[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY, STANFORD, CALIF.]

Terpenoids. XLIX.[1] Preparation of Optically Active Polyalkylcyclohexanones from (+)-Pulegone, (−)-Menthone and (−)-Carvone[2]

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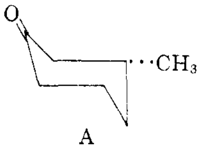
A series of optically active polyalkylated cyclohexanones—suitable for conformational studies by means of optical rotatory dispersion—have been prepared from commercially available terpene intermediates. Starting with (+)-pulegone (I) or in some instances as an alternative with (−)-menthone (VI), there is described *trans*-2,5-dimethyl-2-isopropenyl (or isopropyl or ethyl) cyclohexanone (II, IV, XIX), *cis*-2,5-dimethyl-2-isopropenyl (or isopropyl)-cyclohexanone (III, V) and 2,2,5-trimethylcyclohexanone (XV). The acid-catalyzed addition of methanol to the isopropenyl double bond of (−)-carvone (XXII) has been studied in detail since the resulting methoxyisopropyl substituent (*e.g.*, XXV) can serve as a conformational anchoring group similar to the *t*-butyl function. Optical rotatory dispersion has been used to examine quantitatively the course of the catalytic *vs.* chemical reduction of 3,6-dimethyl-6-isopropyl-Δ^2-cyclohexenone (IX).

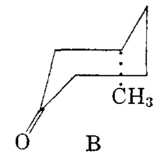
Optical rotatory dispersion[4] has become an useful adjunct in many organic chemical research problems, because frequently the resulting measurements offer information which is either not available or only difficultly so from other physical or chemical approaches. This applies particularly to absolute configurational and conformational studies and it is in these areas that rotatory dispersion has, and probably will, play the most significant role. Our initial empirical conclusions and the subsequent generations such as the "axial haloketone rule"[5] and the "octant rule"[6] were largely based on experimental studies with conformationally frozen steroids[7] and on the recognition[8] that qualitatively the same results would also be obtained with tri- and bi-cyclic molecules, provided that the conformational situation in the immediate environment (usually the bicyclic environment) of the carbonyl chromophore remained unaltered.

In principle, the optical rotatory dispersion information accumulated with the structurally more complicated but stereochemically unambiguous polycyclic model ketones should also be applicable to the conformationally much more difficult case of the monocyclic cyclohexanones. The determination of the preferred conformation in solution of these flexible molecules is one of the most challenging ones of current stereochemical research and *a priori*, rotatory dispersion measurements should represent one of the most sensitive and useful methods for such work. This is so because any conformational change will alter the relative position of the asymmetric substituents with respect to the carbonyl chromophore; the resulting differing interactions usually reflect themselves in the amplitude, shape or sign of the optical rotatory dispersion curve.[9]

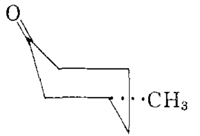
A detailed study of the application of optical rotatory dispersion to conformational problems in the cyclohexanone series requires the preparation of a substantial number of optically active substrates of *known* absolute configuration. The reason for this prerequisite can be illustrated by the following simple example. Suppose that we wish to determine by rotatory dispersion means whether 3-methylcyclohexanone existed in conformation A or B. According to the octant rule,[6] conformer A should exhibit a positive and conformer B a negative Cotton effect. Form C, the antipode of A, also exists in the identical conformation but would, of course, possess a negative Cotton effect, while the converse would apply to D *vs.* B. It follows, therefore, that a conformational problem of this type can be attacked through rotatory dispersion only if the absolute configuration is known.



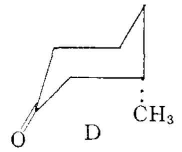
A



B



C



D

Since it would be very laborious to resolve and establish the absolute configuration of the many substituted cyclohexanones required for such measurements, we have selected some readily available terpenes of known absolute configuration[10] as starting materials. The present paper is concerned with the synthetic aspects of our work, while subsequent ones will deal with the interpretation of their rotatory dispersion curves in terms of conformation.[11]

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[1] Paper XLVIII, L. H. Zalkow, F. X. Markley and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 6354 (1960).

[2] We are indebted to the National Institutes of Health for financial assistance in the form of grants No. CRTY-5061 (to Stanford University) and No. CY-2919 (to Wayne State University, where a portion of this research was conducted).

[3] Taken from part of the Ph.D. thesis of Mrs. Jeanne Osiecki, Stanford University, 1960.

[4] C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Gill Book Co., Inc., New York, N. Y., 1960.

[5] C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957).

[6] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *ibid.*, **83**, 4013 (1961). See also chapter 13 in ref. 4 as well as pp. 333–341 by W. Klyne in "Advances in Organic Chemistry" (edited by R. A. Raphael, E. C. Taylor and H. Wynberg), Interscience Publishers, Inc., New York, N. Y., 1960.

[7] *Inter al.*, C. Djerassi, E. W. Foltz and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955); C. Djerassi, W. Closson and A. E. Lippman, *ibid.*, **78**, 3163 (1956); C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956).

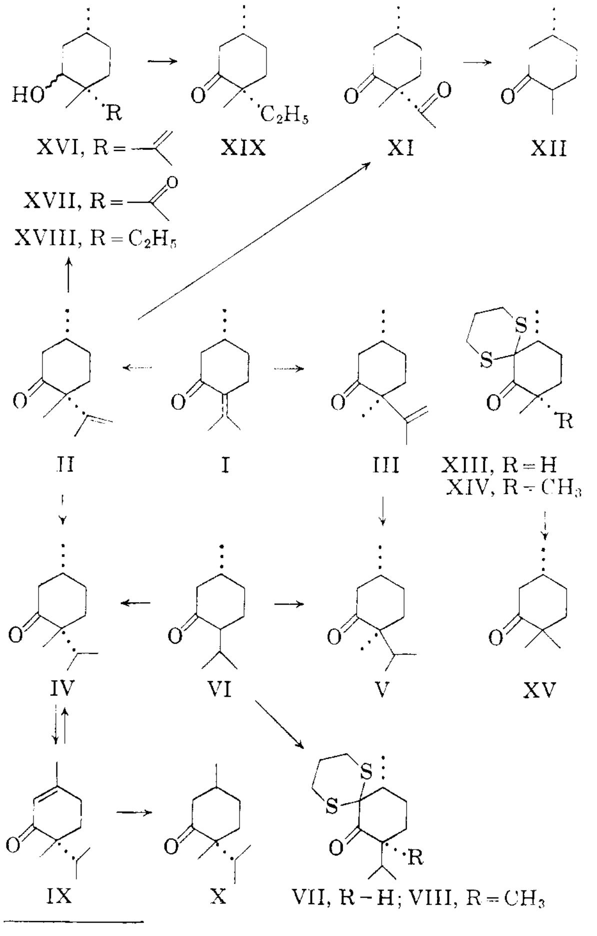
[8] C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362 (1956).

