtered off and washed with benzene. The benzene–ether layer was separated, washed with water, dried ($MgSO_4$–K_2CO_3), and freed from solvents. The residue was taken up in warm light petroleum (b. p. <40°), and the solid (azo-alcohol) which separated on cooling was filtered off. The (−)-pulegol (0·9 g.) obtained after removal of the solvent and distillation had b. p. 80°/4·5 mm., $[\alpha]_D^{18}$ −85° (*c*, 1 in alcohol), m. p. 25°. This procedure is wasteful.

(iii) By the method described for (+)-*trans*-pulegol the *p*-nitrobenzoate (20 g.) gave (−)-pulegol as a camphor-like solid (9 g., 90%), b. p. 50°/0·2 mm., $[\alpha]_D^{18}$ −85° (*c*, I in alcohol), m. p. 25° (Found: C, 77·9; H, 11·75. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%).

The alcohol appears to be a mixture as, although it yields a lævorotatory 3 : 5-dinitrobenzoate (50%) and phthalimidoacetate (15%), the phenyl- and α-naphthyl-urethanes (20—30% yields) were dextrorotatory. (−)-*Pulegyl* 3 : 5-*dinitrobenzoate*, crystallised as pale yellow needles from light petroleum (b. p. 40—60°), had m. p. 70°, $[\alpha]_D^{18}$ −65° (*c*, 1 in chloroform) (Found: N, 8·2. $C_{17}H_{20}O_6N_2$ requires N, 8·05%). (−)-*Pulegyl phthalimidoacetate*, small needles from light petroleum, had m. p. 86°, $[\alpha]_D^{18}$ −11° (*c*, 1 in chloroform) (Found: N, 4·05. $C_{20}H_{23}O_4N$ requires N, 4·1%). A *phenylurethane* was obtained when the sample of (−)-pulegol (1·6 g.) was mixed with phenyl *iso*cyanate (1·4 g.) and left overnight. The product (1 g.) separated from light petroleum (b. p. 60—80°) as fine needles, m. p. 125°, $[\alpha]_D^{18}$ +53° (*c*, 1 in chloroform) (Found: N, 5·4. $C_{17}H_{23}O_2N$ requires N, 5·15%). An *α-naphthylurethane* similarly prepared had m. p. 122—123°, $[\alpha]_D^{18}$ +56° (*c*, 1 in chloroform) (Found: N, 4·55. $C_{21}H_{25}O_2N$ requires N, 4·35%).

Hydrogenation of (−)-*Pulegol.*—(−)-Pulegol (1·5 g.) in ethanol (15 ml.) containing Raney nickel catalyst (0·5 g.) was hydrogenated for an hour at 120°/700 lbs. Working up as in the previous hydrogenation gave a crude menthol mixture (1·3 g., 87%), $[\alpha]_D^{20}$ −24° (*c*, 0·5 in alcohol) which was esterified with 3 : 5-dinitrobenzoyl chloride. Two crystallisations from light petroleum (b. p. 60—80°) gave a pure ester (0·8 g., 30% based on crude menthol), m. p. 153° not depressed on admixture with authentic (−)-menthyl 3 : 5-dinitrobenzoate. No other ester was isolated.

We are indebted to Mr. J. B. Wilton for help in some of the earlier experiments, and to Professor John Read, F.R.S., for the gift of a sample of (+)-*iso*menthol. We thank also Mr. J. B. Willis and Mr. R. Werner for data on the infra-red spectra of pulegol and *iso*pulegol.

JOHNSON CHEMICAL LABORATORIES,
THE UNIVERSITY OF ADELAIDE, AUSTRALIA.

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