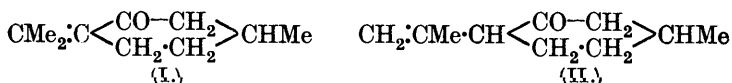CCCXLIII.—*The Chemistry of the Three-carbon System. Part XV. Pulegone and* iso*Pulegone.*

By Wilfred Eynon Hugh, George Armand Robert Kon, and Reginald Patrick Linstead.

THE experiments described in Part X of this series (J., 1926, 3101)
made it clear that pulegone (I) and *iso*pulegone (II) were related in
the same way as the ketones studied by Kon and Linstead (J., 1925,
127, 815), and that they exhibited what was described as retarded
mobility; thus they are quite distinct, but the formation from
pulegone of *iso*pulegoneoxime in the presence of alkali (Wallach,

Annalen, 1909, **365**, 240), and of methyl*iso*pulegone by the action of sodium and methyl iodide, on the one hand, and the conversion of *iso*pulegone into pulegone by baryta (Tiemann and Schmidt, *Ber.*, 1897, **30**, 22), on the other, point to the establishment of an equilibrium.

$$CMe_2:C\underset{CH_2 \cdot CH_2}{\overset{CO-CH_2}{<}}>CHMe \qquad CH_2:CMe \cdot CH\underset{CH_2 \cdot CH_2}{\overset{CO-CH_2}{<}}>CHMe$$
$$(I.) \qquad\qquad\qquad\qquad (II.)$$

Owing to their accessibility, these ketones form a convenient material for the study of tautomerism, but whilst pulegone is well known and readily characterised, the data on *iso*pulegone (especially on its physical properties) are scanty and, in part, conflicting. As a preliminary step, therefore, it appeared necessary to establish definitely the properties of pure *iso*pulegone and to evolve a method of estimating it in mixtures with pulegone.

Probably the simplest method of obtaining *iso*pulegone consists in the preparation of its oxime from pulegone (Wallach, *loc. cit.*), but all our attempts to hydrolyse this oxime led to mixtures containing a high proportion of pulegone and some methyl*cyclo*hexanone.

The ketone is, however, readily obtained by the oxidation of *iso*pulegol (Tiemann and Schmidt, *Ber.*, 1896, **29**, 917), although special precautions are necessary to obtain a pure product (see Experimental). The ketone consists of a mixture of the active and the inactive compound, but in our experiments the latter was only obtained in very small quantities. The optical activity of the active ketone is higher than that previously found.

The method of Harries and Roeder (*Ber.*, 1899, **32**, 3357) is untrustworthy and gives rise to mixtures from which a pure ketone is isolated only with great difficulty; this is *dextrorotatory* and identical with that obtained from *iso*pulegol, as might have been anticipated from the work of Wallach (*loc. cit.*). The lævorotation of the crude ketone is due to the presence of other compounds. The lævorotatory ketone prepared by Grignard (*Compt. rend.*, 1926, **182**, 422) by this method cannot have been *iso*pulegone owing to its totally different physical properties ($d_4^{14°}$ 0·9097, n_D 1·46335); on one occasion we obtained a ketone of very similar properties which consisted mainly of menthone, evidently formed by the reduction of pulegone hydrobromide.

No *iso*pulegone could be found in the three samples of oil of pennyroyal examined. Fractions with properties agreeing with those recorded by Grignard have in every case been isolated, but these consisted mainly of menthone which had already been found

in the oil by Tétry (*Bull. Soc. chim.*, 1902, **27**, 186), a fact which had apparently escaped Grignard's notice. This ketone occurs in a strongly dextrorotatory fraction of the oil, but is, curiously enough, inactive when isolated by means of its semicarbazone. The physical properties of Grignard's natural *iso*pulegone, although almost identical with those of the ketone he prepared by Harries and Roeder's method, differ considerably from those of pure *iso*pulegone; and it appears certain that his material consisted, like ours, of a mixture of pulegone and menthone. It is unfortunate that this material was used by Kon and Nutland (Part X, *loc. cit.*) before its true nature was realised, although the poor yield of methyl*iso*pulegone obtained from " natural *iso*pulegone " was noted at the time. The formation of the methylation product was evidently due to the pulegone still left in the mixture; the methylation has since been repeated with a genuine sample of *iso*pulegone and found to give the same lævorotatory product.

