540. *Reactions of αβ-Unsaturated Cyclic Aldehydes and Ketones. Part IX.** (−)-cis- *and* (+)-trans-*Piperitol from* (−)-*Piperitone.*

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

Reduction of (−)-piperitone by lithium aluminium hydride gives a mixture consisting approximately of 36% of (−)-*cis*-piperitol and 64% of the hitherto little known (+)-*trans*-piperitol.

The two alcohols have been rigidly purified, and what are regarded as the stereochemically pure forms have been obtained and characterised. (−)-*cis*-Piperitol has m. p. 30°, and $[\alpha]_D$ −246° in alcohol or benzene. (+)-*trans*-Piperitol is a viscous liquid which has $[\alpha]_D$ +28° in the same solvents. Several esters of the alcohols are described.

The configurations of the alcohols are established by the hydrogenation of (−)-*cis*-piperitol to (−)-*neo*menthol, and (+)-*trans*-piperitol to (+)-*iso*menthol.

The isolation of piperitols from natural sources has been reported (Baker and Smith, "Eucalypts and their Essential Oils," 2nd edn., 1920, p. 373; Simonsen, *Indian Forest Records*, 1924, **10**, Part VIII) and several syntheses of the epimeric alcohols from the readily

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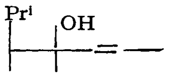
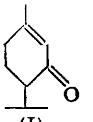
* Part VIII, *J.*, 1951, 1848.

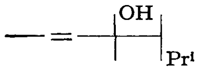
available (—)-piperitone (I) or its derivatives have been carried out (Read and Storey, *J.*, 1930, 2770; Read and Walker, *J.*, 1934, 308). Samples of both alcohols were prepared by these authors. A labile dextrorotatory piperitol was regarded as having the *trans*-configuration (III), but its high rotation, $[\alpha]_D$ +50·8°, was undoubtedly due to contamination by phellandrenes. A second variety obtained by a Ponndorf reduction of the ketone was obtained in relatively low yield, and it was regarded as the *cis*-compound (II).



(II)



(I)



(III)

Barnes, Jackman, and Macbeth (*J.*, 1951, 1848) re-examined the reduction of (—)-piperitone by the Meerwein–Ponndorf reaction, but only one of the epimeric alcohols was isolated, and it was suspected that dehydration of the more labile epimer to a menthadiene occurred. The earlier suggestion by Read that the alcohol was the *cis*-epimer was confirmed by its hydrogenation to (—)-*neo*menthol. Although the alcohol isolated had a higher rotation than that previously recorded and gave a 3 : 5-dinitrobenzoate with $[\alpha]_D$ —256°, it was doubtful if it was optically pure inasmuch as the *p*-nitrobenzoate and phthalimidoacetate prepared from it were inactive, a result suggesting that these esters were derived from some of the racemic alcohol contained in the sample. Better results were hoped for in reduction of the ketone by lithium aluminium hydride, and this work is now described.

The proportions of the *cis*- and the *trans*-forms of the alcohols derived from a series of ketones on reduction by the Meerwein–Ponndorf method were determined by Jackman, Macbeth, and Mills (*J.*, 1949, 2641) and the percentages of the epimers resulting on reduction of a number of monocyclic ketones by lithium aluminium hydride were subsequently examined. Before the results were published, Noyce and Denny (*J. Amer. Chem. Soc.*, 1950, **72**, 5743) reported their results with this reagent, and some of these, which in most cases are essentially the same as our own, are summarised in Table 1. The value for cryptone is added as an additional example, and the figures in parentheses are those for substances obtained by the Meerwein–Ponndorf reduction (*loc. cit.*).

These results suggest that (—)-piperitone, as in the case of the monocyclic ketones examined above, should yield preponderantly the *trans*-piperitol by lithium aluminium hydride reduction. As the reduction is carried out under mild conditions and is not prolonged, there is a good prospect that the *trans*-alcohol will escape dehydration. Further, Noyce and Denny (*loc. cit.*) clearly showed that an asymmetric centre adjacent to a carbonyl or carboxyl group is not affected during reduction by lithium aluminium hydride. For example, when (—)-menthone was reduced, and the resulting mixture of menthols oxidised to the ketone again, the sample of (—)-menthone obtained showed only an insignificant change in optical rotation. Stereochemically pure piperitols may therefore be looked for in the products of such reductions.