[9] For some recent examples see C. Djerassi, L. E. Geller and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 1 (1960); C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, **83**, 736 (1961); C. Djerassi, R. Records and B. Bach, *Chemistry & Industry*, 258 (1961).

[10] See A. J. Birch, *Ann. Repts. Progr. Chem.*, **47**, 192 (1951).

Of principal interest was the synthesis of a series of optically active cyclohexanones with alkyl substituents alpha or beta to the carbonyl group. Some of these would lend themselves to assignment of quantitative values for certain substituents according to the tenets of the octant rule,[6] while others might uncover unexpected conformational problems.[12] The introduction of *t*-butyl groups (or their equivalents) would afford cyclohexanones of "frozen" conformation[13] and synthetic approaches were sought to typical examples of all these types.

One of the most versatile starting materials for such work is (+)-pulegone (I), the principal constituent of the commercially available oil of pennyroyal. Its absolute configuration is known[10] and acid-catalyzed retroaldolization[14] leads to (+)-3-methylcyclohexanone (A). This represents the parent reference substance in our rotatory dispersion studies of flexible cyclohexanones and it also represents a very convenient entry into optically active halogenated cyclohexanones.[9] 1,4-Addition of various reagents results[14,15] in the generation of a *t*-butyl substituent (or its equivalent) adjacent to the carbonyl group, while methylation occurs virtually exclusively at the C-2 position with concomitant formation of an isopropenyl substituent. It is this reaction which first drew our attention as it appeared to afford a valuable approach to some required 2,2,5-trisubstituted cyclohexanones. The earlier workers[16] had shown that the principal product was (−)-methylisopulegone (2,5-dimethyl-2-isopropenylcyclohexanone), but they did not differentiate between the two possible stereoisomeric possibilities II and III. A tentative preference for III has been expressed by Melera and collaborators,[17,18] who used (−)-methylisopulegone to prepare (+)-*trans*-2,5-dimethylcyclohexanone (XII), the C-2 stereochemistry of the intermediate (II or III) being of no consequence as this asymmetric center is again destroyed. For our purposes—namely relating rotatory dispersion curves with conformation of substituted cyclohexanones—a



XVI, R =

XIX

XI

XII

XVII, R =

XVIII, R = C_2H_5

II

I

III

XIII, R = H

XIV, R = CH_3

IV

VI

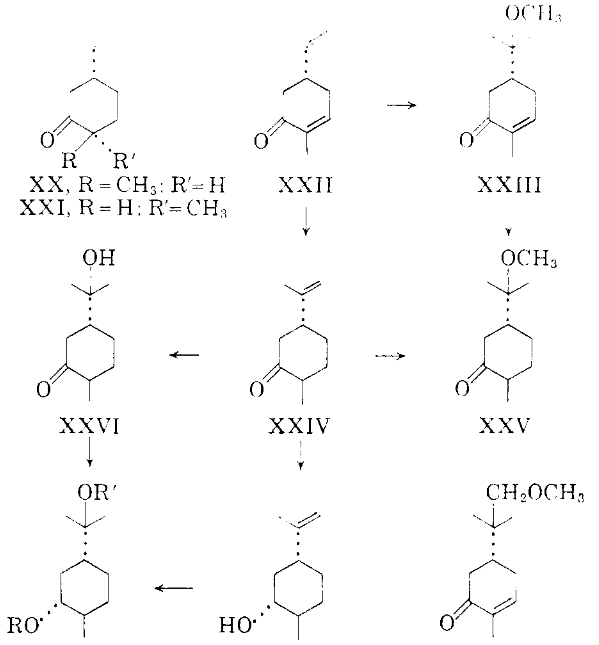
V

XV

IX

X

VII, R = H; VIII, R = CH_3



XX, R = CH_3; R' = H

XXI, R = H; R' = CH_3

XXII

XXIII

XXVI

XXIV

XXV

XXVII, R = R' = H

XXXI

XXXII

XXVIII, R = $C_6H_5CH_2$; R' = H

XXIX, R = $C_6H_5CH_2$; R' = CH_3

XXX, R = H; R' = CH_3

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[11] Some of these results have been reported at a Symposium on Conformational Analysis: C. Djerassi, L. E. Geller, J. Osiecki and E. J. Eisenbraun, Abstracts of A.C.S. Meeting, San Francisco, Calif., April, 1958, p. 30-N.

[12] See for instance ref. 4, p. 106.

[13] S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955). An example of the utility of this "anchoring" device in rotatory dispersion studies has been reported by C. Djerassi, E. J. Warawa, R. E. Wolff and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).

[14] See J. L. Simonsen and L. N. Owen, "The Terpenes," Cambridge University Press, 1953, Vol. I, p. 371.

[15] C. Djerassi, E. J. Warawa, J. M. Berdahl and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 3334 (1961).

[16] G. A. R. Kon and J. H. Nutland, *J. Chem. Soc.*, 3101 (1926); J. M. Conia, *Bull. soc. chim. France*, 943 (1954).

[17] A. Melera, D. Arigoni, A. Eschenmoser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **39**, 441 (1956).

[18] The Swiss investigators (ref. 17) did not offer any justification for their suggested stereochemistry (III). However, in the absence of any other evidence, III would be assumed to be the principal product arising from axial attack of the methyl group upon the anion, whose preferred conformation might be expected to be i.

precise knowledge of the stereochemistry at C-2 was indispensable and, as has been reported elsewhere,[19] the independent establishment of the absolute configuration of C-2 showed that (−)-methylisopulegone is in fact correctly represented by II. Clearly, the stereochemical course of the alkylation is considerably more complicated than might be assumed upon cursory consideration.[18] Catalytic hydrogenation of II led to (+)-dihydromethylisopulegone (IV), which was an important substance for our rotatory dispersion work. Preparative gas phase chromatographic separation of the residue after separation of (−)-methylisopulegone (II) in the form of its semicarbazone afforded an isomer, which was shown below to possess structure III. Analysis of the total crude methylation mixture of pulegone by gas phase chromatography demonstrated that the alkylation product consisted of 83% II and 17% III. Once the two pure isomers were available, it was a simple matter to distinguish between them by rotatory dispersion as II exhibited a strong negative Cotton effect, while III possessed a powerful positive one. That the methyl group in the second isomer (III) had indeed entered at C-2 rather than at C-6 followed from its spectroscopic properties (absence of α,β-unsaturated ketone, presence of terminal methylene group) and from the following independent synthesis of its dihydro derivative V as well as of the latter's antipode (X).