The proportion of pulegone and *iso*pulegone in mixtures of the two ketones can be roughly estimated from the physical properties of the mixture (see Experimental), but a more accurate method has been worked out, based on the different rates of reaction with iodine chloride and similar to that employed by Linstead and May (this vol., p. 2565). This method incidentally provided a ready means of differentiating between *iso*pulegone and mixtures like " natural *iso*pulegone " containing saturated compounds, and supplied the final proof that *iso*pulegone did not occur in the oils examined.

The equilibrium between pulegone and *iso*pulegone was studied in the presence of a variety of reagents with reference both to the rate of equilibration and to the proportion of the constituents in the final product. The results show that the final equilibrium point is so close to pure pulegone that no difference between the latter and the equilibrium mixture can be detected even by the iodometric method employed. The system is evidently very mobile, because in the presence of small quantities of sodium ethoxide (1/50 mol.) the rate of equilibration is already too rapid for exact measurement. With baryta (1/50 mol.) the reaction is complete in 2 hours, but with sodium carbonate it requires several days; piperidine also produces a small change in 24 hours. Cold aqueous sulphuric acid produces little change, but hot acids have a marked effect; this could not be studied quantitatively owing to the ready fission of both pulegone and *iso*pulegone under these conditions, but it is apparent from the fact that, if comparatively large quantities of *iso*pulegonesemicarbazone are hydrolysed by digestion with oxalic acid in a current of steam, the resulting ketone contains up to 50% of pulegone, whereas small quantities can be hydrolysed without

much conversion taking place. The most noteworthy points are the very rapid equilibration in the presence of sodium ethoxide, and the coincidence of the final equilibrium point with pure pulegone, within the limits of experimental error. From these results it is clear that Grignard's figure for the equilibrium between the two ketones (*loc. cit.*) is erroneous; and the great sensitiveness of *iso*pulegone makes its occurrence in essential oils extremely improbable.

EXPERIMENTAL.

Preparation of iso*Pulegone.*—Commercial *iso*pulegol ($\alpha_D^{20°} - 1·22°$), obtained from Messrs. Boake, Roberts & Co., of Stratford, was oxidised exactly as described by Tiemann and Schmidt (*loc. cit.*), and the resulting oil treated with semicarbazide acetate; the semicarbazone was purified by thorough grinding with light petroleum, followed by repeated grinding with cold ether; the ethereal extract gave on evaporation a solid (E), whilst a large proportion remained undissolved (R).

The solid (E) was freed from adhering oil by means of light petroleum, and a portion was recrystallised from methyl alcohol. The various crops obtained were somewhat indefinite and melted at 157—158°. They were combined and hydrolysed by means of oxalic acid; the ketone had b. p. 94—96°/13 mm., $d_4^{18·3°}$ 0·92540, $n_D^{18·3°}$ 1·47241, $\alpha_D + 34·3°$ ($c = 9·1408$ in ethyl alcohol),* and evidently contained some pulegone. Another sample obtained in a similar way was treated with aluminium amalgam (Harries and Roeder, *loc. cit.*) before the final distillation; the greater portion had b. p. 100—102°/20 mm., $d_4^{22·0°}$ 0·91759, $n_D^{22·0°}$ 1·46519, $[R_L]_D$ 45·85, $\alpha_D + 38·0°$ ($c = 6·6708$ in methyl alcohol). The optical activity of the ketone so obtained depends on the number of times the semicarbazone is extracted with ether, the first extract containing the most active material, which is, however, more liable to be impure. Subsequent extracts usually give a semicarbazone which, after several crystallisations from methyl alcohol, forms long, silky needles, m. p. 175—176°.

