Dihydrocarvone

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While the dihydrocarvones are of lesser importance as fragrance and flavor materials than their parent chemicals, (−) and (+)-carvone, the optically corresponding dihydrocarvones (as well as the racemate) are interesting aroma chemicals. The odorous properties of this group of ketones are generally described as a combination of carvone and menthone fragrances.

Among the dihydrocarvones the cis-(−)-dihydrocarvone is of specific interest. It has a diffuse, powerful odor with a herbaceous bynote. Its odor resembles that of (−)-carvone but it is milder and sweeter than its parent chemical.

The dihydrocarvones are also found in nature where they are present for example in caraway seed and dill seed oils. They are available in high purity.

From a chemical point of view dihydrocarvones occupy a very important position. Many of the classical researches that illuminate the path of terpene chemistry hinge on these ketones. The purpose of this paper is to illustrate many interesting chemical aspects, such as methods of preparation and reactions of dihydrocarvones which resulted in important aroma chemicals. Hopefully the following will also open the way to further research in this area.

Proof that formula (1) represents the title compound is furnished by its oxidation with dilute $KMnO_4$ to p-methan-2-one-8:9-diol (2).[1,2] The diol is further converted by chromic acid oxidation to the diketone (3). Dihydrocarvone is a product of oxidation of dihydrocarveol (4) with chromic acid and this implies the existence of the isopropenyl chain in the ketone as in the parent alcohol,[3,4] a conclusion supported by formaldehyde formation on its oxidative degradation.[5a] Spectral properties (UV,[5a,6,12,37] IR,[12,37,46] and PMR[12,17,47,48]) are in tune with the assigned structure.

Dihydrocarvone has been synthesised unambiguously.[7] This comprises reacting 2-formyl-5-isopropenyl-cyclohexanone (5) with methyl iodide in the presence of K-tert-butoxide; the resulting 2-methyl-2-formyl-5-isopropenyl-cyclohexanone (6) is hydrolysed with warm aqueous KOH to (±)-dihydrocarvone.

The most direct route to dihydrocarvone consists of the reduction of (−) or (+)-carvone (7) with Zn dust-KOH/NaOH combination.[8-12,37,44,46,48,49] The optical rotation of the derived ketone is opposite to that of the carvone used. Part of the starting material formed is dicarvelone.[13] Conversion to dicarvelone is minimized by conducting the reaction quickly and by pouring the alkali into the hot, vigorously stirred mixture of zinc, ethanol, and carvone.[11] From the PMR spectrum, it is deduced that the dihydrocarvone derived thus is a mixture of C-l epimers (trans:cis 3:1).[12]

On the other hand, the annihilation of the α, β-unsaturation in (+)-carvone by reduction with lithium in liquid ammonia is distinguished by the fact that the process affords (+)-dihydrocarvone, as a mixture of C-l epimers (trans:cis 3:1).[14,15]

Heterogeneous catalytic reduction of carvone results in the formation of multiple products.[5b,16,24,59] This can be prevented by the homogeneous hydrogenation of the ketone catalyzed by tris(triphenylphosphine)rhodium chloride which results in ~ 90-94% of dihydrocarvone with less than 3% unreacted starting material remaining.[17]

Another contribution is the preferential hydrogenation of carvone utilising an active cobaloxime catalyst.[15] The latter is a complex (or its dimer) comprising of a glyoxime (for example, glyoxime, dimethylglyoxime, diphenylglyoxime, methylphenylglyoxime), cobalt, and a nitrogen or phosphorus Lewis base represented by formula (9) wherein B is the base (for example, pyridine, triphenylphosphine, and triethylamine) and R is hydrogen or a lower alkyl or aryl hydrocarbon radical. Beneficial results in terms of catalyst efficiency and percentage conversion are claimed when a large excess of the glyoxime complex agent to cobalt is at least ~ 16:1 and the molar ratio of carvone to cobalt is at least ~ 100:1; yield > 95%.

Rearrangement of (+)-limonene 1,2-oxide (10) (a mixture of cis and trans, 1:1)[52] is another strategic approach to dihydrocarvone. Earlier investigations relate to the isomerisation of the oxide using activated alumina heated at 310-325°, glacial acetic acid containing ~ 1% con H_2SO_4,[18] fused $ZnCl_2$,[18] or $ZnBr_2$[19] in benzene. Japanese workers have introduced catalysts such as Al_2O_3 Albes C (fibrillar alumina of Beohmite, 100 m^2/g),[20] SiO_2-Al_2O_3, BF_3-ethereate, solid $LiClO_4$,[21] and $FeSO_4$[22] to funnel the modification of (+)-limonene 1,2-oxide to a mixture of cis and trans dihydrocarvone. The study on the time variation of the products over $FeSO_4$ calcined at 600° reveals that trans-(+)-limonene 1,2-oxide is more reactive than the cis-variety.[22] Catalysts newly introduced are 10% Pt-asbestos, 5% Ru-C, and 5% Rh-C.[40] Mechanisms have been proposed to account for the formation of dihydrocarvone.[18,21] In this context, of interest is the

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isomerisation of (±)-limonene 1,2-oxide (10) to dihydrocarvone in 83-85% yield by reacting with KU-1 resin at 130-135° for 4-5 hr.[23]

A technical route to dihydrocarvone is the pyrolysis of limonene 1,2-oxide at ~ 540°.[25] For the reorganisation of the oxide to cis and trans dihydrocarvone use of $HClO_4$ in an inert medium has been patented.[26]

