

268. *Researches in the Carvone Series. Part III. Carvomenthols, l-isoCarvomenthone, and l-isoCarvomenthylamine.*

By ROBERT G. JOHNSTON and JOHN READ.

CARVOMENTHOLS, like menthols, should be capable of existing in eight optically active and four externally compensated forms. The many methods recorded for preparing these substances have clearly led in most instances to complex mixtures of stereoisomerides. The earlier methods consisted in applying sodium and alcohol and other reducing agents to such substances as *dl*-carvenone (Wallach, *Annalen*, 1893, **277**, 130; Marsh and Hartridge, *J.*, 1898, **73**, 857), *d*-dihydrocarveyl acetate (Baeyer, *Ber.*, 1893, **26**, 822), and *dl*-carvotanacetone (Semmler, *Ber.*, 1894, **27**, 895). Later, attempts were made to isolate individual carvomenthols by the controlled hydrogenation of carvacrol, carvone, etc., in presence of various catalysts under different conditions (see *inter alia* Brunel, *Compt. rend.*, 1903, **137**, 1269; 1905, **141**, 1245; Haller and Martine, *Compt. rend.*, 1905, **141**, 1312; Vavon, *ibid.*, 1911, **153**, 70; Ipatiev, *Ber.*, 1911, **44**, 3462).

The carvomenthols obtained by catalytic hydrogenation, etc., from such initial substances as *l*- α -phellandrene, *d*-carvone, *dl*-carvenone, and carvacrol have been studied in detail by Paolini (*Atti R. Accad. Lincei*, 1919, **28**, 82, 134; 1921, **30**, 313, 371; *Gazzetta*, 1925, **55**, 818; etc.), whose methods entailed in particular the fractional crystallisation of the carvomenthyl hydrogen phthalates and various derived salts. The values of $[\alpha]_D$ recorded for the resulting carvomenthols may be arranged in four numerical groups, with the following approximate means: -20° , $\pm 8-9^\circ$, $\pm 2-3^\circ$, and $\pm 1-2^\circ$. All the supposed stereoisomeric forms had the common boiling point, 218° ; the values of d_{15}^{15} ranged only from 0.9071 to 0.9082; those of n_D^{20} fell within the narrow limits, 1.463—1.461; and the substances of highest density had the lowest refractive index. The different preparations were not shown to give rise to stereoisomeric ketones upon oxidation. In view of the considerably greater diversity in physical properties shown by the stereoisomeric menthols, there is little doubt that Paolini's end-products consisted of mixtures of stereoisomerides, in spite of the remarkably good agreement observed for the rotatory powers of certain of the specimens which were prepared from different sources. The same may be said of the carvomenthol, $[\alpha]_D - 1.10^\circ$, recently prepared by Tabuteau (*Compt. rend.*, 1935, **200**, 244) from carvomenthene having $[\alpha]_D + 103.5^\circ$. This conclusion is borne out by the results now described.

The processes outlined below usually entail the separation of only two stereoisomeric alcohols at each stage (cf. *J.*, 1934, 233). For example, *d*-carvone (one asymmetric carbon atom) yields two carveols (two asymmetric carbon atoms), each of which, after separation, furnishes in turn two carvomenthols (three asymmetric carbon atoms). The stereoisomeric alcohols were separated and characterised by means of crystalline esters, the different rates of reaction with the corresponding acid chlorides being sometimes effectively utilised during the separation.

All the optically active substances described in this paper may be referred to *d*-carvone, which when hydrogenated yields an equilibrium mixture of *l*-carvomenthone and *l-iso*-carvomenthone (*J.*, 1934, 227). *l*-Carvomenthone oxime (*loc. cit.*) when reduced with sodium and alcohol yields *d*-carvomenthylamine, which upon deamination gives rise to *d-carvomenthol*, $[\alpha]_D + 27.7^\circ$, with a little terpene. *l-neo*Carvomenthylamine, obtained from *l*-carvomenthone and ammonium formate (*J.*, 1934, 231), is converted chiefly into terpene when deaminated; but at the same time both *d*-carvomenthol and *l-neocarvomenthol*, $[\alpha]_D - 41.7^\circ$, are produced. Each of these alcohols is oxidised by Beckmann's reagent to *l*-carvomenthone, having $[\alpha]_D$ ca. -6° . *d*-Carvomenthol appears to react more rapidly than *l-neocarvomenthol* with acid chlorides. The inter-relationships of *l*-carvomenthone, *d*-carvomenthol and *l-neocarvomenthol* are thus precisely similar to those of *d*-menthone, *d*-menthol and *l-neomenthol*, and the nomenclature is based upon this analogy (cf. *J.*, 1934, 228).

