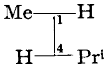
35. *Researches in the Carvone Series. Part V.* Configurations of Carvomenthones and Carvomenthylamines and their Steric Relation to Menthones.*

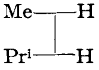
By NEAL L. MCNIVEN and JOHN READ.

Carvomenthyltrimethylammonium hydroxide prepared from (—)-carvomenthone gives on pyrolysis (—)-*trans*-*p*-menth-2-ene of high optical purity. This result is used to supply further evidence for the accepted configurations of the carvomenthones, carvomenthylamine, and *neo*carvomenthylamine, and to establish the stereochemical relationship between the menthone and carvomenthone series. By relating (—)-menthone and (—)-carvomenthone to the same optically active *trans*-*p*-menth-2-ene it has been established that (—)-menthone is related configurationally to (+)-carvomenthone.

JOHNSTON AND READ (*J.*, 1935, 1138) prepared optically pure carvomenthone and *iso*carvomenthone and determined some of their physical properties. Application of von Auwers's rule (*Annalen*, 1920, **420**, 92) led to the conclusion that (—)-carvomenthone had the *trans*-configuration (I), and the configurationally related (—)-*iso*carvomethone the *cis*-configuration (II) :



(I) (—)-Carvomenthone



(II) (—)-*iso*Carvomenthone

No further evidence has hitherto been forthcoming for the configurations of the carvomenthones; in this respect the carvomenthones have not been so fully investigated as the menthones.

Four optically active carvomenthols have been prepared (Johnston and Read, *loc. cit.*). (+)-Carvomenthol and (—)-*neo*carvomenthol have been well characterised and have been shown to be related to (—)-carvomenthone. The remaining pair, (—)-*iso*carvomenthol and (—)-*neoiso*carvomenthol, have not been characterised with as great certainty, but (—)-*iso*carvomenthol has been shown to be related to (—)-*iso*carvomenthone. Preliminary investigations by Johnston and Read showed that (+)-carvomenthol reacted more rapidly than (—)-*neo*carvomenthol with acid chlorides. If steric hindrance by the methyl group is the main factor deterring esterification, the hydroxyl group on carbon atom 2 must be assigned the *cis*-position to the methyl group in (—)-*neo*carvomenthol and the *trans*-position in (+)-carvomenthol.

Three of the corresponding carvomenthylamines have been prepared. The fourth, *neoiso*carvomenthylamine, has not yet been isolated. Hückel and Wilip (*J. pr. Chem.*, 1941, **158**, 21) showed that (—)-*neo*carvomenthylamine, prepared by catalytic hydrogenation of the oxime of (—)-carvomenthone, on treatment with nitrous acid gave a mixture of carvomenthols and a menthene. This menthene was found to contain (—)-*p*-menth-1-ene, racemised *p*-menthene, and 18% of a lævorotatory menthene resistant to racemisation by toluene-*p*-sulphonic acid. As Hückel and Tappe (*Annalen*, 1939, **537**, 126) have shown, the last menthene must be either *trans*- or *cis*-*p*-menth-2-ene. If, on the basis of von Auwers's rule, carvomenthone is considered to have the *trans*-configuration, the menthene in question must be (—)-*trans*-*p*-menth-2-ene. Since (—)-menthone leads to the formation of (+)-*trans*-*p*-menth-2-ene (McNiven and Read, foregoing paper), it follows that (—)-menthone must be related configurationally to (+)-carvomenthone.

The present investigation shows the stereochemical relations between menthone and carvomenthone without requiring the assumption of a *trans*-configuration for carvomenthone. In fact, it supplies additional evidence for the configuration of carvomenthone.

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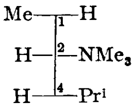
* Part IV, *J.*, 1937, 239.

In addition, a proof for the configuration of the groups on carbon atom 2 of carvomenthylamine and *neo*carvomenthylamine is provided.

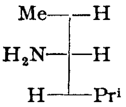
A menthene of high optical purity was prepared from (—)-carvomenthone *via* the quaternary ammonium hydroxide by using the method of Read and Hendry (*Ber.*, 1938, **71**, 2544) with some modifications. The *p*-menthene had $[\alpha]_D^{15}$ —139·5° (*c*, 1·9 in ethanol), which was unaffected by refluxing the hydrocarbon with toluene-*p*-sulphonic acid (showing the absence of active *p*-menth-1-ene). Read and Hendry (*loc. cit.*) reported the value $[\alpha]_D^{17}$ +149·7° (*c*, 1·6 in alcohol) for (+)-*trans*-*p*-menth-2-ene. Since no decrease in rotation occurred on treatment with toluene-*p*-sulphonic acid, the terpene concerned must be a *p*-menth-2-ene; moreover, since *cis*-*p*-menth-2-ene has a much lower optical activity (McNiven and Read, previous paper; Hückel and Wagner, *Ber.*, 1941, **74**, 657), this terpene must be (—)-*trans*-*p*-menth-2-ene.

