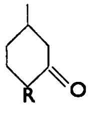
575. *A Synthesis of* (±)-*Pulegone.*

By C. Black, G. L. Buchanan, and (Miss) A. W. Jarvie.

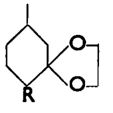
(±)-Pulegone has been synthesised from 3-methyl*cyclo*hexanone.

Pulegone (VI), the main constituent of pennyroyal oil, has been obtained by transformation of citronellal[1] or of citronellic acid,[2] but no direct synthesis has been reported; Wallach's initial claim[3] that pulegone could be prepared from acetone and 3-methyl*cyclo*hexanone (I) was later withdrawn.[4] We have found that by protecting the carbonyl group with a cyclic ketal, the β-oxo-ester (III) can be simply converted into (±)-pulegone (VI).

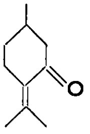
The oxo-ester (III), obtained from 3-methyl*cyclo*hexanone (I) *via* the glyoxylic ester (II) by a modification of Kötz and Hesse's method,[5] was converted into the ketal (IV), the progress of this final step being followed by the value of log ε at 255 mμ. The pure ketal (IV), in contrast to the oxo-ester (III), gave no colour with alcoholic ferric chloride and showed no infrared absorption at 1710—1610 cm.$^{-1}$. It was treated with two mols. of methylmagnesium iodide, and the mixture was decomposed under mild conditions in the



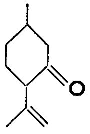
(I); R = H
(II); R = $CO{\cdot}CO_2Et$
(III); R = CO_2Et



(IV); R = CO_2Et
(V); R = $CMe_2{\cdot}OH$



(VI)



(VII)

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[1] Tiemann and Schmidt, *Ber.*, 1896, **29**, 913; 1897, **30**, 22.

[2] Bardhan and Bhattacharyya, *Chem. and Ind.*, 1951, 800; Kuhn and Schinz, *Helv. Chim. Acta*, 1953, **36**, 161.

[3] Wallach, *Annalen*, 1898, **300**, 268.

[4] *Idem, ibid.*, 1912, **394**, 380.

[5] Kötz and Hesse, *ibid.*, 1905, **342**, 315.

expectation of isolating the alcohol (V). The product, however, showed unexpected absorption in the ultraviolet region ($\lambda_{\max.}$ 254, log ε 2·41) and it was assumed that partial hydrolysis and dehydration to pulegone (VI) had occurred. Treatment with dilute acid completed this step, yielding an oil whose infrared spectrum showed, in addition to all the expected bands of pulegone, absorptions at 1706 and 888 cm.$^{-1}$. These may be assigned to non-conjugated $>$C=O and $>$C=CH$_2$ groups, respectively, and suggest the presence of a small amount of *iso*pulegone (VII). Moreover, the oil afforded a mixture of two isomeric 2 : 4-dinitrophenylhydrazones. One was identical in m. p., mixed m. p., and infrared spectrum with the same derivative of natural (+)-pulegone, and as expected its maximum of longest wavelength occurred at 377 mμ (log ε 4·34). The other isomer showed this maximum at 365 mμ (log ε 4·74), a value to be expected from the 2 : 4-dinitrophenylhydrazone of the unconjugated ketone, *iso*pulegone (VII).

It has already been shown [6] that *iso*pulegone is isomerised to pulegone by alkaline reagents, and when the above oil was treated with sodium ethoxide, it gave an analytically pure product, whose infrared spectrum was identical with that of natural (+)-pulegone. Both samples still showed weak absorption at 1706 cm.$^{-1}$. Synthetic (±)-pulegone 2 : 4-dinitrophenylhydrazone was identical in mixed m. p. and infrared spectrum with the derivative from the natural product.

EXPERIMENTAL

Ultraviolet absorption spectra were measured on a Unicam S.P. 500 spectrophotometer and infrared spectra on a model 13 Perkin-Elmer double-beam instrument.

Ethyl 4-*Methyl*-2-*oxo*cyclo*hexanecarboxylate* (III).—The glyoxylic ester (II) was prepared [5] by the condensation of ethyl oxalate and (±)-3-methyl*cyclo*hexanone, catalysed by sodium ethoxide. However, our product was isolated by distillation at 158—163°/14 mm. The product (62% yield), n_D^{18} 1·481, gave a red colour with alcoholic ferric chloride.

The glyoxylic ester (II) (60 g.) and powdered glass (15 g.) were heated at 150° till the evolution of gas ceased (*ca.* 30 min.); the mixture was exhausted with benzene and the 2-oxo-ester (III) obtained in 90% yield; it had b. p. 120—122°/15 mm., n_D^{25} 1·476; ultraviolet absorption, $\lambda_{\max.}$ 255 (log ε 3·92); infrared bands at 2940, 1740, 1715, 1650, 1613, 1272, 1212 cm.$^{-1}$. The 2 : 4-*dinitrophenylhydrazone* had m. p. 136° (ethanol) (Found : C, 52·7; H, 5·45; N, 15·4. $C_{16}H_{20}O_6N_4$ requires C, 52·7; H, 5·5; N, 15·4%).

