185. *Reactions of αβ-Unsaturated Cyclic Aldehydes and Ketones. Part XI.* (±)-cis- and (±)-trans-Piperitol.*

By A. Killen Macbeth, B. Milligan, and J. S. Shannon.

(±)-Piperitone has been reduced by lithium aluminium hydride and by aluminium *iso*propoxide. (±)-*cis*- and (±)-*trans*-Piperitol have been isolated in both cases, and characterised by the preparation of a number of derivatives.

The optically active piperitols derived from (−)-piperitone have already been described (Macbeth and Shannon, *J.*, 1952, 2852), and the racemic alcohols have now been prepared and characterised. Lithium aluminium hydride was found to give the optically active piperitols in a yield of approximately 36% of the *cis*- and 64% of the *trans*-epimer, and the reagent has proved highly satisfactory in the preparation of the inactive alcohols too.

The preparation of optically active piperitols by the Ponndorf reduction of (−)-piperitone (Barnes, Jackman, and Macbeth, *J.*, 1951, 1848) was not satisfactory as the *cis*-epimer which was isolated was partially racemised, whereas the *trans*-epimer was not obtained as it was dehydrated during the reaction. Both epimers were isolated when (±)-piperitone was subjected to the action of aluminium *iso*propoxide and the reaction stopped after 15 hours when the reduction was only partially completed. On fractionation of the crude piperitol so obtained, the lower-boiling fraction yielded pure (±)-*cis*-piperityl 3 : 5-dinitrobenzoate (15%). The combined higher fraction and the still residue gave pure (±)-*trans*-piperityl 3 : 5-dinitrobenzoate (8%). The Ponndorf reaction again lacks the obvious advantages of lithium aluminium hydride as a preparative method.

The configuration of (±)-*cis*-piperitol was established by its hydrogenation to (±)-*neo*menthol, identified as its hydrogen phthalate, that of the (±)-*trans*-piperitol was confirmed by reduction to (±)-*iso*menthol, the identity of which was fixed by its conversion into its 3 : 5-dinitrobenzoate.

Experimental

Unless otherwise stated, light petroleum had b. p. 40—60°.

Lithium Aluminium Hydride Reduction of (±)-Piperitone.—(−)-Piperitone was racemised by sodium ethoxide and purified by distillation (Read and Smith, *J.*, 1923, 2267). The ketone (40 g.) in anhydrous ether (60 ml.) was dropped into a mechanically stirred suspension of lithium aluminium hydride (3 g.) in anhydrous ether (200 ml.) during 1 hr., and the resulting mixture was refluxed for a further 2 hr. The mixture was decomposed with water (50 ml.) and 5% sodium hydroxide solution (10 ml.), and the alumina filtered off. After washing of the ethereal solution and drying ($MgSO_4$) a few drops of dimethyl*cyclo*hexylamine were added, the solvent was removed, and the crude piperitols fractionated through a 24-inch column packed with glass helices. In a typical experiment three fractions were collected: (1) b. p. 60—64°/0·5 mm. (4 g.), (2) b. p. 64—66°/0·5 mm. (5 g.), and (3) b. p. 66—70°/0·5 mm. (19 g.); residue, 6·5 g.

(±)-trans-*Piperitol.*—Fraction (3) was converted into the 3 : 5-dinitrobenzoate by shaking it in light petroleum (300 ml.) containing pyridine (11·0 g.) whilst 3 : 5-dinitrobenzoyl chloride (34 g.) in benzene (50 ml.) was added at such a rate that the temperature did not exceed 30°. After 3 hrs. the mixture was washed with water (200 ml.) and filtered, and the benzene–light petroleum layer washed successively with 5% aqueous sodium hydroxide and water, and dried ($MgSO_4$). The crude ester (18·0 g.) obtained on removal of the solvent was recrystallised (four times) from light petroleum, giving (±)-trans-*piperityl 3 : 5-dinitrobenzoate* as pale yellow granular crystals, m. p. 65° (Found: C, 58·85; H, 5·85; N, 7·9. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·75; N, 8·05%).

The pure dinitrobenzoate (10 g.) in anhydrous ether (100 ml.) was refluxed with potassium hydroxide (4·2 g.) in anhydrous methanol (50 ml.) for 15 min. After 1 hr. the potassium 3 : 5-dinitrobenzoate which separated as red needles was filtered off and washed with ether (50 ml.), and most of the solvent was removed from the combined filtrate and washings under reduced pressure. Water (50 ml.) was added to the residue and the oil extracted thrice with light petroleum (20 ml.). The combined extracts were dried ($MgSO_4$), and the (±)-trans-*piperitol* left after removal of the solvent was distilled; it had b. p. 66—69°/0·2 mm., d_4^{25} 0·9217,

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n_D^{25} 1·4767, $[R_L]_D$ 47·13 (Calc. 47·14) (Found: C, 78·9; H, 11·6. $C_{10}H_{18}O$ requires O, 77·8; H, 11·75%). It gave the following derivatives, which crystallised from light petroleum: p-*nitrobenzoate*, pale yellow needles, m. p. 72° (Found: C, 67·4; H, 7·1; N, 4·65. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 7·0; N, 4·6%); *phthalimidoacetate*, needles, m. p. 88° (Found: C, 70·55; H, 6·9; N, 4·3. $C_{20}H_{23}O_4N$ requires C, 70·35; H, 6·8; N, 4·1%). *phenylurethane*, needles, m. p. 85·5° (Found: C, 74·9; H, 8·45; N, 5·25. $C_{17}H_{23}O_2N$ requires C, 74·5; H, 8·5; N, 5·15%); α-*naphthylurethane*, needles, m. p. 107—107·5° (Found: C, 78·2; H, 7·9; N, 4·4. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·8; N, 4·35%).