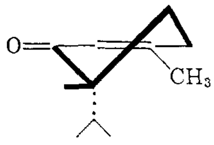
First, there was investigated the direct methylation of (−)-menthone (VI) in the presence of potassium *t*-butoxide. Any C-6 methylation product was separated by condensation with ethyl formate and extraction of the hydroxymethylene ketone with alkali. Cleavage of the hydroxymethylene group with alkali furnished a 2-methylmenthone fraction which according to rotatory dispersion analysis consisted of approximately equal parts of IV and V; this conclusion was confirmed by conversion to the 2,4-dinitrophenylhydrazone and isolation of the pure derivatives of IV and V.

From a preparative standpoint, the direct methylation of menthone was quite unsatisfactory and the following alternative was examined. The C-6 position of menthone (VI) was blocked by treatment[20] of 6-hydroxymethylenementhone with the ditosylate of propane-1,3-dithiol and the resulting dithioketal VII was then methylated with methyl iodide in the presence of potassium *t*-butoxide. Desulfurization with Raney nickel, followed by gas phase chromatographic removal of *ca.* 25% of menthone (arising from unmethylated VII), gave (+)-2-methylmenthone (V) which was identical in all respects with the hydrogenation product V of (+)-methylisopulegone (III). In other words, the predominant stereochemical course of the methylation of pulegone (II) proceeded in the opposite direction from that found with the dithioketal VII.

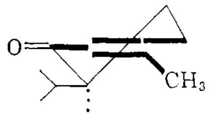
A third and completely rigorous proof of configuration at C-2 of III was developed from (−)-3,6-dimethyl-6-isopropyl-Δ^2-cyclohexenone (IX), which can be prepared[19] by bromination and dehydrobromination of (+)-dihydromethylisopulegone (IV). Catalytic hydrogenation of this α,β-unsaturated ketone gave a separable mixture of (+)-dihydromethylisopulegone (IV) and a new isomer, which possessed a strongly negative Cotton effect and was shown to be the antipode (X) of V. Since X was prepared from (−)-methylisopulegone (II) of established[19] absolute configuration, there can be no doubt about its stereochemistry at C-2, thus leading to the antipodal configuration at that center in its antipode V.

The quantitative aspects of the stereochemical course of the saturation of the double bond of IX are interesting and can be determined very easily by comparing the rotatory dispersion curve of the total reaction mixture with those of the two pure products, IV and X. Such an analysis shows that while the *catalytic hydrogenation* produces approximately 70% of X and 30% of IV, *chemical reduction* of IX with lithium in liquid ammonia resulted in a complete reversal of this isomer ratio, the product consisting of *ca.* 75% of IV and only 25% of X.

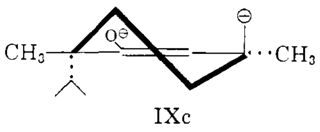
The results of the *catalytic* hydrogenation can be rationalized satisfactorily by assuming that the cyclohexenone IX exists predominantly in conformation IXa and IXb and that adsorption on the catalyst surface and entry of hydrogen occurs from the side opposite to that of the axial substituent. Of the two conformers, IXb is most likely the preferred one (equatorial isopropyl group) and hydrogenation of this form from the α-side (opposite to that of axial methyl group) would produce X, which proved to be the predominant product. A similar analysis in terms of the two most likely conformers[21] IXc and IXd of the presumed intermediate dianion in the *chemical* reduction of IX does not offer a ready explanation for the observed isomer ratio (75% IV *vs.* 25% X) and some very subtle factors appear to be operating here (such as the possible intervention of half-boat rather than half-chair forms). In that connection it should be kept in mind that the energy differences between conformers such as IXc and IXd amount to considerably less than 1 kcal./mol.



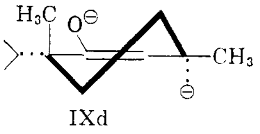
IXa



IXb



IXc



IXd

The above-synthesized optically active cyclohexanones II-V raise some rather complicated

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(19) E. J. Eisenbraun, F. Burian, J. Osiecki and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 3476 (1960).

(20) This blocking agent was introduced by R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(21) It should be emphasized that these representations are idealized ones and that in such cyclohexenes the relevant substituents are not completely axial or equatorial. Furthermore, we are not considering the conformers with the "equatorial anion" because of the apparent need (see G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960)) for overlap between these electrons and the double bond.

problems in conformational analysis[22] and it was deemed important to have available some other *gem* substituents for comparison with the methylisopropenyl (II,III) and methylisopropyl (IV,V) moieties.

The simplest member of this class, (+)-2,2,5-trimethylcyclohexanone (XV) was made by transforming (+)-*trans*-2,5-dimethylcyclohexanone (XII) (available[17] from (−)-methylisopulegone (II) *via* XI) to the dithioketal XIII, methylating it to XIV and then desulfurizing with Raney nickel. For the introduction of an ethyl substituent, (−)-methylisopulegone (II) was reduced with lithium aluminum hydride to the alcohol XVI, ozonized to the methyl ketone XVII and subjected to Wolff–Kishner reduction. The resulting 2,5-dimethyl-2-ethylcyclohexanol (XVIII) was then oxidized to the required (+)-*trans*-2,5-dimethyl-2-ethylcyclohexanone (XIX).

The somewhat unexpected conformational conclusions[12] in the menthone–isomenthone series based on rotatory dispersion measurements made it desirable to extend such measurements to the pair carvomenthone (XX)–isocarvomenthone (XXI).[22] To permit proper interpretation of these data, it was necessary to have available as a reference compound a substance of essentially frozen conformation; in other words, a member of this class with an anchoring group.[13] The obvious candidate—optically active 2-methyl-5-*t*-butylcyclohexanone of known absolute configuration—is not available from a terpene intermediate and its preparation would presumably involve a resolution step and a satisfactory means of settling its absolute configuration. However the methoxyisopropyl moiety $(CH_3)_2\overset{|}{C}(OCH_3)$ should serve essentially the same purpose and such substituents appear to be rather accessible from readily available terpenes. The ready preparation of such optically active cyclohexanones with conformationally suitable anchoring groups seems to have been neglected completely and they might find a number of uses in stereochemical and mechanistic studies.