Ethyl 2-*Ethylenedioxy*-4-*methyl*cyclo*hexanecarboxylate* (IV).—The oxo-ester (III) (90 g.), ethylene glycol (60 g.), and toluene-*p*-sulphonic acid (0·5 g.) in dry benzene (180 ml.) were refluxed in a 700-ml. flask fitted with a Dean–Stark water separator.[7] After 40 hr., separation of water was complete, benzene (50 ml.) was added, and the solution was washed with water, sodium carbonate solution, and again with water till the washings were neutral. The benzene was removed *in vacuo*, and the *ketal* was distilled (twice) at 132—134°/10 mm. (Found : C, 62·8; H, 8·5. $C_{12}H_{22}O_4$ requires C, 63·15; H, 8·8%). The purest sample still showed some absorption at 255 mμ (log ε 1·05); infrared bands at 2950, 1730, 1183 cm.$^{-1}$.

(±)-*Pulegone* (VI).—The ketal (IV) (15 g.) in dry ether (60 ml.) was added slowly, with mechanical stirring, to the Grignard reagent prepared from magnesium (4·26 g.) and methyl iodide (24 g.) in dry ether (*ca.* 100 ml.). The mixture was refluxed for 2 hr. and then decomposed with ammonium chloride (40 g. in 200 ml. of water). The ether layer was washed, dried, and concentrated, and the product distilled at 117°/10 mm. (yield 11 g.). This is probably a mixture as light absorption ($\lambda_{\max.}$ 254; log ε 2·41) and analytical data are inconsistent with structure (V) (Found : C, 67·8; H, 9·3 Calc. for $C_{12}H_{22}O_3$: C, 67·3; H, 10·3%). The substance gave no colour with alcoholic ferric chloride solution, but immediately decolorised aqueous potassium permanganate.

This product (11 g.) in methanol (80 ml.) and water (55 ml.) was treated with concentrated hydrochloric acid (1 ml.) on the water-bath for 2 hr. The solution was then cooled and neutralised with sodium hydrogen carbonate, and the bulk of the methanol removed under reduced pressure. The residual oil was distilled, and the fraction, b. p. 200—220°, refractionated. The fraction, b. p. 220—222°, gave a mixture of 2 : 4-dinitrophenylhydrazones separable by fractional crystallisation into : (*a*) crimson needles (ethanol) (Found : C, 58·0; H, 6·2; N, 16·8.

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[6] Hugh, Kon, and Linstead, *J.*, 1927, 2585.

[7] *Org. Synth.*, 1943, **23**, 38.

Calc. for $C_{16}H_{20}O_4N_4$: C, 57·8; H, 6·0; N, 16·9%), m. p. 148°, undepressed when mixed with (+)-pulegone 2 : 4-dinitrophenylhydrazone. Its infrared spectrum was identical with that of the latter; max. of longest wavelength, 377 mμ (log ε 4·34); (*b*) yellow needles (ethanol), m. p. 141° (Found : C, 58·1; H, 5·9; N, 17·1%); max. of longest wavelength, 365 mμ (log ε 4·47). The above oil was isomerised with 25% alcoholic sodium ethoxide,[6] and pure (±)-pulegone isolated by dilution, and ether extraction; it had b. p. 220—222°, n_D^{18} 1·4846 (Found : C, 78·7; H, 10·2. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·5%); infrared bands at 2917(s), 1706(w), 1678(s), 1611(m), 1448(m), 1372(w), 1342(vw), 1288(s), 1206(s), 1130(w), 1096(vw), 1034(vw), 936(vw), 875(vw) cm.$^{-1}$. This purified material yielded a 2 : 4-dinitrophenylhydrazone, m. p. 148° (Found : C, 57·7; H, 5·9; N, 16·8. Calc. for $C_{16}H_{20}O_4N_4$: C, 57·8; H, 6·0; N, 16·9%), which was identical in mixed m. p. and infrared spectrum with the same derivative of (+)-pulegone.

(+)-*Pulegone* (by J. K. SUTHERLAND).—The product was isolated from oil of pennyroyal by Baeyer and Heinrich's method.[8] It had b. p. 222°; 2 : 4-dinitrophenylhydrazone, m. p. 142°.

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THE UNIVERSITY, GLASGOW, W.2. [*Received, February* 27*th*, 1956.]

[8] Baeyer and Heinrich, *Ber.*, 1895, **28**, 652.