405. *Reactions of αβ-Unsaturated Cyclic Aldehydes and Ketones. Part VIII.* Alcohols derived from (−)-Piperitone.*

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A stable (−)-piperitol is isolated in satisfactory yield on reduction of (−)-piperitone by aluminium alkoxide. Some racemisation occurs in the process, and some dehydration, probably of the labile piperitol epimer, also takes place with the production of hydrocarbons.

(−)-Piperitol has m. p. 30° and $[\alpha]_D$ −39·4°, and has been characterised by the preparation of a number of derivatives. Its configuration follows from its conversion into (−)-*neo*menthol on hydrogenation.

Read was of the opinion that α-phellandrene was produced by the dehydration of the piperitols, but at least part of the hydrocarbon must be β-phellandrene as the crystalline tetrabromide (Berry and Macbeth, *J.*, 1947, 1039) has been isolated.

Piperitols have been isolated from natural sources by Baker and Smith ("A Research on the Eucalypts," 2nd edn., 1920, p. 373) and by Simonsen (*Indian Forest Records*, 1924, **10**, Part VIII). Both the alcohols are stable, the former being related to (−)-piperitone and having α −34·1° (homogeneous); but the latter was associated with (+)-piperitone and had α +41·9° (homogeneous). A synthesis of (−)-piperitol from (−)-α-phellandrene has been described (Howard and Son, B.P. 532,614/1941). Earlier, Read and Storey (*J.*, 1930, 2770) obtained an inactive alcohol from trimethylpiperitylammonium iodide, from which after resolution and careful fractionation they isolated two active alcohols which they named *d*-piperitol and *d-neo*piperitol; they were of the opinion that the natural piperitols had the same configuration as their higher-boiling synthetic alcohol, and suggested that they were *cis*-compounds. Read and Walker (*J.*, 1934, 308) further examined the reaction and showed that the resulting piperitol was extremely labile when special care was taken to remove all traces of the base. Since this purified alcohol lost water spontaneously, even on storage for a short time, it was named *neo*piperitol. These workers also prepared in low yield a stable piperitol by the Ponndorf reduction of piperitone. From this a 3 : 5-dinitrobenzoate, m. p. 84—85°, was prepared in 13% yield. The alcohol had [α] −24·5° (alcohol), and the ester −30° (chloroform).

A modified Ponndorf technique (Macbeth and Mills, *J.*, 1949, 2646) gave a yield of some 85% in the reduction of (−)-piperitone, but the product was not critically examined. It seemed advisable to study the reaction further as greatly increased yields of piperitol seemed assured, and it was hoped that both epimeric forms might be isolated. Several modified reductions were carried out. A yield of some 58% of constant-boiling product (presumably crude piperitol), together with some 6% each of hydrocarbon and higher-boiling residue, was obtained when the addition of piperitone was uniformly spread over 24 hours and the reaction continued for 24 hours thereafter. In a reduction when the ketone was added within 0·5 hour and the reaction continued for a further 47 hours the yield of crude alcohol fell to some 43% and more than 20% of hydrocarbon was formed. Modified reductions in the presence of fluorenol (Baker and Adkins, *J. Amer. Chem. Soc.*, 1940, **62**, 3305) reduced the time to 30 hours, but the yields obtained were not significantly improved.

As the long times involved in the preceding reductions obviously favour hydrocarbon formation, and as some racemisation of the piperitone was also found to occur, the ordinary alkoxide reduction was re-examined in the hope of improving the yields recorded by Read and Walker (*loc. cit.*). A sample of (−)-piperitone from *E. dives* after repeated crystallisation at −50° (Huggett, *J. Soc. Chem. Ind.*, 1941, **60**, 67) had $[\alpha]_D^{20}$ −67·8° (homogeneous). Its reduction product when distilled at 0·2 mm. pressure gave three fractions, (i) b. p. 55—61°, α_D^{19} −58·2°, (ii) b. p. 61°, α_D^{19} −51·2°, and (iii) b. p. 62—64°, α_D^{19} −50°. Fractions (ii) and (iii) represented a 90% yield if calculated as piperitol, but Sutherland (private communication) has shown that the reduction product contains a piperityl ether (cf. Human, Macbeth, and Rodda, *J.*, 1949, 350) and any of this product formed would probably be present in these fractions.