Similar inter-relationships exist in the *iso*-series. *l-iso*Carvomenthylamine, obtained

by reducing *l*-isocarvomenthone oxime, yields upon deamination *l*-isocarvomenthol, $[\alpha]_D - 17.7^\circ$, with a little terpene. This last alcohol oxidises to *l*-isocarvomenthone, which, like the optically active isomenthones, yields a viscid oxime. As in the menthone series, the isoketone has the higher numerical rotatory power, and the densities and refractive indices of isocarvomenthone and the isocarvomenthols are greater than those of carvomenthone and the carvomenthols. A similar statement applies to *d*-, *l*-neo-, and *l*-isocarvomenthylamine: no *neoisocarvomenthylamine* has yet been isolated.

d-Carvomenthol and *l*-neocarvomenthol have each been prepared in four different ways from *d*-carvone, and *l*-isocarvomenthol has been prepared in two ways: the rotatory powers of the various specimens show substantial agreement. The supposed *l*-neoisocarvomenthol, $[\alpha]_D - 34.7^\circ$, has as yet been prepared by one method only, and in very small amount; so the data for this alcohol (as also to a less extent for *l*-isocarvomenthol) are put forward with reserve. Discussion of relative molecular configurations and of relationships between optical rotatory powers in this group is deferred until *iso*- and *neoisocarvomenthol* and the carvomenthones have been more fully characterised, and the comparative reaction velocities of the four series of carvomenthols have been studied (cf. J., 1934, 1779). The need for caution is emphasised by the occasional tendency of the nitrobenzoates in this series to form mixed crystals; e.g., the *p*-nitrobenzoates of *d*-*trans*- (m. p. 77° , $[\alpha]_D + 264^\circ$) and *d*-*cis*-carveol (m. p. 28° , $[\alpha]_D - 57^\circ$) form a constant-crystallising mixture having m. p. 84° , $[\alpha]_D + 85^\circ$.

d-*cis*-Carveol (J., 1934, 235) upon hydrogenation yields a mixture of *d*-carvomenthol and *l*-neoisocarvomenthol; while *d*-*trans*-carveol gives *l*-neo- and *l*-iso-carvomenthol. In practice, however, *d*-carvomenthol is best obtained by deaminating *d*-carvomenthylamine, and *l*-neocarvomenthol by the Ponndorf reduction of *l*-carvomenthone.

The leading characteristics of *l*-carvomenthone and *l*-isocarvomenthone are summarised below:

	<i>l</i> -Carvomenthone.	<i>l</i> -isoCarvomenthone.
$[\alpha]_D$	$- 6.0^\circ/17^\circ$	$- 56.5^\circ/20^\circ$
n_D	$1.4548/17^\circ$	$1.4558/20^\circ$
d_{40}^{20}	$0.9033 *$	0.9102
Oxime: m. p.	$99-100^\circ$	syrup
$[\alpha]_D$ (<i>c</i> 2, alcohol)	$- 38.7^\circ$	$- 79.5^\circ$
Semicarbazone: m. p.	192°	$171-172^\circ$
$[\alpha]_D$ (<i>c</i> 2, chloroform)	$- 13.3^\circ$	$- 117.0^\circ$

* For a specimen having $[\alpha]_D^{20} - 25.0^\circ$ and thus containing about 62% of *l*-carvomenthone and 38% of *l*-isocarvomenthone.

The equilibrium mixture of these two ketones produced by leaving either of them in contact with cold alcoholic sodium ethoxide contains about 80% of *l*-carvomenthone; the preparations made by hydrogenating *d*-carvone in presence of Rupe's nickel catalyst (cf. J., 1934, 229), with $[\alpha]_D^{20} - 25.0^\circ$, contain about 62% of *l*-carvomenthone.

Approaches to carvomenthols are also being studied from carvotanacetone, carvotanacetols, and a 1 : 2-menthanediol (m. p. $112-114^\circ$) which has recently been obtained.