Thus it has been shown that (—)-carvomenthone is configurationally related to (—)-*trans*-*p*-menth-2-ene. It can therefore be concluded that (—)-carvomenthone has the *trans*-configuration. In addition it has already been shown by Read and Hendry (*loc. cit.*) that (—)-menthone is configurationally related to (+)-*trans*-*p*-menth-2-ene. Accordingly, (—)-menthone and its related compounds must belong to the same steric series as (+)-carvomenthone, thus confirming Hückel's conclusion (*J. pr. Chem.*, 1941, **158**, 21).

Since quaternary ammonium hydroxides on thermal decomposition form olefins by a bimolecular ionic mechanism dependent on *trans*-elimination (Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2117), the exclusive formation of (—)-*trans*-*p*-menth-2-ene from carvomenthyltrimethylammonium hydroxide can occur only if the configuration of the groups on carbon atom 2 is as shown in (III) :



(III)



(IV)

It follows that (+)-carvomenthylamine must have a similar configuration.

Consequent on the establishment of the configuration of this amine, which was obtained by sodium reduction of the oxime of (—)-carvomenthone, the configuration of (—)-*neo*carvomenthylamine obtained by catalytic hydrogenation of the oxime of (—)-carvomenthone (Hückel and Wilip, *loc. cit.*) must be the epimeric form shown in (IV) with the amino-group on carbon atom 2 in the *cis*-position to the methyl group.

EXPERIMENTAL

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

Carvomenthyltrimethylammonium Hydroxide.—(+)-Carvone (240 g.), $[\alpha]_D^{16}$ +53·60° (*l* = 1 dm.; homogeneous) in methanol (500 ml.) was hydrogenated, 2 teaspoonsfuls of Raney nickel catalyst being used. After 3 hours at room temperature the absorption of hydrogen stopped when one molecular equivalent had been added. After the temperature had been raised to 90° the second molecular equivalent was taken up in a further 3½ hours. The resulting (—)-carvomenthone (221 g., 90%), $[\alpha]_D^{16}$ —24·29° (*l* = 1 dm.; homogeneous) was brought to the equilibrium mixture (Read and Johnston, *J.*, 1934, 230) by allowing it to stand at room temperature for 19 hours in sodium ethoxide solution (42 g. of sodium in 1 l. of ethanol). The resulting carvomenthone mixture, $[\alpha]_D^{16}$ —13·41° (*l* = 1 dm.; homogeneous), and hydroxylamine acetate in ethanol at room temperature (24 hours) gave crystalline (—)-carvomenthone oxime (130 g., 62·5%), m. p. 97—98°, $[\alpha]_D^{16}$ —39·3° (*c*, 1·27 in ethanol). This oxime (67 g.) was reduced by sodium and ethanol, Wallach's procedure (*Annalen*, 1893, **276**, 301) being used, to carvomenthylamine (58 g., 94%). The hydrochloride after 4 recrystallisations from ethyl acetate had the constant rotation $[\alpha]_D^{17}$ +11·0° (*c*, 2·2 in water). The benzoyl derivative had m. p. 165°, $[\alpha]_D^{16}$ +41·0° (*c*, 1·17 in chloroform). Read and Johnston (*loc. cit.*) reported $[\alpha]_D^{16}$ +12·2° for the hydrochloride, and m. p. 161°, $[\alpha]_D^{25}$ +45·1° for the benzoyl derivative. The free carvomenthylamine liberated from the above hydrochloride (5·3 g.) was converted into (+)-carvomenthyltrimethylammonium iodide (7·1 g., 95%) by the method used for (—)-menthylamine by McNiven and Read (foregoing paper); after recrystallising from acetone this gave colourless crystals of (+)-*carvomenthyltrimethylammonium iodide*, m. p. 141°, $[\alpha]_D^{15}$ +24·8° (*c*, 2·18 in water) (Found : I, 39·9. $C_{13}H_{28}NI$ requires I, 39·1%). The iodide was converted into the quaternary ammonium hydroxide by the method described by McNiven and Read (*loc. cit.*) for (—)-menthylamine.

Pyrolysis of Carvomenthyltrimethylammonium Hydroxide.—The above quaternary ammonium hydroxide from 4·7 g. of iodide, after concentration on a steam-bath, was distilled at 166°/20 mm. (bath-temp.). The oily distillate, after being washed with dilute hydrochloric acid and then sodium carbonate solution and dried (Na_2SO_4), gave (—)-*trans*-*p*-menth-2-ene (0·05 g., 3%), $[\alpha]_D^{15}$ —139·5° (*c*, 1·86 in ethanol). An oily base (2·1 g., 80%), probably carvomenthyldimethylamine, was recovered from the acid washings.

Attempted Racemisation of (—)-trans-p-*Menth-2-ene.*—This menthene was refluxed with alcoholic toluene-*p*-sulphonic acid for 4 hours, following Hückel's method (*Annalen*, 1940, **543**, 191). Since the resulting menthene had $[\alpha]_D^{15}$ —142·2° (*c*, 1·10 in ethanol), no racemisation had taken place.

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