Hydrogenation of (±)-trans-*Piperitol*.—(±)-*trans*-Piperitol (1·0 g.) in ethanol (10 ml.) containing Raney nickel catalyst (0·5 g.) was hydrogenated at 100°/1000 lb. for 2 hr. The catalyst was filtered off and most of the ethanol removed under reduced pressure. An oil with a menthol-like odour separated on addition of water to the residue. This was extracted with light petroleum, washed once with water, and dried ($MgSO_4$). On removal of the solvent the residual oil (0·9 g.) crystallised overnight. With 3 : 5-dinitrobenzoyl chloride it gave an ester (1·0 g., 50% based on piperitol) which when twice recrystallised from light petroleum gave pure (±)-*iso*menthyl 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 128°.

(±)-cis-*Piperitol*.—Fractions (1) and (2) (9·0 g.) of the distilled piperitol were esterified in the usual way with 3 : 5-dinitrobenzoyl chloride (17·1 g.) and the crude ester (12·0 g.) was recrystallised (six times) from light petroleum (b. p. 60—80°), to give pure (±)-cis-*piperityl* 3 : 5-*dinitrobenzoate* (6·0 g.) as needles, m. p. 98° (Found: C, 58·6; H, 5·6; N, 8·05%). An ethereal solution of the dinitrobenzoate (10 g.) was hydrolysed by methanolic potassium hydroxide and worked up as described in the case of the *trans*-ester. Pure (±)-cis-*piperitol* formed needles, m. p. 28° (Found: C, 77·5; H, 11·7%). It gave a *phthalimidoacetate*, needles (from light petroleum), m. p. 122° (Found: C, 70·7; H, 6·85; N, 4·45%), phenylurethane, needles, m. p. 110·5° (from light petroleum), and an α-*naphthylurethane*, needles, m. p. 128·5°, from light petroleum (b. p. 60—80°) (Found: C, 78·2; H, 7·8; N, 4·3%).

Hydrogenation of (±)-cis-*Piperitol*.—(±)-*cis*-Piperitol (0·5 g.) was hydrogenated as described for the *trans*-compound at 130°/1300 lb. A viscid oil (0·45 g., 90% based on piperitol) was isolated and converted into the hydrogen phthalate by phthalic anhydride (0·45 g.) and pyridine (0·75 g.) on the steam-bath (1 hr.). kept overnight and acidified with 10% hydrochloric acid (50 ml.); the ester was extracted twice with chloroform (25 ml.) and the solution washed twice with 5% sodium carbonate solution (25 ml.). The hydrogen phthalate precipitated on acidification of the alkaline extract was twice recrystallised from benzene, to give (±)-*neo*menthyl hydrogen phthalate (0·3 g.), m. p. 175° (176° on admixture with an authentic sample, m. p. 177°).

Ponndorf Reduction of (±)-*Piperitone*.—(±)-Piperitone (100 g.) in *iso*propyl alcohol (100 ml.) was added to aluminium *iso*propoxide in *iso*propyl alcohol (930 ml.; M) which was distilling through a 48-inch column packed with single-turn glass helices, the rate of addition being controlled to maintain constant volume in the reaction flask. After addition was complete the fractionation was continued for 14 hr. and although the distillate still gave a faint test for acetone the remaining *iso*propanol was removed through a Dufton column. Water (200 ml.), then 5% sodium hydroxide solution (250 ml.), was added, and alumina filtered off. The filtrate was extracted thrice with light petroleum (b. p. 60—80°; 200 ml.), and the extract was successively washed with water, 5% sodium hydroxide solution, and water, and dried ($MgSO_4$–K_2CO_3). After removal of the solvent the crude piperitol was distilled under reduced pressure and three fractions collected: (i) b. p. 60—70°/1·0 mm. (5·7 g.), (ii) b. p. 70—77°/1·0 mm. (12 g.), and (iii) b. p. 77—82°/0·8 mm. (54 g.); residue, 19 g. (±)-*cis*-Piperityl 3 : 5-dinitrobenzoate was isolated from fractions (i) and (ii) in light petroleum (250 ml.) containing pyridine (6·2 g.) on esterification with 3 : 5-dinitrobenzoyl chloride (17·2 g.) in benzene. The crude ester (10 g.; 30% based on piperitol) after five recrystallisations from light petroleum (b. p. 60—80°) gave the pure ester (5 g., 15% based on piperitol) as needles, m. p. 98°. The still residue (18 g.) gave a crude dinitrobenzoate (4 g.) which after four recrystallisations from light petroleum gave the pure *trans*-ester (3 g., 8%), m. p. 65°.

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JOHNSON CHEMICAL LABORATORIES, UNIVERSITY OF ADELAIDE. [*Received, November 10th,* 1952.]