EXPERIMENTAL.

d-Carvomenthol.—(1) Upon mixing *d*-carvomenthylamine hydrochloride (J., 1934, 230) with sodium nitrite (1 mol.) in concentrated aqueous solution, a precipitate of *d*-carvomenthylamine nitrite was produced. Nitrogen was expelled on the water-bath, and the immiscible layer steam-distilled. Usually, deamination approached 75%: in a typical experiment, 37.2 g. of hydrochloride gave 2.7 g. of a terpene fraction, b. p. $61-101^\circ/16$ mm., $n_D^{15} 1.4595$, $\alpha_D + 0.32^\circ$ ($l = 1$), and 17.3 g. of a carvomenthol fraction with b. p. $101-104^\circ/16$ mm., $n_D^{15} 1.4631$, $\alpha_D^{15} + 19.58^\circ$. Unchanged base was recovered and used again. A mixture of several of the higher-boiling fractions gave a crude 3 : 5-dinitrobenzoate having $[\alpha]_D + 44.4^\circ$ (*c* 2.0, chloroform); upon recrystallisation from alcohol-ethyl acetate, this readily yielded pure *d*-carvomenthyl 3 : 5-dinitrobenzoate, m. p. 107° , $[\alpha]_D^{13} + 52.8^\circ$. When heated under reflux with 5% methyl-alcoholic potassium hydroxide (140 c.c.) for 40 minutes, this ester (30 g.) yielded *d*-carvomenthol (11.8 g.) having b. p. $101.8-102.0^\circ/14$ mm.; $n_D^{12} 1.4650$, $n_D^{17} 1.4629$; $d_4^{18} 0.9056$; $\alpha_D^{13} + 25.08^\circ$, $[\alpha]_D^{13}$

+ 27.69°; $[R_L]_D$ 47.62 (calc. 47.70) (Found : C, 76.4; H, 12.8. $C_{10}H_{20}O$ requires C, 76.8; H, 12.9%). This alcohol was oxidised by Beckmann's reagent to *l*-carvomenthone having $[\alpha]_D^{17} - 6.0^\circ$ (J., 1934, 229).

(2) A solution of palladium chloride (0.2 g.) in hot distilled water (20 c.c.) containing 3 drops of 2*N*-hydrochloric acid was mixed with gum-arabic (0.4 g.) in water (100 c.c. at 60–70°), together with *d*-dihydrocarveol (16 g.; $[\alpha]_D + 34.2^\circ$; J., 1934, 236). Upon hydrogenating in the usual way, practically the full amount of hydrogen was absorbed within 5 minutes. The resulting *d*-carvomenthol formed the exclusive product of the reaction, and had b. p. 104–105°/17 mm., n_D^{20} 1.4617, d_4^{20} 0.8995, $\alpha_D^{15} + 23.71^\circ$, $[\alpha]_D^{15} + 26.35^\circ$, $[R_L]_D$ 47.65.

(3) *d*-*cis*-Carveol (24 g., $[\alpha]_D^{25} + 23.9^\circ$; J., 1934, 235 *) was submitted to two successive hydrogenations in methyl alcohol (120 c.c.) with a 2% palladised calcium carbonate catalyst (6 g.). The product (19.4 g.) had n_D^{15} 1.4665, $\alpha_D^{15} + 4.32^\circ$ ($l = 1$), b. p. 102–105°/18 mm. The derived crude 3 : 5-dinitrobenzoate (43 g.) had $[\alpha]_D + 23.2^\circ$ (c 2.0, chloroform); after several recrystallisations, long, pale yellow needles were obtained, with $[\alpha]_D + 51.0^\circ$ (7.2 g.), and the liberated *d*-carvomenthol had n_D^{17} 1.4632, $\alpha_D^{17} + 23.44^\circ$. This was converted into *d*-carvomenthyl hydrogen phthalate, which crystallised readily from light petroleum (b. p. 60–80°) in clusters of transparent six-sided leaflets or prisms, m. p. 90–91°, $[\alpha]_D + 57.8^\circ$ (c 2.0, alcohol) (Found : C, 71.1; H, 8.1. $C_{18}H_{24}O_4$ requires C, 71.0; H, 8.0%). The mother-liquors from the above 3 : 5-dinitrobenzoate contained *l*-neoisocarvomenthyl 3 : 5-dinitrobenzoate (see below).

When boiled for 2 hours with acetic anhydride (40 c.c.) and anhydrous sodium acetate (1 g.), *d*-*cis*-carveol (8 g.) gave *d*-*cis*-carveyl acetate, $\alpha_D^{15} + 46.4$ ($l = 1$); upon hydrogenation as described under (2), this yielded a mixed product consisting chiefly of *d*-carvomenthyl acetate.