The residue (R) on crystallisation from methyl alcohol separated in silky needles, m. p. 176—177°, although a small amount representing the least soluble portion formed transparent prisms, m. p. 180°, doubtless belonging to the inactive ketone (compare Wallach, *loc. cit.*); mixtures of the two melted at about 178°. The ketone regenerated from the pure material, m. p. 176—177°, and treated with aluminium amalgam had b. p. 105—106°/23 mm., $d_4^{25·2°}$ 0·91731, $n_D^{25·2°}$ 1·46589, $\alpha_D + 23·8°$ ($c = 6·6676$ in methyl alcohol), and gave an oxime, m. p. 134° after one crystallisation from methyl

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* All the rotations recorded in this paper were measured in a 2-dcm. tube.

alcohol. Another sample similarly obtained from the less soluble portions of (E) had $d_{4^\circ}^{22\cdot5^\circ}$ 0·91994, n_D 1·46689, $\alpha_D + 26\cdot6^\circ$. When a large quantity of semicarbazone (*e.g.*, 100 g.) was hydrolysed all at once, the product contained as much as 60% of pulegone ($d_{4^\circ}^{18\cdot9^\circ}$ 0·93161, n_D 1·47917); the aluminium-amalgam process of purification is not altogether satisfactory in this case because an appreciable quantity of pulegone is reduced to menthone; but the amount of menthone formed is negligible if the crude *iso*pulegone contains but small quantities of pulegone. For this reason it is necessary to hydrolyse *iso*pulegonesemicarbazone in small portions (about 20 g.). A separate experiment showed that *iso*pulegone was unaffected by treatment with aluminium amalgam, the material having the same physical properties and iodine-absorption before and after treatment (see below).

isoPulegone from Pulegone Hydrobromide.—The preparation was carried out as described by Harries and Roeder (*loc. cit.*). The results were extremely variable, pulegone being usually almost the sole product obtained. This is removed in the process of reduction, but the product then contains menthone; thus, on one occasion a ketone regenerated from the crude semicarbazone had b. p. 84°/9 mm., $d_{4^\circ}^{18\cdot0^\circ}$ 0·90846, $n_D^{18\cdot0^\circ}$ 1·45833, $\alpha_D - 11\cdot6^\circ$, in good agreement with Grignard's figures (*loc. cit.*); it was reconverted into a semicarbazone from which considerable quantities of menthone-semicarbazone were isolated. In most cases a semicarbazone is formed with great difficulty as already observed by Harries and Roeder (*loc. cit.*). Sometimes, however, almost pure *iso*pulegone is formed; *e.g.*, on one occasion a considerable amount of an optically inactive fraction, b. p. 104—105°/18 mm., was obtained; the refractive index approximated to that of *iso*pulegone, although the density was too high (this was always the case). The product was treated with aluminium amalgam and converted into the semi-carbazone. The ketone regenerated from it had b. p. 101—102°/17 mm., $d_{4^\circ}^{20\cdot0^\circ}$ 0·920855, $n_D^{20\cdot0^\circ}$ 1·46669, $[R_L]_D$ 45·81, $\alpha_D + 24\cdot7^\circ$ ($c = 5\cdot5532$ in methyl alcohol), agreeing well with the properties of *iso*pulegone prepared from *iso*pulegol ($d_{4^\circ}^{20\cdot4^\circ}$ 0·92177, $n_D^{20\cdot4^\circ}$ 1·46787). The latter are regarded as the physical constants of the *pure* ketone.

When pulegone hydrobromide was allowed to stand for 4 days with a slight excess of piperidine in light petroleum solution, the resulting ketone proved to be pulegone.

Estimation of Pulegone and isoPulegone *in Mixtures.*

The proportion of the two ketones in a mixture can be roughly estimated by means of the density or the refractive index, an

examination of several synthetic mixtures having shown that these two properties could be satisfactorily expressed by a straight-line relationship. For the accurate analysis of mixtures, however, the iodometric method of Linstead and May (*loc. cit.*) has been adopted.