Treibs[23] has claimed that treatment of carvone (XXII) with methanol and sulfuric acid results in addition of the elements of dimethyl ether (XXXII) and a similar reaction was recorded[23] also for dihydrocarvone (XXIV). Büchi and Erickson[24] have called attention to the unprecedented nature of this reaction and largely on mechanistic grounds have postulated the much more plausible structures XXIII and XXV for these addition products. Since these groupings would serve our purpose in terms of approximately equal steric requirement by comparison with a *t*-butyl function, we have reinvestigated this reaction and are herewith presenting unequivocal evidence in support of Büchi's structures.[24]

Treatment of (−)-carvone (XXII) with methanol and sulfuric acid led in 34% yield to (−)-8-methoxycarvotanacetone (XXIII), which was shown to be homogeneous by gas phase chromatography. Hydrogenation afforded (+)-8-methoxycarvomenthone (XXV), which could also be prepared by the addition of methanol to the isopropenyl double bond of (+)-dihydrocarvone (XXIV). The physical constants were in good agreement for those recorded earlier[23,24] in the antipodal series and our elementary analyses were only consistent with the addition of the elements of methanol[24] rather than of dimethyl ether.[23] The hydration of (+)-dihydrocarvone (XXIV) to (+)-8-hydroxycarvomenthone (XXVI) has already been known for a long time[25] and the latter was selected for the following structure proof. Reduction with lithium aluminum hydride provided the crystalline (−)-8-hydroxycarvomenthol (XXVII), which could be re-oxidized in excellent yield to the ketone XXVI. Alternatively, the diol XXVII could be obtained from (+)-dihydrocarvone (XXIV) by reduction with lithium aluminum hydride and hydration of the resulting dihydrocarveol (XXXI). Conversion of the diol XXVII into the benzyl ether XXVIII now permitted selective methylation of the tertiary hydroxyl group and this was accomplished by transformation to the sodium salt and methylation in dimethylformamide solution. Hydrogenolytic removal of the benzyl grouping of the mixed ether XXIX led to (−)-8-methoxycarvomenthol (XXX), which was identical with the lithium aluminum hydride reduction product of (+)-8-methoxycarvomenthone (XXV), thus completing the latter's proof of structure.

As will be shown elsewhere, the presently described cyclohexanones together with some naturally occurring terpenes, such as the menthones and carvomenthones, represent an important series of compounds which lend themselves to conformational studies by means of rotatory dispersion.

Experimental[26]

(−)-Methylisopulegone (II).[16,27]—Commercial oil of pennyroyal (Fritzsche Bros., New York, 400 cc.) was distilled through a Podbielniak spiral column equipped with a total reflux variable take-off head and the fractions with b.p. 115–118° (25 mm.) (71 g.) and 118–128° (26 mm.) (118 g.) were combined and purified by preparative gas phase chromatography using a Beckman Megachrom instrument with Ucon Polar packing and a temperature of 180°. The resulting (+)-pulegone (I) was redistilled and the material (117 g.) with the following constants was used for the subsequent alkylation: b.p. 117° (27 mm.), $\alpha^{27}D$ +23.6° (neat), $n^{26}D$ 1.4835, λ_{max}^{EtOH} 253 mμ (ϵ 7370).

The methylation was performed by adding 87.5 cc. of *t*-amyl alcohol to 20.3 g. of sodium ribbon in 336 cc. of dry benzene and heating under reflux until all the sodium had dissolved (*ca.* 30 hr.). The hot solution was added slowly to a stirred solution of 106.4 g. of (+)-pulegone (I) and 61.6 cc. of methyl iodide in 560 cc. of dry ether while cooling in an ice-bath and the mixture was then heated under reflux for

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[22] These will be discussed in a forthcoming paper together with their optical rotatory dispersion curves.

[23] W. Treibs, *Ber.*, **70**, 384 (1937).

[24] G. Büchi and R. E. Erickson, *J. Am. Chem. Soc.*, **76**, 3493 (1954).

[25] H. Rupe and K. Lichtenhain, *Ber.*, **39**, 1124 (1906). This work was actually conducted in the antipodal series.

[26] Melting points and boiling points are uncorrected. We are indebted to Miss B. Bach for the ultraviolet and infrared spectral measurements and to Mr. E. Meier (Stanford University Microanalytical Laboratory) and Dr. A. Bernhardt (Mühlheim, Germany) for the microanalyses. Unless noted otherwise, all rotations were measured in chloroform solution.

[27] We are indebted to Prof. D. E. White, Fulbright scholar from the University of Western Australia during the 1960 Spring quarter, for some experimental improvements.

3 hr. Water was added, the organic layer was separated, washed with water, dried and the solvent evaporated. Fractionation through a Vigreux column afforded 89 g. of crude methylisopulegone, b.p. 117–127° (23–25 mm.). As far as the composition of this material is concerned, gas phase chromatography on Ucon Polar indicated that except for a small amount of unreacted pulegone, it consisted of apapproximately 83% of II and 17% of III.

In large scale experiments, the known[16,17] isomer (−)-methylisopulegone (II) is separated most effectively by conversion to its semicarbazone. In a typical experiment, 56 g. of crude product was mixed with 75 g. of semicarbazide hydrochloride and 112.5 g. of sodium acetate in 500 cc. of water and sufficient ethyl alcohol to afford a clear solution. After standing at room temperature over-night, the crude semicarbazone was isolated and recrystallized three times from isopropyl alcohol. There was thus obtained 41.5 g. of pure semicarbazone (m.p. 201–202.5°, $[\alpha]_D$ −167°), which was steam distilled in the presence of 80 g. of oxalic acid to afford 23.2 g. of (−)-methylisopulegone (II), b.p. 104–106°, α_D−122.6° (neat), n^{27}_D 1.4692, $\lambda_{\max}^{\text{capill}}$ 5.82 μ and terminal double bond bands at 6.07 and 11.20μ. The ultraviolet absorption spectrum ($\lambda_{\max}^{\text{EtOH}}$ 297 mμ, ε 45; $\lambda_{\max}^{\text{cyclohexane}}$ 193.5 mμ,[28] ε 8320) showed the complete absence of α,β-unsaturated ketone.

(+)-Dihydromethylisopulegone (IV).—Catalytic hydrogenation of 404 mg. of (−)-methylisopulegone (II) with 105 mg. of 10% palladized charcoal catalyst in 5 cc. of ethanol resulted in the uptake of one equivalent of hydrogen within 35 min. Filtration of the catalyst and distillation at 100–105° (8 mm.) provided 355 mg. of the dihydro ketone IV, n^{26}_D 1.4568, α^{22}_D +17.5° (neat), $\lambda_{\max}^{\text{capill}}$ 5.84 μ with complete absence of 6.1 and 11.2 μ bands, $\lambda_{\max}^{\text{EtOH}}$ 292 mμ, ε 28.9, $\lambda_{\max}^{\text{cyclohexan}}$ 189 mμ, ε 1150.[28]

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98; O, 9.51. Found: C, 78.54; H, 11.99; O, 8.98.

The semicarbazone, after recrystallization from dilute ethanol, exhibited m.p. 188–189°, $[\alpha]^{25}_D$ −76.5°.