(4) From *l*-carvomenthone (see below).

d-Carvomenthyl Esters.—The 3 : 5-dinitrobenzoate, obtained in 97% yield, crystallises from alcohol-ethyl acetate in long needles with a faint yellow tinge, m. p. 107°, $[\alpha]_D^{13} + 52.8^\circ$ (c 2.0, chloroform) (Found : C, 58.2; H, 6.3. $C_{17}H_{22}O_6N_2$ requires C, 58.3; H, 6.3%). The *p*-nitrobenzoate separates from alcohol in flat rectangular prisms with a faint yellow tinge, m. p. 60°, $[\alpha]_D^{17} + 51.7^\circ$ (c 2.0, chloroform) (Found : C, 66.6; H, 7.5. $C_{17}H_{23}O_4N$ requires C, 66.8; H, 7.6%). The *l*-menthoxyacetate is a thin, transparent syrup, $[\alpha]_D^{15} - 18.1^\circ$ (c 2.0, chloroform); the *d*-menthoxyacetate is an oil, $[\alpha]_D^{15} + 93.4^\circ$. The *d*-camphor-10-sulphonate is a thick syrup, $[\alpha]_D^{15} + 59.6^\circ$; when heated to 164–165° it decomposes into *l*- Δ^1 -menthene and *d*-camphor-10-sulphonic acid. The *l*-camphor-10-sulphonate is very soluble in alcohol, from which it crystallises in elongated prisms, m. p. 57–58°, $[\alpha]_D^{15} + 8.0^\circ$; when heated to 166° it decomposes, yielding *l*- Δ^1 -menthene and *l*-camphor-10-sulphonic acid.

l-neocarvomenthol.—(1) *l*-neocarvomenthylamine hydrochloride (14.7 g., $[\alpha]_D^{16} - 31.9^\circ$ in water; J., 1934, 231), when treated with nitrous acid as above, gave an oil which yielded the following fractions : b. p. 59–95°/16 mm., n_D^{14} 1.4573, $\alpha_D^{14} - 40.46^\circ$ (6.0 g.); b. p. 95–99°/16 mm., n_D^{14} 1.4618, $\alpha_D^{14} + 1.96^\circ$ (1.75 g.). The first fraction appeared to consist mainly of *l*- Δ^1 -menthene. Much of the *d*-carvomenthol present in the second fraction was removed by partial esterification with *p*-nitrobenzoyl chloride. The unesterified *l*-rotatory alcohol was converted into 3 : 5-dinitrobenzoate; this, when recrystallised, yielded a product with m. p. 126–127°, $[\alpha]_D - 16.0^\circ$ (c 2.0, chloroform), which showed no depression in m. p. when mixed with an authentic specimen of *l*-neocarvomenthyl 3 : 5-dinitrobenzoate (see below). The respective proportions of *d*-carvomenthol and *l*-neocarvomenthol indicated by the rotatory power of the crude second fraction are about 60% and 40%.

(2) When *l*-neodihydrocarveol ($\alpha_D^{14} - 33.22^\circ$; J., 1934, 237) was hydrogenated in presence of a palladium catalyst, as described under (2) above, it was converted readily into *l*-neocarvomenthol, b. p. 95–96°/11.5 mm., n_D^{18} 1.4652, $\alpha_D^{18} - 35.0^\circ$; this yielded the characteristic 3 : 5-dinitrobenzoate, m. p. 129°.

(3) (a) *d*-*trans*-Carveol (10 g., $\alpha_D + 201^\circ$; J., 1934, 235), when hydrogenated in presence of the palladium catalyst indicated under (2) above, absorbed more than the calculated amount of hydrogen. Most of the product distilled below 90°/9 mm., and appeared to consist largely of *p*-menthane. The alcohol fraction (2.8 g.) had n_D^{15} 1.4647, $\alpha_D - 20.72^\circ$.

* It is advantageous to replace *isopropyl* alcohol by *isobutyl* alcohol in reducing carveone to a mixture of *cis*- and *trans*-carveol. With *isobutyl* alcohol and aluminium *isobutoxide* reduction reached 75–80% in 8 hours and the crude product had $\alpha_D + 102$ –107° ($l = 1$), whereas with *isopropyl* alcohol these values were often much lower. In certain experiments with aluminium *isopropoxide* which had been distilled 3 times, the reduction reached only about 50%, and the crude product, which appeared to contain a larger proportion of *cis*-carveol than usual, had $\alpha_D + 56$ –62°.

