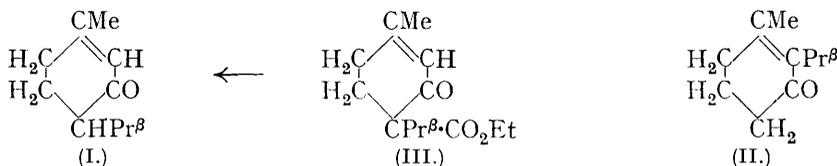


373. A Synthesis of dl-Piperitone (dl- Δ^1 -p-Menthen-3-one).

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THE constitution of piperitone has been shown to be Δ^1 -p-menthen-3-one (I) by oxidative degradation (Simonsen, J., 1921, 119, 1644; Penfold, *J. Proc. Roy. Soc. N.S.W.*, 1921, 55, 139). Callenbach (*Ber.*, 1897, 30, 639) claimed to have synthesised a menthenone having formula (I), but, as his starting material (Hagemann, *Ber.*, 1893, 26, 876) did not have the constitution which he supposed it to have (Rabe and Rahm, *Ber.*, 1905, 38, 969; Merling, *ibid.*, p. 982), doubt was cast on the presumed constitution (I) of his menthenone (Wallach, *Annalen*, 1908, 362, 274; Merling and Welde, *ibid.*, 1909, 366, 149); its derivatives (Kötz and Anger, *Ber.*, 1911, 44, 466) certainly differ in their properties from those of the corresponding ones of dl-piperitone (I). Dieckmann (*Ber.*, 1912, 45, 2704) showed by oxidative degradation that Callenbach's ketone actually had the constitution (II).



Since the conversions of terpinen-1-ol (Wallach and Meister, *Annalen*, 1908, 362, 272) and menthone (Walker and Read, J., 1934, 238) into piperitone can scarcely be termed syntheses of the latter, the present work constitutes the first complete synthesis of piperitone (I).

β -Chloroethyl methyl ketone was condensed with ethyl sodio- α -isopropylacetoacetate in alcoholic solution, yielding ethyl Δ^1 -p-menthen-3-one-4-carboxylate (III) directly. Difficulty was experienced in hydrolysing the ester (III) in an acid medium, but dl-piperitone (I) was obtained in good yield on alkaline hydrolysis. The ketone had constants in complete agreement with those of the racemised natural product; the habits and melting points of the oximes from the synthetic and the natural ketone were identical and there was no depression of the melting point on admixture.

EXPERIMENTAL.

Ethyl Δ^1 -p-Menthen-3-one-4-carboxylate (III).— β -Chloroethyl methyl ketone (5 g.; 1 mol.) (Blaise and Maire, *Bull. Soc. chim.*, 1908, 3, 268) in absolute ethyl alcohol (10 c.c.) was added to a solution of ethyl α -isopropylacetoacetate (8.1 g.; 1 mol.) in absolute ethyl alcohol (25 c.c.) containing sodium ethoxide (1.2 g. of sodium; 1.1 atoms). There was an immediate separation of sodium chloride and a considerable evolution of heat. After remaining for 20 hours at room temperature, the mixture was refluxed on the water-bath for 7 hours, then added to much water and extracted with ether. The ethereal solution, washed (10% sodium hydroxide solution), dried (anhydrous sodium sulphate), and evaporated, left a pale yellow oil (11.2 g.) and on fractional distillation under reduced pressure two fractions were obtained: (i) b. p. to 150°/16 mm., consisting essentially of unchanged ethyl α -isopropylacetoacetate (5.4 g.); (ii) b. p. 155—160°/16 mm., a colourless, fairly mobile oil (3.6 g.), n_D^{18} 1.4825 (Found: C, 69.2; H, 9.1. C $_{13}$ H $_{20}$ O $_3$ requires C, 69.6; H, 9.0%).

Hydrolysis to dl-Piperitone (I).—The above ester was recovered unchanged after 6 hours' treatment with 20% hydrochloric acid under reflux (bath 150°). The ester (2.4 g.; 1 mol.) was refluxed (bath 150°) for 12 hours with 20% methyl-alcoholic potassium hydroxide solution (3 mols.) and the mixture was then added to water and extracted with ether. The ethereal solution was washed with sodium carbonate solution, dried over anhydrous sodium sulphate, and evaporated. The crude product was distilled under diminished pressure, a practically colourless, mobile oil (1.2 g.; 74% yield on the ester; 26% overall yield) with the odour of piperitone passing over at 107—109°/12 mm., n_D^{15} 1.4854 (Found: C, 78.3; H, 10.4. Calc. for C $_{10}$ H $_{16}$ O: C, 78.9; H, 10.5%). For carefully purified l-piperitone Read and Smith (J., 1923, 123, 2269) found b. p. 110°/15 mm. and n_D^{20} 1.4848.

Oximation.—The ketone was boiled for 6 hours in aqueous-alcoholic solution with hydroxylamine hydrochloride (10% excess) and sodium acetate crystals (20% excess). After dilution

with water *dl*-piperitone α -oxime was extracted in ether, recovered by means of dilute sulphuric acid (two extractions), and liberated by neutralisation with sodium hydroxide solution. After crystallisation from absolute ethyl alcohol and from light petroleum (b. p. 60—80°) the fine colourless prisms had m. p. 117° (Found: C, 72.0; H, 10.1; N, 8.3. Calc. for $C_{10}H_{17}ON$: C, 71.8; H, 10.2; N, 8.4%), alone or mixed with the oxime (m. p. 117°) prepared from a racemised specimen of the natural ketone, kindly supplied by Professor R. Robinson, F.R.S.

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