Anal. Calcd. for $C_{12}H_{23}N_3O$: C, 63.96; H, 10.29; O, 7.10. Found: C, 64.30; H, 10.49; N, 7.53.

The light yellow **2,4-dinitrophenylhydrazone** was recrystallized from dilute ethanol, whereupon it showed m.p. 85–86°, $[\alpha]^{25}_D$ −178°, $\lambda_{\max}^{\text{CHCl}_3}$ 368 mμ, ε 28,200.

Anal. Calcd. for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.94. Found C, 58.93; H, 7.23.

(+)-Methylisopulegone (III).—The combined mother liquors from the (−)-methylisopulegone (II) semicarbazone were subjected to steam distillation in the presence of oxalic acid and the ketone mixture was then fractionated by gas phase chromatography in a Beckman Megachrome with a Ucon Polar packing. Three peaks were encountered of which the third was not investigated further. The second peak proved to be II, while the first one was the isomer (+)-methylisopulegone (III). Aside from the rotatory dispersion curves[22] which were of opposite sign, the infrared spectra could be used for purposes of differentiation since III exhibited bands at 8.27(s), 9.31(m), 9.63(m) and 9.89(m) μ, while II was characterized in that region by bands at 8.30(w), 9.50(w) and 9.75(m) μ. (+)-Methylisopulegone was redistilled at a bath temperature of 95–100° (25 mm.), whereupon it showed $[\alpha]^{24}_D$ +240°, $\lambda_{\max}^{\text{MeOH}}$ 294 mμ, ε 54; $\lambda_{\max}^{\text{capill}}$ 5.85 6.10 and 11.10 μ.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91; O, 9.63. Found: C, 79.29; H, 10.73; O, 10.13.

The semicarbazone possessed m.p. 197–198.5°, $[\alpha]^{24}_D$ +127°.

Anal. Calcd. for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.62; H, 9.42; N, 18.54.

The yellow colored **2,4-dinitrophenylhydrazone** was recrystallized from dilute ethanol and exhibited m.p. 130–131.5°, $[\alpha]^{24.5}_D$ +152°.

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.40; N, 16.17. Found: C, 59.03; H, 6.18; N, 16.14.

(+)-2-Methylmenthone (V). (a) By Catalytic Hydrogenation of (+)-Dihydromethylisopulegone (III).—The catalytic hydrogenation of III proceeded exactly as described for (−)-methylisopulegone (II) and after distillation at 95–100° (17 mm.) the saturated ketone exhibited a single infrared band at 5.86 μ, $\lambda_{\max}^{\text{MeOH}}$ 292 mμ, ε 32, $[\alpha]_D$ +126°.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.50; H, 11.87.

The 2,4-dinitrophenylhydrazone formed orange needles with m.p. 152–153°, $[\alpha]_D$ +11°.

Anal. Calcd. for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.94; N, 16.09. Found: C, 58.61; H, 6.98; N, 15.87.

(b) **From (−)-Spiro-(1,3-dithian-2,6′-menthone) (VII).**—To a suspension of 12 g. of sodium ethoxide in 280 cc. of dry ether and 60 cc. of dried ethyl formate was added dropwise a solution of 7.1 g. of (−)-menthone (VI) (b.p. 207–208°, $[\alpha]_D$ −15° (dioxane)) in 40 cc. of ether. After standing overnight at room temperature, water was added and the ether layer was extracted with 2% aqueous potassium hydroxide solution. The basic extracts were acidified with concd. hydrochloric acid to *p*H 6, ether extracted, and after drying and removal of the ether the residual **6-hydroxymethylenementhone** was distilled at 140–150° (6 mm.), yield 8.0 g. The substance gave a violet color with alcoholic ferric chloride and exhibited strong infrared carbonyl bands at 6.10 and 6.25 μ.

The freshly prepared hydroxymethylene ketone (14.5 g.) and 42 g. of the ditosylate of propane-1,3-dithiol[20] were dissolved in 520 cc. of warm absolute ethanol and 57.3 g. of freshly fused potassium acetate was added slowly together with 140 cc. of absolute ethanol. The solution became yellow as it was heated under reflux in a current of nitrogen for 7 hr., at the end of which time the ethanol was removed *in vacuo*. The residue was extracted thoroughly with hexane and after drying and removal of the hexane, the residue (15 g.) was chromatographed on Woelm grade I neutral alumina. The combined hexane eluates were distilled at 130–140° (0.25 mm.) to afford 7.1 g. of the desired **(−)-spiro-(1,3-dithian-2,6′-menthone)** (VII), n^{27}_D 1.5450, $\lambda_{\max}^{\text{capill}}$ 5.80 μ; R.D. in methanol (*c* 0.130): $[\alpha]_{700}$ −89°, $[\alpha]_{589}$ −126°, $[\alpha]_{330}$ −2554°, $[\alpha]_{295}$ + 1530°, $[\alpha]_{280}$ +1138°.

Anal. Calcd. for $C_{13}H_{22}OS_2$: C, 60.44; H, 8.59; O, 6.19; S, 24.78. Found: C, 60.11; H, 8.58; O, 6.38; S, 24.85.

The above dithioketal VII (3.5 g.) was heated under reflux in a nitrogen atmosphere with 60 cc. of dry benzene, 65 cc. of *t*-butyl alcohol and 8.5 g. of potassium *t*-butoxide. Methyl iodide (10 cc.) was added dropwise and refluxing was continued for an additional 20 min., whereupon the solution was washed well with water, dried and evaporated. The residue was chromatographed on neutral grade I Woelm alumina and those hexane eluates which exhibited a carbonyl band at 5.80 μ and characteristic absorption at 7.3 μ were combined and distilled at 125–140° (0.03 mm.), yield 0.40 g.; R.D. in methanol (*c* 0.09): $[\alpha]_{589}$ −78°, $[\alpha]_{335}$ −1815°, $[\alpha]_{294}$ +1700°, $[\alpha]_{285}$ +1267°. As shown below in the desulfurization experiment, this material represents **(−)-spiro-(1,3-dithian-2,6′-methylmenthone)** (VIII) contaminated by some precursor VII.

Anal. Calcd. for $C_{14}H_{24}OS_2$: C, 61.74; H, 8.88; S, 23.48. Found: C, 61.75; H, 8.64; S, 22.59.