Only partial hydrogenations of *d-trans*-carveyl benzoate (75%), *p*-nitrobenzoate (65%) and 3 : 5-dinitrobenzoate (45%) were possible under the conditions adopted. *d-trans*-Carveyl acetate (18 g., $\alpha_D^{14} + 177.5^\circ$), dissolved in pure ether (50 c.c.), readily absorbed (2 hours) the calculated amount of hydrogen when treated similarly. The product, when hydrolysed and steam-distilled, furnished a liquid (14.8 g.) which yielded two fractions upon distillation in a vacuum: the first (3.3 g.), collected up to $90^\circ/8.5$ mm., consisted chiefly of *l*- Δ^1 -menthene; the second (6.1 g.) had b. p. $90\text{--}93^\circ/8.5$ mm., $n_D^{14} 1.4658$. When esterified with 80% of the calculated amount of *p*-nitrobenzoyl chloride, the second fraction yielded a crude ester (6.5 g., $[\alpha]_D + 56^\circ$) which could not be separated into its constituents by fractional crystallisation, owing to the formation of mixed crystals (m. p. 88.5° , $[\alpha]_D + 87.2^\circ$). The unesterified part of the second fraction readily gave colourless needles of pure *l-neocarvomenthyl 3 : 5-dinitrobenzoate*, m. p. 129° , $[\alpha]_D - 22.6^\circ$ (*c* 2.0, chloroform), when the product of reaction with 3 : 5-dinitrobenzoyl chloride was crystallised from alcohol (Found: C, 58.4; H, 6.3. $C_{17}H_{22}O_6N_2$ requires C, 58.3; H, 6.3%). The *l-neocarvomenthol* derived from this ester by hydrolysis had b. p. $90^\circ/9$ mm., $n_D^{18} 1.4641$, $\alpha_D^{16} - 36.42^\circ$. The derived *p*-nitrobenzoate had m. p. 95° , $[\alpha]_D^{16} - 22.1^\circ$ (*c* 2.0, chloroform). The mixture of alcohols obtained by hydrogenating *d-trans*-carveol in this way contained more than 30% of *l-neocarvomenthol*.

(b) *d-trans*-Carveol (90 g., $[\alpha]_D^{25} + 198.0^\circ$) was hydrogenated in methyl alcohol in presence of 2% palladised calcium carbonate. The reduction was more difficult than that of *d-cis*-carveol (see above), three successive treatments being necessary. Slight dehydration occurred during the process, a terpene fraction being obtained on distilling the crude product. The alcoholic fraction (97 g.) had $\alpha_D - 12.25^\circ$ (*l* = 1), $n_D^{19} 1.4658$. Fractional crystallisation of the *p*-nitrobenzoate made from this material gave crude *l-neocarvomenthyl p*-nitrobenzoate (30 g.), m. p. $92\text{--}93^\circ$, $[\alpha]_D - 1^\circ$ (*c* 2.0, chloroform). The derived 3 : 5-dinitrobenzoate, after several recrystallisations, yielded pure *l-neocarvomenthyl 3 : 5-dinitrobenzoate* (17 g.), m. p. 129° , $[\alpha]_D - 22.0^\circ$ (*c* 2.0, chloroform). *l-neocarvomenthol*, obtained by saponifying this ester, had $\alpha_D^{17} - 36.46^\circ$ (*l* = 1), $n_D^{17} 1.4642$. The mother-liquors from the crystallisation of the above crude *p*-nitrobenzoate contained some *l-isocarvomenthyl p*-nitrobenzoate (see below).

(4) Crude *l*-carvomenthone, obtained by hydrogenating *d*-carvone, was treated with alcoholic sodium ethoxide (J., 1934, 229) and then converted via *l*-carvomenthone oxime into *d*-carvomethylamine hydrochloride. The crude deamination product of this base (see above) was benzoylated; the distilled benzoyl derivative, b. p. $188\text{--}190^\circ/15$ mm., when saponified gave a mixture of carvomenthols having $n_D^{19} 1.4621$, $\alpha_D^{19} + 22.36^\circ$. Oxidation with Beckmann's chromic acid mixture yielded a purified *l*-carvomenthone, having b. p. $98.5^\circ/18$ mm., $n_D^{17} 1.4550$, $\alpha_D^{17} - 7.80^\circ$ (*loc. cit.*). The crude mixture of alcohols obtained by reducing this ketone in the usual way (J., 1934, 235) with aluminium *isopropoxide* had b. p. $103\text{--}106^\circ/18$ mm., $n_D^{22} 1.4612$, $\alpha_D^{22} - 2.00^\circ$, thus corresponding to a mixture of about 57% *d*- and 43% *l-neo*-carvomenthol. When treated in pyridine with half the calculated quantity of *p*-nitrobenzoyl chloride, this yielded crude *d*-carvomenthyl *p*-nitrobenzoate, and the unchanged alcohol contained about 69% *l-neocarvomenthol*.