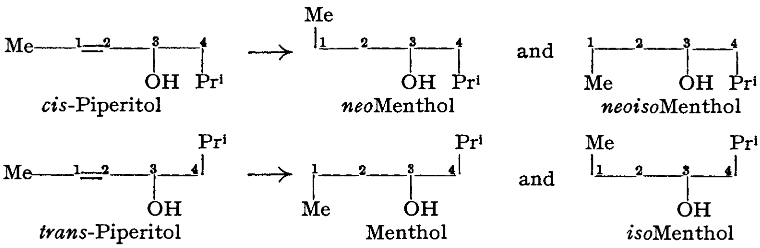
TABLE 1.

Ketone reduced	Percentage of *cis*-alcohol
(±)-2-Methyl*cyclo*hexanone	36 (50)
(±)-3-Methyl*cyclo*hexanone	8 (55)
4-Methyl*cyclo*hexanone	19 (33)
(—)-Menthone	29 (70)
(—)-4-*iso*Propyl*cyclo*hex-2-en-1-one (cryptone)	25 (39)

These expectations have in fact been realised, and a mixture of piperitols having α_D^{18} —30° (homogeneous) and $[\alpha]_D^{18}$ —72° (*c*, 1 in benzene) was produced in very good yield. Attempts to separate the alcohols from this mixture by fractional crystallisation of the 3 : 5-dinitrobenzoates were wasteful, and a preliminary fractionation of the crude piperitols through an efficient column was first carried out. The first fraction, α_D^{18} —164° (homogeneous), and the residue, α_D^{18} +54° (homogeneous), were converted into the 3 : 5-dinitrobenzoates in yields of some 90%. Seven recrystallisations of the (—)-ester gave (—)-*cis*-piperityl 3 : 5-dinitrobenzoate, m. p. 104°, $[\alpha]_D^{16}$ —268° (*c*, 1 in chloroform), in 30%

yield, while in the case of the (+)-ester only five recrystallisations were necessary to give upwards of 50% yield of (+)-*trans*-piperityl 3 : 5-dinitrobenzoate, m. p. 83°, $[\alpha]_D^{16}$ +164° (*c*, 1 in chloroform). Both esters are readily hydrolysed to the respective alcohols, which were characterised by the preparation of a number of derivatives summarised in Tables 2 and 3. The optical purity of the (—)-alcohol is suggested by the fact that all the derivatives, which are formed in excellent yield, require only one crystallisation to bring them to their maximum optical rotation; and by the further fact that both the phthalimidoacetate ($[\alpha]_D$ —274°) and the *p*-nitrobenzoate ($[\alpha]_D$ —304°) have high specific rotations in contrast with the inactivity reported in the earlier paper.

The configurations of the piperitols are conveniently established by hydrogenation, since the configurations of the reference substances, the menthols, have already been established (Zeitschel and Schmidt, *Ber.*, 1926, **59**, 2303; Read, Robertson, and Cook, *J.*, 1927, 1276; Read and Grubb, *J.*, 1934, 313) and recently confirmed by McNiven and Read (*J.*, 1952, 153). Thus (—)-*cis*-piperitol should yield a mixture of *neo*menthol and *neoiso*menthol, whereas the (+)-*trans*-piperitol will yield menthol and *iso*menthol:



In the case of (—)-*cis*-piperitol the earlier results of Barnes, Jackman, and Macbeth (*loc. cit.*) on configuration were confirmed by the isolation of pure (—)-*neo*menthyl 3 : 5-dinitrobenzoate from the mixture of menthols obtained by pressure hydrogenation of the alcohol over Raney nickel. The *trans*-configuration of the (+)-piperitol was established by hydrogenation to a mixture of menthols from which (+)-*iso*menthyl 3 : 5-dinitrobenzoate was prepared in good yield. The (+)-*trans*-piperitol is stable when kept in a closed vessel and, so far, has shown no tendency to dehydrate spontaneously. The present position of the piperitols is summarised in Tables 2 and 3.