Preliminary experiments were made to ascertain suitable condi⋅ tions. An $M/300$-solution of each ketone in chloroform was allowed to stand with the theoretical quantity of iodine solution with the following result :

Time (mins.).	2.	10.	20.	27.
% Reaction with pulegone	5·2	9·9	15·4	— (complete in 45 hrs.)
,, ,, *iso*pulegone *	32·1	57·5	—	72·6

* The sample of *iso*pulegone used in the preliminary work was not quite pure.

FIG. 1.

*Absorption of iodine by pulegone–*iso*pulegone mixtures.*
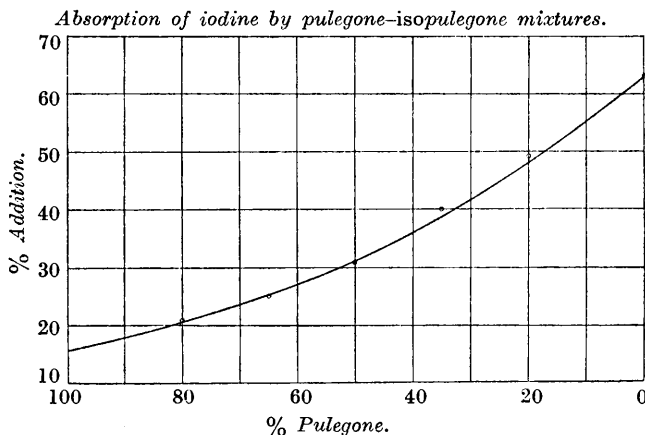
A standard time of 10 minutes was therefore adopted. Mixtures of pure pulegone and *iso*pulegone, made by mixing $M/300$-solutions in chloroform, were then titrated, with the following results (mean of 3 concordant determinations in each case) :

Mixture (% pulegone)	0	20	35	50	65	80	100
% Addition	64·7	58·5	55·1	48·9	40·1	30·9	16·6

From the above data the reference curve (Fig. 1) was constructed.

Examination of Oil of Pennyroyal.

Spanish Oil.—Two samples of this oil gave practically identical results, of which one is recorded : Light green oil, $d_4^{22·5°}$ 0·9324, $\alpha_D^{22·5°}$ approx. $+ 22°$. 1370 G. distilled under reduced pressure (fractionating column) gave :

$< 92°/11$—12 mm.	92—98°/11 mm.	98—105°/11 mm.	Residue.	Loss.
194 g.	1110 g.	7 g.	30 g.	29 g.

The low fraction was refractionated and another large fraction, b. p. 90—91°/10 mm., was obtained, which was increased by a third fractionation. This fraction had $n_D > 1.48$ and was therefore added to the main pulegone fraction, which thus amounted to 1270 g., or 93% of the original oil; it had $d_4^{16.6°}$ 0.93869, n_D 1.48820; titrations with iodine gave 12.9% addition (mean of 3), showing that no appreciable amount of *iso*pulegone was present. The low fractions gave on refractionation at 10 mm. : 48—52°, 13 g.; 58—62°, 4 g.; 84—90°, 10 g. The terpene fractions were progressively refractionated under atmospheric pressure, but were not definitely separated; a portion, b. p. 168—174°, had $d_4^{14.7°}$ 0.85569, $n_D^{14.7°}$ 1.46768, α_D — 23° in alcohol; its odour suggested limonene. These were not further investigated. The fraction 84—90°/10 mm. still contained pulegone and terpenes.

750 C.c. of the pulegone fraction were treated with sodium hydrogen sulphite and alcohol until no further precipitation occurred, and the solid was filtered off and washed with alcohol and ether. The oil recovered from the mother-liquor and washings still contained pulegone and was therefore again treated with bisulphite. The portion which had failed to combine was isolated and distilled, but was found to contain pulegone; it was finally reduced by means of aluminium amalgam in ether, and fractionated at 10 mm. :

	Fraction.	Weight.	$d_4^{18°}$.	n_D.
(1)	<83°	3.8 g.	—	—
(2)	83—83	7.9 g.	0.89522	1.45763
(3)	84—87	5.7 g.	0.90822	1.46250
(4)	87—90	6.5 g.	0.91728	1.46669
(5)	High	2.1 g.	—	1.47014