The unesterified alcohol had $n_D^{24} 1.4621$, $\alpha_D^{24} - 16.15^\circ$, and was shown to contain *l-neocarvomenthol*. In reaction with *p*-nitrobenzoyl chloride it furnished an ester which gave colourless leaflets of pure *l-neocarvomenthyl p*-nitrobenzoate, m. p. 95° , $[\alpha]_D - 22.8^\circ$ (*c* 2.0, chloroform), after four recrystallisations from alcohol (Found: C, 66.7; H, 7.5. $C_{17}H_{23}O_4N$ requires C, 66.8; H, 7.6%). *l-neocarvomenthol*, obtained by hydrolysing this ester with 5% methyl-alcoholic potassium hydroxide, had b. p. $102^\circ/18$ mm., $n_D^{20} 1.4632$, $d_4^{20} 0.9012$, $[R_L]_D 47.64$ (calc. 47.70), $\alpha_D^{21} - 37.58^\circ$, $[\alpha]_D^{21} - 41.70^\circ$. It is a viscous liquid with a somewhat nauseous odour, reminiscent of *d-trans*-carveol and *l-neodihydrocarveol*; the vapour has a powerful mentholic odour when diffused in steam (Found: C, 76.5; H, 12.7. $C_{10}H_{20}O$ requires C, 76.8; H, 12.9%).

When oxidised with Beckmann's mixture, *l-neocarvomenthol* yielded *l*-carvomenthone with $\alpha_D^{17} - 8.02^\circ$ (*l* = 1), $n_D^{17} 1.4552$. *l-neocarvomenthyl hydrogen phthalate* is much less soluble in light petroleum than *d*-carvomenthyl hydrogen phthalate (see above); after four recrystallisations it was obtained in colourless needles, m. p. $123\text{--}124^\circ$, $[\alpha]_D - 48.7^\circ$ (*c* 2.0, alcohol).

dl-neocarvomenthol.—A solution of *dl-trans*-carveol (18 g.; J., 1934, 236) in a mixture of methyl alcohol (150 c.c.) and water (50 c.c.) was hydrogenated under a pressure of 4 atm. in presence of 2% palladised calcium carbonate (8 g.; cf. Busch, *Ber.*, 1916, 49, 1063; 1929, 62, 1458). After an induction period of 10 minutes, the calculated amount of hydrogen was absorbed in 50 minutes. The steam-distilled product (17.2 g.), apart from a small fraction containing

terpene (0.9 g., b. p. 65—105°/20 mm.), distilled completely at 105—109°/20 mm.; the distillate had n_D^{18} 1.4650. Hence, little dehydration occurred with this catalyst.

The latter fraction (16.0 g.), when esterified in pyridine solution with half the calculated quantity of *p*-nitrobenzoyl chloride, yielded crude *dl*-isocarvomenthyl *p*-nitrobenzoate (11.6 g.; see below). The unesterified alcohol had n_D^{20} 1.4629; the derived *p*-nitrobenzoate (19.0 g.), after being twice recrystallised from alcohol, yielded a fraction (5.6 g.) which retained its characteristics after further recrystallisation. This ester was regarded as pure *dl*-neocarvomenthyl *p*-nitrobenzoate: it consisted of a bulky mass of light leaflets, m. p. 91—92° (Found: C, 66.6; H, 7.7. $C_{17}H_{22}O_4N$ requires C, 66.8; H, 7.6%). When hydrolysed in the usual way it yielded *dl*-neocarvomenthol, a viscous liquid which did not solidify at -12°; n_D^{20} 1.4637. The *dl*-alcohol has the odour of the *l*-form, but in a milder degree; when vaporised, it has a pungent mentholic aroma. *dl*-neocarvomenthyl 3:5-dinitrobenzoate crystallises from alcohol in small leaflets, m. p. 101°.

l-isocarvomenthol.—(1) When hydrogenated in presence of 2% palladised calcium carbonate, *d*-*trans*-carveol (120 g.) yielded a mixture of *l*-*neo*- and *l*-*iso*-carvomenthol (3*b*, above). The mother-liquors from the recrystallisation of the *p*-nitrobenzoate derived from the original product of hydrogenation furnished a small quantity (6 g.) of fine, pale yellow needles, m. p. 64.5°, $[\alpha]_D - 27.3^\circ$ (*c* 2.0, chloroform). The *p*-nitrobenzoate remaining after the removal of these needles and the crude *l*-neocarvomenthyl *p*-nitrobenzoate was saponified. The resulting alcohol (51 g.), having $\alpha_D^{19} - 10.85^\circ$ (*l* = 1), n_D^{19} 1.4660, was re-esterified with 3:5-dinitrobenzoyl chloride in pyridine. Fractional crystallisation of the resulting ester from alcohol-ethyl acetate gave *l*-isocarvomenthyl 3:5-dinitrobenzoate (22.7 g.) in the form of stout, pale yellow needles, m. p. 111°, $[\alpha]_D - 26.7^\circ$ (*c* 2.0, chloroform) (Found: C, 58.7; H, 6.4. $C_{17}H_{22}O_6N_2$ requires C, 58.3; H, 6.3%). Saponification yielded *l*-isocarvomenthol, b. p. 106°/17 mm.; n_D^{14} 1.4683, n_D^{20} 1.4662; d_{20}^{20} 0.9133, d_4^{20} 0.9109; $\alpha_D^{16} - 16.14^\circ$, $[\alpha]_D^{16} - 17.72^\circ$; $[R_L]_D$ 47.54 (calc. 47.70). This alcohol was more viscid than *d*-carvomenthol or *l*-neocarvomenthol, but it did not crystallise at -25°; its odour is the most mentholic of all the carvomenthols. The derived *p*-nitrobenzoate, m. p. 64.5°, was identical with the fine, pale yellow needles described above.