The desulfurization was conducted by heating under reflux 0.8 g. of the methylated thioketal VIII in 200 cc. of ethanol with 9 g. of deactivated[29] W-2 Raney nickel catalyst (4 months old). The mixture was cooled, the catalyst was filtered and the filtrate was distilled at 90–95° (2 mm.) to give 0.325 g. of material, which by gas phase chromatography was found to consist of 75% of V and 25% of menthone (VI) arising from unmethylated VII. The pure (+)-2-methylmenthone (V) was obtained by gas phase chromatography (on a silicone grease-firebrick column at 147° with helium as the carrier gas) and proved to be identical by infrared analysis and rotatory dispersion measurement[22] with the material prepared according to (a). The 2,4-dinitrophenylhydrazone exhibited m.p. 149–151°, $[\alpha]_D$ +10°, $\lambda_{\max}^{\text{CHCl}_3}$ 368 mμ, ε 30,200, and its melting point was not depressed upon admixture with the specimen described under (a).

Direct Methylation of (−)-Menthone (VI).—An 8.0-g. sample of (−)-menthone (VI) was heated under reflux for 1 hr. in a current of nitrogen with 16.8 g. of potassium *t*-

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(28) We are indebted to Prof. C. A. Grob, of the University of Basel for this measurement.

(29) The catalyst was heated for 2.5 hr. under reflux with ethyl acetate, the solvent was removed, acetone was added and the process was repeated. Acetone was then replaced by ethanol and the suspension added to the reaction vessel.

butoxide and 7 cc. of methyl iodide in 320 cc. of *t*-butyl alcohol. The product was isolated and converted as described above into the hydroxymethylene derivative, which was extracted with 2% aqueous potassium hydroxide solution. The hydroxymethylene group was then removed by treatment with hot 5% potassium hydroxide solution and steam distillation.[30] The volatile ketone was distilled at 90–100° (10 mm.) (yield 4.2 g.) and was shown by gas phase chromatography to consist of one part of unreacted menthone (VI) to two parts of methylmenthone. The latter was separated by gas phase chromatography and its rotatory dispersion curve in methanol solution (c 0.130: $[a]_{589}$ $+30°$, $[\alpha]_{312.5}$ $+1810°$, $[\alpha]_{270}$ $-2542°$, $[\alpha]_{260}$ $-2350°$) when compared with those of pure IV and V showed that these two isomeric methylmenthones were present in about equal proportions.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98; O, 9.51. Found: C, 78.59; H, 12.20; O, 9.40.

The presence of both isomers was confirmed by conversion to the 2,4-dinitrophenylhydrazone and fractional crystallization, whereupon yellow crystals, m.p. 81–83° (undepressed when mixed with the derivative of IV), and orange ones, m.p. 143–145° (undepressed on admixture with V 2,4-dinitrophenylhydrazone), were obtained.

Reduction of (−)-3,6-Dimethyl-6-isopropyl-Δ²-cyclohexenone (IX).[19] **(a) By Catalytic Hydrogenation.**—One equivalent of hydrogen was consumed in 35 min. when 996 mg. of IX[19] was hydrogenated at room temperature and atmospheric pressure with 135 mg. of 5% palladized charcoal catalyst in 30 cc. of methanol. Distillation of the product at 105–110° (9 mm.) afforded 840 mg. of liquid (absence of unsaturated ketone demonstrated by infrared analysis), whose rotatory dispersion curve in methanol (c 0.124: $[\alpha]_{700}$ $-58°$, $[\alpha]_{589}$ $-77°$, $[\alpha]_{310}$ $-2161°$, $[\alpha]_{270}$ $+1977°$, $[\alpha]_{250}$ $+1358°$) showed that it consisted of approximately 70% of (−)-2-methylmenthone (X) (see below for R.D. of pure isomer) and 30% of (+)-dihydromethylisopulegone (IV). Conversion of this material to the 2,4-dinitrophenylhydrazone and recrystallization from dilute ethanol provided orange crystals of the 2,4-dinitrophenylhydrazone of pure X, m.p. 149–151°, $[\alpha]_D$ $-10°$, whose infrared spectrum was identical with that of the 2,4-dinitrophenylhydrazone of the antipode V.

Pure X could be obtained most readily by taking advantage of the relative insolubility of the semicarbazone of the minor component (IV) of the hydrogenation mixture. Recrystallization of the semicarbazone of the mixture provided the pure semicarbazone of IV, m.p. 188-189°, undepressed upon admixture with an authentic sample. The mother liquors were steam distilled in the presence of oxalic acid and the residual **(−)-2-methylmenthone** (**X**) was distilled at a bath temperature of 95–98° (8 mm.); R.D. in methanol (c 0.096): $[\alpha]_{700}$ $-65°$, $[\alpha]_{589}$ $-79°$, $[\alpha]_{312.5}$ $-3210°$ $[\alpha]_{272.5}$ $+3282°$, $[\alpha]_{250}$ $+2330°$. Its infrared spectrum proved to be identical with that of its antipode V.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.20; H, 11.81.

(b) **By Chemical Reduction.**—A solution of 900 mg. of (−)-3,6-dimethyl-6-isopropyl-Δ²-cyclohexenone (IX)[19] in 60 cc. of anhydrous ether was added dropwise over a period of 30 min. to a stirred solution of 900 mg. of lithium in 500 cc. of liquid ammonia. After stirring for an additional 75 min., 12 g. of ammonium chloride was added slowly and the ammonia was then allowed to evaporate. Water was added, the ether layer was separated and, after washing with dilute hydrochloric acid and water, the dried solution was distilled. The product (743 mg.) exhibited a small hydroxyl band in the infrared, presumably due to over-reduction to the alcohol and the entire material was, therefore, oxidized with chromium trioxide in acetone solution.[31] The infrared spectrum of the resulting ketone did not contain any hydroxyl band in the infrared and from its rotatory dispersion curve in methanol (c 0.168: $[\alpha]_{700}$ $-25°$, $[\alpha]_{589}$ $-29°$, $[\alpha]_{305}$ $-649°$, $[\alpha]_{270}$ $+41°$, $[\alpha]_{260}$ $+14°$) it was possible to calculate that it consisted of approximately 75% of (+)-dihydromethylisopulegone (IV) and 25% of (−)-2-methylmenthone (X).

(+)-2,2,5-Trimethylcyclohexanone (**XV**).—(−)-Methylisopulegone (II) was transformed in 40% yield into (+)-*trans*-2,5-dimethylcyclohexanone (XII) according to the literature directions[17] and thence into the hydroxymethylene derivative.[17] The latter was then treated with the ditosylate of propane-1,3-dithiol in the manner described above for menthone (VI → VII) and after chromatography on alumina and recrystallization from hexane, **(−)-spiro-[1,3-dithian-2,6′-(2′,5′-dimethylcyclohexanone)]** (**XIII**) was obtained as colorless crystals, m.p. 58–59°; R.D. in methanol (c 0.04) $[\alpha]_{589}$ $-320°$, $[\alpha]_{327.5}$ $-8112°$, $[\alpha]_{280}$ $+4950°$, $[\alpha]_{270}$ $+4412°$.