TABLE 2. (—)-cis-*Piperitol.*

	Source	$[\alpha]_D$ *	Derivatives
(—)-Piperitol [a]	Reduction of (—)-piperitone with $Al(OPr^i)_3$	—25·5°	3 : 5-Dinitrobenzoate, m. p. 84—85°, $[\alpha]_D$ —30°
(—)-Piperitol [b]	Reduction of (—)-piperitone with $Al(OPr^i)_3$	—39·5	3 : 5-Dinitrobenzoate, m. p. 98—99°, $[\alpha]_D$ —256° Phenylurethane, m. p. 138°, $[\alpha]_D$ —328° α-Naphthylurethane, m. p. 128—129°, $[\alpha]_D$ —46°
—)-Piperitol [c]	Reduction of (—)-piperitone with $LiAlH_4$	—246°	3 : 5-Dinitrobenzoate, m. p. 104°, $[\alpha]_D$ —268° *p*-Nitrobenzoate, m. p. 73°, $[\alpha]_D$ —304° Phthalimidoacetate, m. p. 92°, $[\alpha]_D$ —274° Phenylurethane, m. p. 133°, $[\alpha]_D$ —338° α-Naphthylurethane, m. p. 121°, $[\alpha]_D$ —260°

[a] Read and Walker (*loc. cit.*); [b] Barnes, Jackman, and Macbeth (*loc. cit.*); [c] Present workers.
* In alcohol.

TABLE 3. (+)-trans-*Piperitol.*

	Source	$[\alpha]_D$ *	Derivatives
(+)-Piperitol [a]	Trimethyl-(—)-piperityl ammonium iodide	+50·8°	—
(+)-Piperitol [b]	Reduction of (—)-piperitone with $LiAlH_4$	+28	3 : 5-Dinitrobenzoate, m. p. 83°, $[\alpha]_D$ +164° *p*-Nitrobenzoate, m. p. 69°, $[\alpha]_D$ +180° α-Naphthylurethane, m. p. 94°, $[\alpha]_D$ +122°

[a] Read and Walker (*loc. cit.*); [b] Present workers. * In alcohol.

EXPERIMENTAL

Reduction of (–)-*Piperitone.*—A sample of piperitone from *E. dives*, $[\alpha]_D^{18}$ –48° (homogeneous), was recrystallised from light petroleum (b. p. 40—60°) at a temperature below –40° (Huggett, *J. Soc. Chem. Ind.*, 1941, **60**, 67). After four crystallisations and subsequent distillation, the ketone had b. p. 65/1·0 mm., $[\alpha]_D^{18}$ –67° (homogeneous).

The ketone (304 g.) in anhydrous ether (500 ml.) was dropped into a mechanically stirred suspension of lithium aluminium hydride (25 g.) in anhydrous ether (800 ml.) during 2½ hours, and the resulting mixture gently refluxed for a further hour. The mixture was decomposed with water and then sodium hydroxide (5% solution). The alumina was removed by filtration at the pump, and the separated ethereal layer washed with water. After the addition of a few drops of dimethyl*cyclo*hexylamine, the ethereal solution was dried ($MgSO_4$–K_2CO_3). After removal of the ether, the crude mixture of piperitols {277 g., α_D^{18} –30° (homogeneous), $[\alpha]_D^{18}$ –72° (*c*, 2 in benzene)} was fractionally distilled through a 24-inch column packed with single-turn glass helices, and fitted with a heating jacket and reflux divider. Four fractions were initially collected: (i) 30 g., b. p. 47°/0·03 mm., α_D^{18} –164° (homogeneous); (ii) 55 g., b. p. 47—48°/0·03 mm., α_D^{18} –120° (homogeneous); (iii) 47 g., b. p. 48°/0·03 mm., α_D^{18} –84° (homogeneous); (iv) 59 g., b. p. 48—49°/0·03 mm., α_D^{18} 0° (homogeneous). Fraction (iv) and the residue, 80 g., α_D^{18} +48°, were combined and refractionated to give the following fractions: (a) 30 g., b. p. 48°/0·04 mm., α_D^{18} –50°; (b) 9 g., b. p. 48—49°/0·04 mm., α_D^{18} +16°; (c) 18 g., b. p. 48—49°/0·04 mm., α_D^{18} +32°; residue, 77 g., α_D^{18} +54°.