(2) In Part I of this series (J., 1934, 232), a supposed carvomethylamine was mentioned, which gave a benzoyl derivative having m. p. 151—152°, $[\alpha]_D - 38.8^\circ$ (*c* 2.0, chloroform). Further work indicates that this was slightly impure *l*-isocarvomethylamine (see below). Upon treatment with nitrous acid in the usual way, the hydrochloride of this base (7.6 g., $[\alpha]_D - 11.8^\circ$ in water) gave an oily product. When distilled, this yielded two fractions with the following characteristics: b. p. to 98°/21 mm., n_D^{23} 1.4520 (1.5 g.); b. p. 98—105°/21 mm., n_D^{23} 1.4598, $\alpha_D - 14.96^\circ$ (*l* = 1). The second fraction gave a solid 3:5-dinitrobenzoate (4.7 g.) having $[\alpha]_D - 17.8^\circ$ (*c* 2.0, chloroform); after two recrystallisations from alcohol, a fraction (0.35 g.) was obtained having $[\alpha]_D - 25.5^\circ$, m. p. 107°, not depressed when the material was mixed with the above *l*-isocarvomenthyl 3:5-dinitrobenzoate of m. p. 111°, $[\alpha]_D - 26.7^\circ$ (Found: C, 58.1; H, 6.3%).

dl-isocarvomenthol.—Crude *dl*-isocarvomenthyl *p*-nitrobenzoate (11.6 g.) obtained in the hydrogenation of *dl*-*trans*-carveol (see above), when twice recrystallised from alcohol, yielded *dl*-isocarvomenthyl *p*-nitrobenzoate, m. p. 85.5°, in the form of hard prisms with a pale yellow tinge. When hydrolysed with hot 5% methyl-alcoholic potassium hydroxide, the ester gave *dl*-isocarvomenthol, b. p. 110°/20 mm., n_D^{18} 1.4669, d_4^{20} 0.904. Although the alcohol became very viscous at -12°, it did not solidify. *dl*-isocarvomenthyl 3:5-dinitrobenzoate crystallised from alcohol in colourless leaflets, m. p. 94.5° (Found: C, 58.7; H, 6.5. $C_{17}H_{22}O_6N_2$ requires C, 58.3; H, 6.3%).

l-neoisocarvomenthol.—As indicated above, *d*-*cis*-carveol, when hydrogenated in methyl alcohol in presence of 2% palladised calcium carbonate, yielded a mixture of carvomenthols from which nearly pure *d*-carvomenthol was isolated in the form of long, pale yellow needles of the 3:5-dinitrobenzoate. The mother-liquors from this ester yielded fractions consisting of a mixture of needles and leaflets, which were partly separated by hand. Systematic recrystallisation from alcohol yielded a small quantity (3.3 g.) of leaflets having $[\alpha]_D - 15.6^\circ$ (*c* 2.0, chloroform); a final recrystallisation gave large, five-sided leaflets with a pale greenish-yellow tinge, m. p. 71—72°, $[\alpha]_D - 16.0^\circ$, which were regarded provisionally as *l*-neoisocarvomenthyl 3:5-dinitrobenzoate (Found: C, 57.9; H, 6.4. $C_{17}H_{22}O_6N_2$ requires C, 58.3; H, 6.3%). The derived *l*-neoisocarvomenthol had a viscosity similar to that of *l*-isocarvomenthol, and it failed to solidify at -25°. The odour was distinct from that of *l*-isocarvomenthol. The following constants were observed: n_D^{18} 1.4689, n_D^{20} 1.4676; d_{20}^{20} 0.9127, d_4^{20} 0.9102; $\alpha_D^{17} - 31.70$, $[\alpha]_D^{17}$