As Read and Walker (*loc. cit.*) had reported a yield of piperitol 3 : 5-dinitrobenzoate of only 13% it was thought that better results in the purification of crude piperitol might be obtained by esterifying the alcohol with an acid chloride in which less steric hindrance might be expected.

* Part VII, *J.*, 1949, 350.

The phthalimidoacetate seemed a suitable derivative to aim at as experiment showed that the readily dehydrated alcohol 4-methylpent-3-en-2-ol gave almost 90% of ester when treated with phthalimidoacetyl chloride under special conditions. It was not an altogether satisfactory ester, however, in the case of piperitol as the pure piperityl phthalimidoacetate, m. p. 125—126°, which was obtained after repeated crystallisation was found to be the (±)-ester.

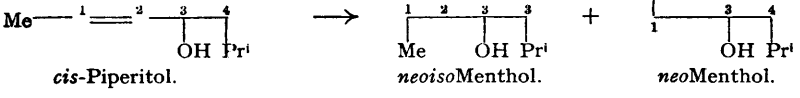
The relative solubilities of the racemic and optically active esters reported above evidently do not hold in the case of 3 : 5-dinitrobenzoates, as the sample of ester obtained by the previous workers had $[\alpha]_D^{14}$ −30° (alcohol). It seemed probable that the yield might be improved by modifying the esterification technique, and that the ester might then be suitable for isolation of the optically active piperitol. As the piperitols undergo an acid-catalysed dehydration (Read and Walker, *loc. cit.*) it is desirable to avoid steam-distillation in the preparation of the ester. Further, current theories of acids and bases (Luder and Zuffanti, " Electronic Theory of Acids and Bases," 1946; Bell, *Quart. Reviews*, 1947, **1**, 113) indicate that in a non-aqueous solvent such as pyridine a pyridinium ion which may act as an acid-catalyst will be formed in the presence of pyridine hydrochloride, and this would favour the dehydration of piperitol during esterification by an acid chloride in the presence of excess of pyridine.*

When using modified conditions of esterification it was found that piperitol could be converted into its 3 : 5-dinitrobenzoate in a yield of nearly 60% when a slight excess of the acid chloride in benzene was gradually added to a solution of the alcohol in light petroleum containing an amount of pyridine equivalent to the acid chloride used. Pyridine hydrochloride is precipitated from the esterification mixture as it is formed. Steam-distillation was avoided in the isolation of the ester, purification being carried out by crystallisation from methanol or light petroleum, preferably the latter. After five crystallisations piperityl 3 : 5-dinitrobenzoate, m. p. 98—99°, $[\alpha]_D^{14\cdot5}$ −256° (chloroform), was obtained in 30—35% yield. The ester is readily hydrolysed to (−)-piperitol which was obtained in 30% yield calculated on the (−)-piperitone reduced. It is doubtful if this sample of (−)-piperitol is stereochemically pure, as small amounts of a (±)-phthalimidoacetate and of an inactive *p*-nitrobenzoate were derived from it. The present position of the piperitols is summarised in the Table.

	Source.	[α].	Derivatives.
(−)-Piperitol [a]	*E. radiata*	−34·1° (homogeneous)	—
(+)-Piperitol [b]	Species of *Andropogon*	+41·9° (homogeneous)	—
(−)-Piperitol [c]	Reduction of (−)-piperitone	−24·5° (alcohol)	3 : 5-Dinitrobenzoate, m. p. 84—85°, $[\alpha]_D$ −30°.
(−)-Piperitol [d]	Reduction of (−)-piperitone	−39·4° (alcohol or benzene)	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°.