The two lowest fractions were combined and redistilled under ordinary pressure, a part boiling below 200°, and the rest about 207°. The same semicarbazone was obtained from each in moderate yield and melted at 181—182° after washing with petroleum, extraction with ether, and crystallisation from methyl alcohol; this was identified as menthonesemicarbazone (Found : C, 62.5; H, 10.1. Calc. : C, 62.6; H, 9.9%). The fraction (4), which corresponds with Grignard's *iso*pulegone fraction, had α_D + 43.16° ($c = 5.22$ in alcohol), and on treatment with semicarbazide gave a sparingly soluble semicarbazone (fine needles from methyl alcohol, m. p. 184—185°) together with a portion which dissolved in ether, from which it was obtained on evaporation as a brown syrup. The ketone regenerated from this by means of oxalic acid was again treated with semicarbazide and gave a product consisting mainly of menthonesemicarbazone. The presence of *iso*pulegone in fraction (4) could not be demonstrated, although its behaviour

towards iodine suggested the presence of some unsaturated material, corresponding with an *iso*pulegone content of 25%. This unsaturated material, however, appeared to be non-ketonic and accumulated in the light-petroleum washings from the menthone-semicarbazone, from which it could be obtained on evaporation; it appeared to be a mixture of menthol and terpenes and was highly unsaturated (iodine number, Hübl : 154·3).

French Oil.—A sample of French oil was found to have properties closely agreeing with those of the Spanish oils : $d_4^{15·9°}$ 0·93671, n_D 1·48627. On distillation, some 1·5% of terpene fraction was isolated; 93% boiled at 98—103°/16 mm. and had $d_4^{15·5°}$ 0·93525, n_D 1·48724; titrations with iodine gave a mean addition of 16%, showing that no appreciable quantity of *iso*pulegone could be present.

The whole of this fraction (839 g.) was treated with sodium hydrogen sulphite for a fortnight, and the oil which had failed to react was isolated and treated again until no further precipitation occurred. The resulting oil amounted to 59 g. and gave the following result on fractionation at 12 mm. :

Fraction.	Weight (g.).	$d_4^{17·7°}$.	$n_D^{17·7°}$.	a_D (in methyl alcohol).
(1) Below 79°	11·3	0·87113	1·45323	+13°
(2) 79—84	4·3			
(3) 84—88	14·9	0·89360	1·45893	+33·0
(4) 88—92	9·2	0·90617	1·46201	
(5) 92—98	4·8	0·91166	1·46728	+29·7
(6) 98—105	4·5	0·91771	1·47309	
Residue	10·0			

Fraction (1) consisted of a mixture of terpenes, whilst fraction (2) contained some menthone; fraction (3) was almost pure menthone, which was also present in most of the other fractions. It was isolated in the form of its semicarbazone, which, after being washed with petroleum, crystallised from alcohol in fine needles, m. p. 184—185°, unaltered on admixture with a sample prepared from *l*-menthone. The regenerated ketone had b. p. 88°/12 mm., $d_4^{19·0°}$ 0·89774, $n_D^{19·0°}$ 1·45233, $[R_L]_D$ 46·35 (Calc., 46·20), but was *inactive*.* Owing to the small amounts of material available it was impossible to decide as to the nature of the menthone originally present, especially as a solid oxime was not obtained; the rotations of the menthone fractions were diminished somewhat by treatment with sodium ethoxide (compare Read and Robertson, J., 1926, 2209). The petroleum washings from the menthonesemicarbazone were evaporated and gave an oil with a strong mint-like odour; on distillation a fraction, b. p. 92—96°/15 mm., was obtained which

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* The hydrolysis of the semicarbazone was carried out with oxalic acid on two separate occasions; the product was inactive in each case.

was probably mainly menthol (Found : C, 76·9; H, 12·3. Calc. : C, 76·9; H, 12·8%), but still contained some unsaturated material; it had $\alpha_D + 27\cdot2°$, $d_4^{20°}$ 0·89151, n_D 1·45623.