— 34.7°; $[R_L]_D$ 47.66 (calc. 47.70). The derived *p*-nitrobenzoate was very soluble and given to supercooling: it separated from methyl alcohol in long, almost colourless needles, m. p. 54—55°, $[\alpha]_D - 23.7^\circ$ (*c* 2.0, chloroform). It behaved as a homogeneous substance upon fractional recrystallisation (Found: C, 66.2; H, 7.4. $C_{17}H_{23}O_4N$ requires C, 66.8; H, 7.6%).

l-isoCarvomenthone.—When oxidised with Beckmann's reagent, *l*-isocarvomenthol having $[\alpha]_D^{16^\circ} - 17.72^\circ$ yielded a limpid liquid resembling carvomenthone (J., 1934, 229) in odour and having the following physical constants: $n_D^{18.5^\circ} 1.4562$, $n_D^{20^\circ} 1.4558$; $d_4^{20^\circ} 0.9042$; $\alpha_D^{20^\circ} - 51.12^\circ$, $[\alpha]_D^{20^\circ} - 56.5^\circ$.

The oxime was a very viscid syrup which could not be obtained crystalline: it had $[\alpha]_D - 79.5^\circ$ (*c* 2.0, alcohol). When reduced with sodium in absolute alcohol, the oxime gave a base from which pure benzo-*l*-isocarvomethylamide, m. p. 153°, was readily prepared; the crude hydrochloride of this base had $[\alpha]_D - 15.0^\circ$ (*c* 2.0, water).

l-isoCarvomenthone semicarbazone in the crude state had m. p. 166—172°, $[\alpha]_D - 115.8^\circ$ (*c* 2.0, chloroform); the microcrystalline powder obtained after three crystallisations from methyl alcohol had m. p. 171—172°, $[\alpha]_D - 117.0^\circ$ (Found: C, 62.7; H, 9.9. $C_{11}H_{21}ON_3$ requires C, 62.5; H, 10.0%).

Some of the above ketone having $\alpha_D^{20^\circ} - 51.12^\circ$ ($l = 1$) was kept for 16 hours in cold alcoholic sodium ethoxide: the recovered ketone had $\alpha_D^{20^\circ} - 15.24^\circ$, $[\alpha]_D^{20^\circ} - 16.9^\circ$, and thus contained about 79% *l*-carvomenthone and 21% *l*-isocarvomenthone (cf. J., 1934, 229).

l-isoCarvomethylamine.—(1) This may be prepared by reducing the viscid oxime of *l*-isocarvomenthone, as indicated above.

(2) Syrupy material obtained as a by-product in the preparation of crystalline *l*-carvomenthone oxime (J., 1934, 230, 232) had $[\alpha]_D^{17^\circ} - 48.0^\circ$ (*c* 2.0, alcohol). When reduced (44 g.) with sodium in absolute alcohol, it yielded a basic product which formed a hydrochloride (39 g.) having $[\alpha]_D - 7.2^\circ$ (*c* 2.0, water). The derived hydrogen *d*-tartrate (57 g.) had $[\alpha]_D + 8.1^\circ$. After 7 successive crystallisations from aqueous methyl alcohol (2:1), this furnished opaque, satiny needles (3.1 g.) of an apparently homogeneous substance with m. p. 179°, $[\alpha]_D + 5.3^\circ$ (*c* 2.0, water), consisting presumably of *l*-isocarvomethylamine hydrogen *d*-tartrate (Found: C, 53.8; H, 9.2. $C_{14}H_{27}O_6N$, $0.5H_2O$ requires C, 53.5; H, 9.0%).

l-isoCarvomethylamine, liberated from this salt, had b. p. 90°/15 mm., $n_D^{16^\circ} 1.4642$, $n_D^{25^\circ} 1.4611$; $d_4^{25^\circ} 0.8587$; $\alpha_D^{18^\circ} - 12.66^\circ$, $[\alpha]_D^{18^\circ} - 14.7^\circ$; $[R_L]_D 49.55$ (calc. 49.53).

The hydrochloride had $[\alpha]_D - 14.3^\circ$ (*c* 2.0, water); the acetyl derivative crystallised from acetone in transparent, fragile needles, m. p. 96°, $[\alpha]_D - 57.4^\circ$ (*c* 2.0, chloroform); the benzoyl derivative separated from ethyl acetate in large transparent needles, m. p. 153°, $[\alpha]_D - 40.7^\circ$ (Found: C, 78.5; H, 9.4. $C_{17}H_{25}ON$ requires C, 78.7; H, 9.7%).

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THE UNIVERSITY, ST. ANDREWS.

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