[a] Baker and Smith (*loc. cit.*). [b] Simonsen (*loc. cit.*). [c] Read and Walker (*loc. cit.*). [d] Present workers.

The configuration of the piperitol prepared by the Ponndorf reduction of piperitone has been established by the hydrogenation of the alcohol over Raney nickel to menthols. In this way a sample of (±)-piperitol gave a mixture of menthols from which (±)-*neo*menthol was isolated as its hydrogen phthalate and 3 : 5-dinitrobenzoate. The hydroxyl and *iso*propyl groups are therefore in the *cis*-position in piperitol.



cis-Piperitol. *neoiso*Menthol. *neo*Menthol.

This result was supported by the similar hydrogenation of (−)-piperitol to a mixture of menthols from which a 3 : 5-dinitrobenzoate, m. p. 155—156°, $[\alpha]_D$ −21·4° (in benzene), was obtained. An authentic sample of (−)-*neo*menthyl 3 : 5-dinitrobenzoate was not available, but admixture of the experimental compound with an equimolecular amount of the (+)-*neo*menthol ester and crystallisation gave an inactive compound, m. p. 130°, not depressed on admixture with an authentic sample of (±)-*neo*menthyl 3 : 5-dinitrobenzoate. In view of the *cis*-configuration of the stable variety of piperitol (which was predicted by Read) and its

* This modification of the conventional method of esterification with acid chlorides was suggested by Mr. J. A. Mills, who has investigated the reaction more fully (Barnes, *J.*, 1951, in the press).

consequent relation to the *neo*menthols its seems unfortunate that because of the instability of the compounds the name *neo*piperitol was assigned to the easily dehydrated alcohol at a time when the configuration of the menthol series had not been firmly established.

It was hoped that both forms of piperitol might be isolated from the alkoxide reduction products, but we have only succeeded in characterising one. Whether the labile form survives reduction and breaks down during the formation of derivatives one cannot definitely say, but since hydrocarbons occur in the reduction products it is more probable that one form of piperitol does not long survive its formation.

As Sutherland (private communication) is examining the hydrocarbons occurring in the reduction products this aspect has not been studied by us further than to isolate a tetrabromide [m. p. 112°; $[\alpha]_D^{22}$ +57·3° (*c* 0·6 in chloroform)] from a sample of hydrocarbon, α −30·7° (homogeneous).

Experimental.

Reduction of (−)-Piperitone.—A sample of piperitone from *E. dives* {$[\alpha]_D^{17}$ −49·5° (homogeneous)} was recrystallised from light petroleum (b. p. 40—60°) at below −40° (Huggett, *loc. cit.*), and after four such crystallisations the oil, distilled under reduced pressure, had b. p. 65°/1·05 mm. and $[\alpha]_D^{16}$ −67·6° (homogeneous). The ketone (100 g.) in dry *iso*propanol (150 ml.) was added to a boiling solution of aluminium *iso*propoxide in *iso*propanol (950 ml. of 0·7M.), during 20 minutes, and the reduction was continued under reflux in the usual way for 15 hours. After removal of the excess of *iso*propanol under reduced pressure, the clear light brown residue was chilled and ether (300 ml.) added. Aluminium alkoxide was decomposed by addition of a slurry of ice and sodium hydroxide (*ca.* 5% solution), the aqueous layer was twice extracted with ether (100 ml.), and after the addition of a few drops of dimethyl-*cyclo*hexylamine the combined extracts were dried ($MgSO_4$ + K_2CO_3). After removal of the solvent the residue was distilled under reduced pressure, giving fractions: (i) b. p. up to 61°/0·2 mm., α_D^{19} −58° (homogeneous) (2·4 g.); (ii) b. p. 61°/0·2 mm., α_D^{19} −51·2° (homogeneous) (59 g.); and (iii) b. p. 61—62°, α_D^{15} −49° (homogeneous) (31 g.)