Anal. Calcd. for $C_{11}H_{18}OS_2$: C, 57.38; H, 7.88. Found: C, 56.86; H, 7.79.

The methylation of 810 mg. of the dithioketal XIII was conducted exactly as described above for the conversion of VII to VIII and provided, after chromatography and distillation at 130–140° (0.02 mm.), 800 mg. of **trimethyl derivative XIV** (as shown below, this is still contaminated by some unreacted XIII); R.D. in methanol (c 0.108): $[\alpha]_{589}$ $-137°$, $[\alpha]_{330}$ $-3315°$, $[\alpha]_{295}$ $+2150°$, $[\alpha]_{285}$ $+1695°$.

Anal. Calcd. for $C_{12}H_{20}SO_2$: C, 59.00; H, 8.25. Found: C, 58.69; H, 7.99.

Desulfurization of 800 mg. of the methylated dithio-ketal XIV with 8 g. of deactivated[29] Raney nickel catalyst was performed in the above-recorded manner and after distillation at 90–100° (15 mm.) gave 400 mg. of crude ketone. Gas phase chromatographic analysis showed that this ketone consisted of *ca.* 25% of XII (arising from unmethylated XIII) and 75% of the desired **(+)-2,2,5-trimethylcyclohexanone** (**XV**). The latter[22] was purified by gas phase chromatography whereupon it exhibited $n^{24}D$ 1.4432.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.65; H, 11.25.

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate; m.p. 111–112°, $[\alpha]D^{25}$ $+36°$.

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; O, 19.98. Found: C, 55.83; H, 6.44; O, 20.03.

(+)-trans-2,5-Dimethyl-2-ethylcyclohexanone (**XIX**).—(−)-Methylisopulegone (II, 2.5 g.) was reduced in ether solution with excess lithium aluminum hydride to afford 2.3 g. of (+)-2-methylisopulegol (XVI), b.p. 75° (5 mm.), $[\alpha]^{25}D$ $+25.5°$ (methanol); $\lambda_{\max}^{\text{capill}}$ 2.9, 6.05 and 11.2 μ.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.14; H, 11.82.

A 1.5-g. sample of the above alcohol XVI in 50 cc. of methylene chloride was ozonized at −70° for 1 hr. until a blue color persisted. The ozonide was decomposed by stirring with water overnight (23°) followed by steam distillation. The resulting ketone XVII (1.08 g.), b.p. 100° (5 mm.), $\lambda_{\max}^{\text{capill}}$ 2.90 and 5.80 μ, was benzoylated directly at room temperature with benzoyl chloride in pyridine solution and the benzoate (49% yield), b.p. 110–120° (0.3 mm.), was then subjected to Wolff–Kishner reduction without further purification. This was accomplished by heating for 2 hr., at 140–160°, 700 mg. of the benzoate of XVII, 700 mg. of potassium hydroxide, 600 mg. of anhydrous hydrazine and 7 cc. of diethylene glycol, followed by heating for 7 hr. at 200–210°. The product (strong menthol odor) was isolated by steam distillation and purified by chromatography on alumina (elution with pentane–ether mixtures) and distillation at 100° (8 mm.); yield 150 mg., $[\alpha]^{25}D$ $+9.5°$ (hexane).

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90; O, 10.24. Found: C, 77.36; H, 13.00; O, 9.80.

The alcohol XVIII (107 mg.) was oxidized with chromium trioxide in acetone solution[31] and the ketone XIX[22] distilled at 100° (15 mm.) (80 mg.), $\lambda_{\max}^{\text{capill}}$ 5.82 μ.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76; O, 10.37. Found: C, 77.63; H, 11.52; O, 10.89.

(−)-8-Methoxycarvotanacetone (**XXIII**).—The reaction of (−)-carvone (XXII)[32] (90 g.) with 180 cc. of methanol and 18 g. of concd. sulfuric acid was performed as described in the literature[23,24] for the (+)-antipode. Distillation afforded a fraction with b.p. 134–135° (8 mm.), which, how-

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[30] See F. W. King, T. J. King and J. G. Topliss, *J. Chem. Soc.*, 919 (1957).

[31] See K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *ibid.*, 39 (1946); C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

[32] This material was obtained from Farmer's Chemical Co., Kalamazoo, Mich., and after redistillation exhibited the following constants: b.p. 122–124°/25 mm., α_D $-58.7°$ (neat), $n^{25}D$ 1.4970, R. D. in dioxane (c, 0.095): $[\alpha]_{700}$ $-47°$, $[\alpha]_{589}$ $-66°$, $[\alpha]_{380\ 377.5}$ $-213°$, $[\alpha]_{347.5}$ $+7°$, $[\alpha]_{297.5}$ $-810°$, $[\alpha]_{287.5}$ $-663°$.

ever, contained a contaminant as evidenced by gas phase chromatography. Chromatography on neutral Woelm alumina grade I and elution with hexane provided 37 g. of homogeneous material, b.p. 130–131° (7 mm.), $[\alpha]^{25}\text{D}$ $-40.6°$ (lit.[23,24] $+40.6°$ for the antipode), $\lambda_{\max}^{\text{capill}}$ 5.98 μ; R.D. in methanol (*c* 0.12): $[\alpha]_{700}$ $-52°$, $[\alpha]_{589}$ $-60°$, $[\alpha]_{360}$ $-312°$, $[\alpha]_{320}$ $+250°$, $[\alpha]_{290}$ $-207°$.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; O, 17.56. Found: C, 72.30; H, 9.60; O, 17.81.

The semicarbazone was recrystallized from aqueous methanol and showed m.p. 164.5–166°, $[\alpha]^{25}\text{D}$ $-37.5°$ (lit.[24] m.p. 166.5–168° for the antipode).

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56; 0, 13.37. Found: C, 60.51; H, 9.04; N, 17.28; 0, 13.17.

(+)-**8-Methoxycarvomenthone** (**XXV**) was obtained in 80% yield by catalytic hydrogenation (10% palladized charcoal in methanol) of (−)-8-methoxycarvotanacetone (XXIII) or in 38% yield by treatment of (+)-dihydrocarvone (XXIV)[33] with methanol and sulfuric acid[23,24]; b.p. 137–140° (15 mm.), $\lambda_{\max}^{\text{capill}}$ 5.82 μ, $[\alpha]\text{D}$ $+19.4°$ (lit.[24] $-22.9°$ for antipode).

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; 0, 17.37. Found: C, 71.94; H, 10.77; 0, 17.21.

The semicarbazone (recrystallized from aqueous ethanol) had m.p. 137–139° (lit.,[23] 142°).

Anal. Calcd. for $C_{12}H_{23}N_3O_2$: C, 59.72; H, 9.61; N, 17.41; O, 13.26. Found: C, 59.86; H, 9.47; N, 17.64; O, 12.85.