(–)-*Piperityl* 3 : 5-*dinitrobenzoate.* A solution of 3 : 5-dinitrobenzoyl chloride (47 g.) in dry benzene (70 ml.) was added to a mechanically stirred solution of (–)-piperitol (30 g., α_D^{18} –164°) in light petroleum (b. p. 40—60°; 450 ml.) containing pyridine (15 g.), the rate of addition being such that the temperature did not rise above 35°. After a further 3 hours, the reaction mixture was shaken with water (*ca.* 300 ml.), and the solution filtered. The benzene–light petroleum layer was washed successively with sodium hydroxide (5% solution) and water. After drying ($MgSO_4$–K_2CO_3), the solvent was removed, leaving the crude ester (60 g., 88% based on piperitol) as a red oil which readily crystallised on the addition of a small amount of light petroleum (b. p. 40—60°). Seven recrystallisations from this same solvent gave the pure *ester* (20 g., 33% of crude ester) as very pale yellow glistening plates, m. p. 104°, $[\alpha]_D^{16}$ –256° (*c*, 1 in benzene), –268° (*c*, 1 in chloroform) (Found: C, 58·9; H, 5·6; N, 8·3. $C_{17}H_{20}O_6N_2$ requires C, 58·95; H, 5·5; N, 8·05%).

(–)-cis-*Piperitol.*—A solution of (–)-piperityl 3 : 5-dinitrobenzoate (15 g., $[\alpha]_D^{16}$ –268°) in methanol (120 ml.) containing potassium hydroxide (6·5 g.) was refluxed for 5 minutes, the solution becoming red and depositing potassium 3 : 5-dinitrobenzoate. After being kept at room temperature for an hour, the mixture was filtered from the potassium salt, which was washed with methanol. The combined filtrate and washings were distilled under reduced pressure to remove most of the methanol, and water (*ca.* 60 ml.) added to the residue. The piperitol separated as a white solid and was taken up in light petroleum (b. p. 40—60°), and the aqueous layer again extracted twice with the same solvent. The combined extracts were washed once with water and dried ($MgSO_4$–K_2CO_3). After removal of the solvent, the (–)-*piperitol* was distilled (b. p. 55°/0·1 mm.) and quickly crystallised to a mass of fine white needles (6 g., 91% based on the ester), m. p. 30°, $[\alpha]_D^{17}$ –246° (*c*, 2 in benzene or alcohol) (Found: C, 77·8; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%).

The p-*nitrobenzoate*, prepared from *p*-nitrobenzoyl chloride (1·3 g.) in dry benzene and a solution of (–)-piperitol (1 g.) in light petroleum containing dry pyridine (0·6 g.), and worked up in the usual way after 3 hours, on recrystallisation from light petroleum (b. p. 40—60°) formed pale yellow needles (1·7 g., 85% based on piperitol, m. p. 72°, $[\alpha]_D^{18}$ –304° (*c*, 1 in benzene) (Found: C, 67·35; H, 6·8; N, 4·7. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·95; N, 4·6%).

The *phthalimidoacetate*, from the acid chloride (1·1 g.) in dry benzene and (–)-piperitol (0·7 g.) in light petroleum containing pyridine (0·4 g.), and worked up after 1½ hours, had m. p. 92°, $[\alpha]_D^{17}$ –274° (*c*, 1 in benzene) (1·4 g., 88% based on piperitol) (Found: C, 70·2; H, 6·5; N, 4·2. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·7; N, 4·1%), after one recrystallisation from benzene–light petroleum (b. p. 40—60°).

The *phenylurethane*, from phenyl *iso*cyanate (0·7 g.) and (–)-piperitol (0·8 g.) in light petroleum (3 ml.), after being kept overnight, separated after one crystallisation from light petroleum (b. p. 60—80°) in long white needles (1·2 g., 84% based on piperitol), m. p. 133°, $[\alpha]_D^{19}$ –338° (*c*, 1 in chloroform) (Found: C, 74·8; H, 8·4; N, 5·2. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·4; N, 5·1%).

The *α-naphthylurethane*, similarly prepared from α-naphthyl *iso*cyanate (1·3 g.) and (−)-piperitol (0·7 g.), and similarly crystallised, formed a felted mass of white needles (1·25 g., 85% based on piperitol), m. p. 121°, $[\alpha]_D^{19}$ −260° (*c*, 1 in chloroform) (Found: C, 78·2; H, 7·7; N, 4·6. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·75; N, 4·3%).

Hydrogenation of (−)-cis-*Piperitol* ($[\alpha]_D^{17}$ −246°).—(−)-Piperitol (1·5 g.) in ethanol (15 ml.) containing Raney nickel (0·5 g.) was hydrogenated at 130° and 800 lb./sq. in. for an hour. After the catalyst had been filtered off, most of the ethanol was removed by distillation under reduced pressure, and water (*ca.* 40 ml.) added to the residue. The oil that separated had a pronounced menthol-like odour and was taken up in light petroleum (b. p. 40—60°). After being washed once with water, the light petroleum solution was dried ($MgSO_4$). After filtration the light petroleum solution was treated with 3 : 5-dinitrobenzoyl chloride and pyridine, and the resulting ester was recovered in the usual way. The crude ester was recrystallised five times from light petroleum (b. p. 60—80°), giving pale yellow needles, m. p. 156°, $[\alpha]_D^{20}$ −22° (*c*, 1 in benzene). On admixture with an authentic sample of (−)-*neo*menthyl 3 : 5-dinitrobenzoate there was no depression of m. p.