Esters.—(a) *4-Methylpent-3-en-2-yl phthalimidoacetate.* Phthalimidoacetic acid (Reese, *Annalen*, 1887, **242**, 1) was converted into the acid chloride by thionyl chloride (cf. Gabriel, *Ber.*, 1907, **40**, 2648). The alcohol (2 g.) with dry pyridine (1·7 g.) was dissolved in light petroleum (b. p. 60—80°; 50 ml.) and cooled in ice. The acid chloride (4·5 g.) in dry benzene (25 ml.) was run in with stirring and the mixture left overnight in the refrigerator. After being washed with dilute sodium carbonate solution, then water, the solvent was dried and evaporated, and the residue crystallised from light petroleum (40—60°). The *ester* (88% yield, 5 g.) had m. p. 81—82° (Found: C, 66·85; H, 5·8. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9%).

(b) *(±)-Piperityl phthalimidoacetate.* (−)-Piperitol [fractions (i) and (ii) above, 90 g.] with dry pyridine (51·5 g.) was dissolved in light petroleum (b. p. 40—60°; 500 ml.), and a solution of phthalimidoacetyl chloride (150 g.) in dry benzene (200 ml.) was added dropwise with mechanical stirring at such a rate that the temperature did not exceed 35°. Pyridine hydrochloride was immediately precipitated, and the mixture was set aside overnight. After stirring with sodium hydroxide (500 ml.; 5%) and addition of benzene (350 ml.) the mixture was filtered and the benzene–light petroleum layer was again washed with dilute aqueous sodium hydroxide and then water (thrice). After drying (K_2CO_3) and removal of solvent under reduced pressure, the residual red oil (125 g.) was dissolved in hot methanol (125 ml.) and on cooling at 10° deposited some of the ester (43 g.). A further small quantity (4 g.) separated on removal of part of the methanol and cooling to 0°. The combined ester (47 g.) had $[\alpha]_D^{16}$ −98° (*c*, 5 in benzene) and melted over the range 100—112°. Systematic crystallisations (five) from methanol (*ca.* 1 ml. per 3·6 g.) gave the *piperityl phthalimidoacetate* as small white crystals, m. p. 124—125°, but the ester was obtained in small amount (9·3 g.) and was only slightly optically active {$[\alpha]_D^{16}$ −4·6 (*c*, 5 in benzene)}. Recrystallisation from ethanol or light petroleum (b. p. 60—80°) gave the inactive ester, m. p. 125° (Found: C, 70·6; H, 6·7. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·7%).

(c) *(−)-Piperityl 3 : 5-dinitrobenzoate.* A solution of 3 : 5-dinitrobenzoyl chloride (145 g.) in dry benzene (200 ml.) was added dropwise to a mechanically stirred solution of (−)-piperitol (88 g.) in light petroleum (b. p. 40—60°; 500 ml.) containing pyridine (51·5 g.), the rate of addition being such that the temperature did not rise above 35°. After a further 3 hours the crude ester was obtained as described in the preceding case. After addition of an equal volume of methanol to the reddish oil the ester separated as pale yellow needles on cooling (112 g., 56% calculated on piperitol). Light petroleum (b. p. 60—80°; *ca.* 6—7 ml. per g.) was found to be a more suitable solvent for purification than methanol and five crystallisations gave the pure ester (73 g., 61% of the crude ester) as pale yellow glistening plates, m. p. 98—99°, $[\alpha]_D^{15}$ −256° (*c*, 1 in chloroform) and −242° (*c*, 1 in benzene) (Found: C, 59·0; H, 5·65. Calc. for $C_{17}H_{20}O_6N_2$: C, 58·95; H, 5·5%). Some impure ester (18 g.) of much lower rotation was recovered from the light petroleum mother-liquors, and a little (3·5 g.) from the methanolic liquor.