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate; m.p. 147–148°, $[\alpha]^{25}\text{D}$ $+194.5°$ (lit.[24] m.p. 152–153° for the antipode).

(−)-8-Hydroxycarvomenthol (XXVII). (a) By Lithium Aluminum Hydride Reduction of (+)-8-Hydroxycarvomenthone (XXVI).—The hydration[25] of (+)-dihydrocarvone (XXIV, 30.4 g.) was performed by stirring for 20 hr. at 15–18° with 100 cc. of 40% sulfuric acid giving 48% of (+)-8-hydroxycarvomenthone (XXVI), b.p. 144–145° (8 mm.) $\lambda_{\max}^{\text{capill}}$ 2.90 and 5.82 μ. Gas phase chromatography indicated a 5% impurity, which was best removed by conversion to the crystalline alcohol XXVII and re-oxidation.

The above ketone (7.65 g.) and 4.5 g. of lithium aluminum hydride in 300 cc. of ether was heated under reflux overnight and, after addition of methanol, the reaction mixture was worked up by the sodium sulfate technique to afford after three recrystallizations from hexane–chloroform 6.2 g. of (−)-**8-hydroxycarvomenthol** (**XXVII**),[34] m.p. 102–103° (plates changing to needles at 80–85°), $[\alpha]^{25}\text{D}$ $-7.25°$.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.64; H, 11.44.

The oxidation of XXVII was conducted in the usual manner[31] with chromium trioxide in acetone solution and provided pure (+)-**8-hydroxycarvomenthone** (**XXVI**), $\lambda_{\max}^{\text{capill}}$ 2.90 and 5.83 μ, $\lambda_{\max}^{\text{EtOH}}$ 278 mμ, ε 29, $[\alpha]^{25}\text{D}$ $+22.4°$ (lit.[25] $-18.5°$ (ethanol) for the antipode), which was used for the subsequent studies.[22]

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; O, 18.80. Found: C, 70.31; H, 10.49; O, 19.19.

The 2,4-dinitrophenylhydrazone was prepared at 0° and recrystallized from ethanol–ethyl acetate. The light orange plates exhibited a double m.p. 93–95° and 132–133°, $[\alpha]^{25}\text{D}$ $+161.5°$.

Anal. Calcd. for $C_{16}H_{22}N_4O_5$: C, 54.84; H, 6.33; N, 15.99; O, 22.83. Found: C, 54.59; H, 6.37; N, 15.92; O, 22.51.

The semicarbazone (recrystallized from hexane–chloroform) had m.p. 151–152°, $[\alpha]^{24}\text{D}$ $+98°$ (lit.[35] m.p. 151° for the antipode).

(b) **From Dihydrocarveol (XXXI).**—(+)-Dihydrocarvone (XXIV) was reduced with lithium aluminum hydride in 87% yield to dihydrocarveol (XXXI) ($\lambda_{\max}^{\text{capill}}$ 2.97, 6.08 and 11.25 μ) and 8.9 g. of this alcohol (without further purification) was stirred for 20 hr. at 15–18° with 40 cc. of 40% sulfuric acid. Dilution with water, neutralization with sodium carbonate, saturation with salt and ether extraction, followed by evaporation of the ether and two recrystallizations from hexane–chloroform, gave 8.6 g. of (−)-8-hydroxycarvomenthol (XXVII), m.p. 102–103°, undepressed on admixture with material prepared according to (a).

(−)-**8-Methoxycarvomenthol** (**XXX**).—A solution of 8.60 g. of (−)-8-hydroxycarvomenthol (XXVII) in 40 cc. of anhydrous dioxane was added slowly to a solution of 1.95 g. of potassium in 100 cc. of liquid ammonia.[36] The ammonia was removed on the steam-bath and to the stirred suspension of the potassium salt in dioxane was added rapidly 9.41 g. of benzyl bromide. After stirring and heating under reflux for 18 hr., the dioxane was removed *in vacuo* and the residue partitioned between ether and water. The ether extract was washed, dried and evaporated. Distillation of the residue at 182–184° (4 mm.) afforded 6.55 g. of the **benzyl ether XXVIII**, whose analysis and gas phase chromatographic behavior indicated a small amount of contaminant. No further purification was attempted and the substance was used directly in the next step.

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 76.48; H, 10.08.

The benzyl ether XXVIII (2.62 g.) was dissolved in 80 cc. of dry benzene and heated under reflux for 4.5 hr. with 0.50 g. of sodium dispersion. After cooling to room temperature, 50 cc. of dry and redistilled dimethylformamide was added (the solution becoming clear at this point) followed by 3 cc. of methyl iodide.[37] The mixture was heated under reflux for 3 hr. and, following the addition of 1 cc. of methyl iodide, it was stirred overnight at room temperature, all operations having been conducted in an atmosphere of nitrogen. The mixture was diluted with saturated salt solution and extracted with hexane. Evaporation of the dried hexane solution and distillation of the residue at 195–220° (4 mm.) provided 1.72 g. of (−)-9-methoxycarvomenthol benzyl ether (XXIX), which was directly hydrogenated in 20 cc. of glacial acetic acid with 170 mg. of 10% palladized charcoal catalyst. Filtration of the catalyst, dilution with sodium hydroxide solution, ether extraction, followed by distillation at 170–180° (3 mm.) provided (−)-8-methoxycarvomenthol (XXX), $[\alpha]^{24}\text{D}$ $-9.7°$, which was shown to be identical by infrared comparison and mixed gas phase chromatogram with the lithium aluminum hydride reduction product of (+)-8-methoxycarvomenthone (XXV).

Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.91. Found: C, 70.67; H, 11.47.

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[33] Obtained in 72% yield by zinc–potassium hydroxide–dilute ethanol reduction (O. Wallach, *Ann.*, **279**, 378 (1894)) of (−)-carvone (XXII); b.p. 117–120° (15 mm.); $\lambda_{\max}^{\text{capill}}$ 5.82, 6.08 and 11.20 μ; $n^{24}\text{D}$ 1.4700, $[\alpha]^{24}\text{D}$ $+20.3°$; $\lambda_{\max}^{\text{EtOH}}$ 285 mμ, ε 29.

[34] See H. Rupe and P. Schlochoff, *Ber.*, **38**, 1719 (1905).

[35] E. Knoevenagel and O. Samel, *ibid.*, **39**, 677 (1906).

[36] These conditions are adapted from the benzyl neopentyl ether preparation of C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

[37] This method was selected since methylation of the tertiary alcoholic function of XXVIII with diazomethane (see M. C. Caserio, J. D. Roberts, M. Neeman and W. S. Johnson, *ibid.*, **80**, 2584 (1958)) failed.