The small fraction (5), which would correspond with Grignard's *iso*pulegone, was specially investigated, but menthone was still the principal constituent, probably accompanied by some pulegone; no trace of *iso*pulegone could be isolated. The slightly high iodine-absorption of the original pulegone fraction is evidently due to the presence of terpenes, which were found to react rapidly with iodine. The terpene fraction obtained in the first fractionation of the oil was feebly lævorotatory (α_D —13·5°), whilst the terpenes isolated from the main fraction were dextrorotatory and had a lower refractive index. The small amounts obtained did not allow of investigation.

FIG. 2.

Change of iso*pulegone into pulegone in presence of barium hydroxide.*

Time (minutes).
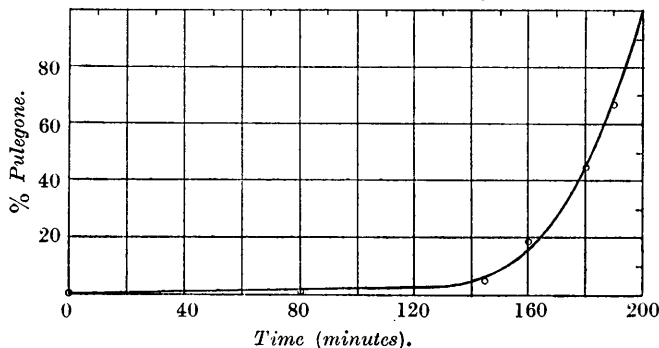
Equilibrium between Pulegone and iso*Pulegone.*—The following procedure was used throughout. The ketone (4 c.c.) was mixed with the catalyst, and the whole made up to 50 c.c. with ethyl alcohol. After standing for the requisite time, the mixture was diluted with water and thoroughly extracted with ether, the extract was washed, dried, and evaporated with the aid of a long column, and the residue was distilled under reduced pressure from a glycerol-bath, the first two drops of distillate being rejected; the remainder was collected (about 3·5 c.c.). The physical properties of the distillate were determined in all cases as an additional check. An $M/300$-solution of the distillate in pure chloroform was then made up and three titrations with iodine were carried out. The catalyst used and its concentration are specified at the head of the corresponding results in the table, and the results with barium hydroxide are illustrated in Fig. 2.

1. *Sodium ethoxide* (10 c.c. of $M/10$-solution).

Initial material.		Time (mins.).	Temp.	d.	n_D.	% Addition.
isoPulegone *	...	30	19·0°	0·93448	1·48337	16·9
,,	...	20	19·6	0·93440	1·48483	17·2
Pulegone	....	720	19·4	0·93599	1·48551	16·6

2. *Barium hydroxide* (10 c.c. of 3% solution).

isoPulegone	......	10	21·4	0·92540	1·47408	55·2
,,	......	20	21·8	0·92828	1·47751	46·3
,,	......	40	19·0	0·93100	1·48142	30·9
,,	......	55	18·0	0·93251	1·48337	21·0
,,	......	120	19·5	0·93327	1·48483	17·5
,,	......	200	19·6	0·93407	1·48531	17·0
Pulegone	....	1440	22·6	0·93508	1·48521	16·9

3. *Sodium carbonate* (10 c.c. of $M/10$-solution).

isoPulegone	......	120	25·0	0·91994	1·47113	58·4
,,	......	900	22·2	0·92419	1·47359	50·4
Pulegone	....	1440	20·4	0·93506	1·48531	16·9

4. *Piperidine* (10 c.c. of $M/10$-solution).

isoPulegone	......	1440	20·4	0·92358	1·47408	61·4
Pulegone	....	1440	21·6	0·93266	1·48483	16·6

5. *Sulphuric acid* (10 c.c. of $M/10$-solution).

isoPulegone †	...	480	22·2	0·92086	1·46966	64·7
,,	......	1440	22·0	0·92092	1·46408	64·7
Pulegone	....	1440	22·0	0·93508	1·48521	16·6

* In this case 25 c.c. of 12% sodium ethoxide solution were used.

† In this case 10 c.c. of 12·5% sulphuric acid solution were used.

The composition of the mixtures can be readily ascertained from the reference curve in Fig. 1.

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