(+)-trans-*Piperityl* 3 : 5-*Dinitrobenzoate.*—(+)-Piperitol (77 g., α_D^{18} +54°) in light petroleum (b. p. 40—60°) containing pyridine (45 g.) was esterified with 3 : 5-dinitrobenzoyl chloride (127 g.) by the method described for (−)-piperityl 3 : 5-dinitrobenzoate. The crude ester (156 g., 90% based on piperitol) readily crystallised on the addition of a little light petroleum (b. p. 40—60°), and five recrystallisations from this solvent gave the pure *ester* (90 g., 58% of the crude ester) as short, pale yellow needles, m. p. 83°, $[\alpha]_D^{18}$ +164° (*c*, 1 in chloroform) (Found: C, 58·9; H, 5·9; N, 8·05. $C_{17}H_{20}O_6N_2$ requires C, 58·95; H, 5·5; N, 8·05%).

(+)-trans-*Piperitol.*—The foregoing 3 : 5-dinitrobenzoate (39 g., $[\alpha]_D^{18}$ +164°) was hydrolysed with methanolic potassium hydroxide as described for the (−)-piperityl ester. The (+)-*piperitol* had b. p. 57°/0·15 mm., $[\alpha]_D^{17}$ +28° (*c*, 2 in benzene), d_4^{25} 0·9203, n_D^{25} 1·4762, $[R_L]_D$ 47·21 (Calc.: 47·14) (Found: C, 78·1; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%); it is a viscous, colourless liquid of menthol-like odour and is stable when kept in a sealed container.

Its p-*nitrobenzoate*, prepared as already described, and twice recrystallised from light petroleum (b. p. 40—60°), formed pale yellow needles, m. p. 69°, $[\alpha]_D^{18}$ +180° (*c*, 1 in benzene) (80% based on piperitol) (Found: C, 67·4; H, 6·9; N, 4·9. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·95; N, 4·6%).

The *α-naphthylurethane*, prepared as described above and crystallised once from light petroleum (b. p. 40—60°), formed fine white needles, m. p. 94°, $[\alpha]_D^{18}$ +122° (*c*, 1 in benzene) (Found: C, 77·9; H, 7·7; N, 4·6. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·75; N, 4·3%).

Hydrogenation of (+)-trans-*Piperitol.*—(+)-Piperitol (5 g.) in ethanol (50 ml.) containing Raney nickel (2 g.) was hydrogenated at 135° and 800 lb./sq. in. for an hour. The product was worked up in the usual way; the yield was 5 g., $[\alpha]_D^{18}$ +24° (*c*, 1 in benzene), and the m. p. 71—76°. 3 : 5-Dinitrobenzoyl chloride (1·8 g.) in dry benzene was added to the reduction product (1·2 g.) in light petroleum (10 ml.) containing pyridine (0·7 g.). The ester was worked up in the usual way and two recrystallisations from light petroleum (b. p. 40—60°) gave a product, m. p. 145° undepressed on admixture with an authentic sample of (+)-*iso*menthyl 3 : 5-dinitrobenzoate.

Reduction of (−)-*Cryptone.*—(−)-Cryptone [20 g., α_D^{26} −65° (homogeneous)] in anhydrous ether (50 ml.) was dropped into a stirred suspension of lithium aluminium hydride (2·76 g.) in anhydrous ether (100 ml.) during 10 minutes, and the resulting mixture refluxed for a further ½ hour, then decomposed with ice-water and sulphuric acid (10%). The ethereal layer was separated and washed successively with sodium carbonate (5%) and water and finally dried ($MgSO_4$). After removal of the ether, the mixed cryptols were distilled, having b. p. 72—74°/0·7 mm. (19 g., 95%, based on cryptone), α_D^{17} −81° (homogeneous), representing 25% of (+)-*cis*- and 75% of (−)-*trans*-cryptol. The rotations of the pure epimers were determined by Gillespie, Macbeth, and Mills (*J.*, 1948, 996).

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