Hydrolysis of Piperityl 3 : 5-Dinitrobenzoate.—A solution of (−)-piperityl 3 : 5-dinitrobenzoate (73 g.; $[\alpha]_D^{16}$ −256°) in methanol (600 ml.) containing potassium hydroxide (31 g.) when refluxed for 1 hour became red and deposited potassium 3 : 5-dinitrobenzoate. After cooling, filtration, and washing of the salt with methanol, the combined filtrate and washings were distilled under reduced pressure to remove most of the methanol. Water (*ca.* 200 ml.) was added to the residue, and the oil which separated was taken up in light petroleum (b. p. 40—60°; 50 ml.), the aqueous layer was again extracted twice with the same solvent, and the combined extracts were dried (K_2CO_3). All the apparatus used in the removal of solvent and distillation of the piperitol was previously soaked in dilute sodium hydroxide (0·5%) and dried before use. The (−)-piperitol had b. p. 61°/1 mm. and quickly solidified to a mass of fine white

needles (28 g., 87·3%), m. p. 30°, $[\alpha]_D^{17\cdot5}$ −39·4° (*c*, 2 in benzene) (Found: C, 77·7; H, 11·6. Calc. for $C_{10}H_{18}O$: C, 77·9; H, 11·7%). The alcohol was stable and had an odour similar to that of menthol.

The piperitol and phenyl *iso*cyanate (10% excess) were dissolved in light petroleum (5 parts) and set aside overnight. Four recrystallisations from light petroleum (b. p. 60—80°) gave (−)-*piperityl phenylurethane*, long white needles m. p. 138°, $[\alpha]_D^{15}$ −328° (*c*, 1 in chloroform) (Found: C, 74·95; H, 8·5. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·4%). (−)-*Piperityl α-naphthylurethane* was similarly obtained as a felted mass of fine white needles, m. p. 128—129°, $[\alpha]_D^{15}$ −46° (*c*, 1 in chloroform) after recrystallisation (thrice) from light petroleum (b. p. 60—80°) (Found: C, 78·1; H, 7·6. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·75%).

Attempts to prepare the *p*-nitrobenzoate and the phthalimidoacetate from the pure piperitol gave inactive esters. (±)-*Piperityl* p-*nitrobenzoate* crystallised from aqueous methanol as pale yellow plates, m. p. 79—80° (Found: C, 67·6; H, 6·9. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·95%). The phthalimidoacetate was identical with that already described.

Hydrogenation of (−)-*Piperitol.* (−)-neo*Menthyl* 3 : 5-*Dinitrobenzoate.*—(−)-Piperitol (3 g.) in ethanol (30 ml.) containing Raney nickel (1·5 g.) was hydrogenated at 100—120°/1440 lb. for an hour. After removal of most of the alcohol, water (100 ml.) was added, and the reduction product extracted with light petroleum (b. p. 60—80°; 3 × 20 ml.). After drying ($MgSO_4$) and removal of solvent the residue was distilled under reduced pressure (b. p. 59°/1 mm.). The oil (2·8 g.), which had a pronounced menthol-like odour, was esterified with 3 : 5-dinitrobenzoyl chloride (4·65 g.) in benzene (50 ml.) containing dry pyridine (1·6 g.). The ester, which was worked up in the usual way, gave a yellow solid (5·4 g.) on steam distillation, and this after six recrystallisations from light petroleum (b. p. 60—80°) gave pale yellow needles, m. p. 156°, $[\alpha]_D^{19}$ −21·4° (*c*, 2 in benzene). When mixed with an equal weight of (+)-*neo*menthyl 3 : 5-dinitrobenzoate and crystallised from ethanol (twice) this gave inactive pale yellow needles, m. p. 131° not depressed on admixture with authentic (±)-*neo*menthyl 3 : 5-dinitrobenzoate.

Two of us (L. M. J. and C. S. B.) express our indebtedness to the Commonwealth Research Fund which enabled us to participate in the work.

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