Finally, mention may be made of the formation of dihydrocarvone in the reduction of nitrosopinene dibromide (11) with Zn and acetic acid[27] and in the electrolytic reduction of carvone (7)[28] and carvoxime (8).[29]

Whereas distillation of crude dihydrocarvone derived by Wallach's procedure affords GLC homogenous sample,[13] earlier literature recommends its purification through the sodium bisulphite addition compound[8] or semicarbazone.[30,49] The ketone can be characterised by the preparation of the oxime,[3,7,18,32] semicarbazone,[18,31,49,52] and 2,4-dinitrophenyl hydrazone.[7]

Extensive work has been done on the isomerisation of dihydrocarvone to carvenone (12). Elevated temperature,[33] dilute H_2SO_4,[33] con H_2SO_4,[31] formic acid,[34] hydrochloric acid,[35] and KU-23 resin[23] cause the migration of the exterior double bond into the ring.

Dihydrocarvone is aromatised to carvacrol (13) by boiling it with ferric chloride in acetic acid[33] or with 10% Pd-C catalyst.[36]

Dihydrocarveol (4) is obtained by reduction of the ketone with Na/C_2H_5OH or with aluminium isopropoxide.[49]

We shall now concentrate our attention on the halogen derivatives of dihydrocarvone initially probed by Wallach[37] and Baeyer.[38] Bromine adds to dihydrocarvone in glacial acetic acid to give a liquid dibromide formulated as (14) since it collapses with alkali to the monobromide (15) which by reduction with Na/C_2H_5OH is converted to dihydrocarveol (4).

Absorption of HBr or HCl by dihydrocarvone affords the hydrobromide or hydrochloride (16)[38,42] through which entry into a wide range of products has been achieved. Induced by alkali, the hydrohalides undergo ring closure to the remarkably versatile bicyclic ketone, carone (18).[41-46] Of all the modifications of dihydrocarvone, thus would perhaps rank as the most outstanding since it constitutes a simple and efficient route from the p-menthane to the carane system.

With sodium acetate/acetic acid, dihydrocarvone dihydrobromide (16) yields a mixture of dihydrocarvone (1) and carvenone (12). Esterification of the dihydrobromide in glacial acetic acid with silver acetate furnishes (17) which on hydrolysis and then reduction with Na/C_2H_5OH gives the glycol (19).[38]

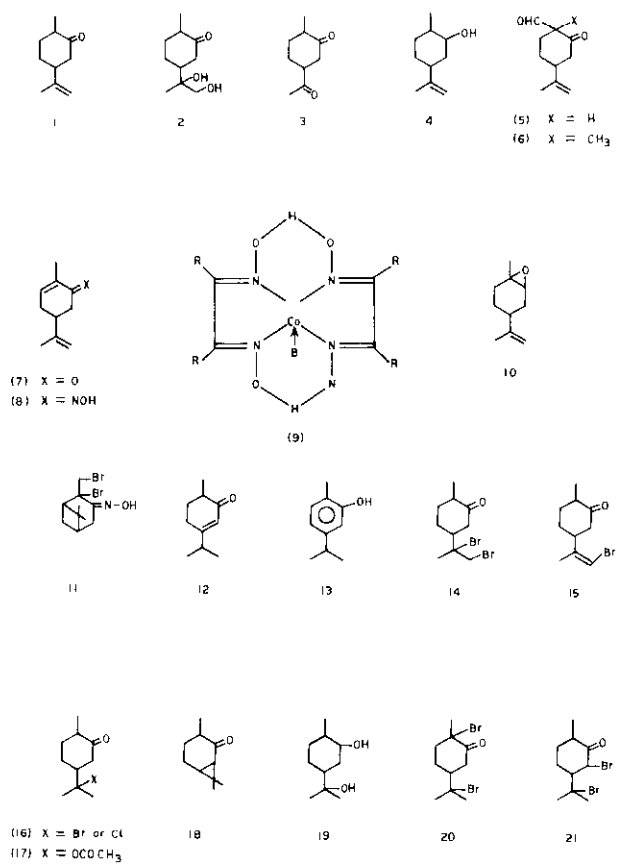
Addition of two atoms of bromine to a chilled solution of dihydrocarvone in glacial acetic acid containing hydrogen bromide gives a crystalline dibromide [(−)-m.p. 69-70°, (±)-m.p. 96-97°].[37] Of the two formulas (20 and 21) open for this derivative, the former is favoured for the following reasons:

By reacting at a low temperature with a mixture of ethyl nitrite and a few drops of acetyl chloride, dihydrocarvone dihydrobromide affords the bis-nitroso derivative (22); this on processing with a glacial acetic acid or ethanolic solution of HBr yields a bis-nitrosylic acid (23) and dihydrocarvone dibromide (20). The latter is identical with that originating from the bromination of the dihydrocarvone hydrobromide.[38]

Recently (in 1977) Wallach's researches on the halogen derivatives from (−)-dihydrocarvone have been comprehensively reinvestigated.[48] The PMR spectrum of the crystalline dibromide (m.p. 70-71°) derived from the (−)-epimers of dihydrocarvone (see above) lacks the low field CH_3Br multiplet and all the methyl protons appear as equivalent. The strong positive Cotton effect in the rotatory dispersion curve and ultraviolet maximum at 311 μ are diagnostic of an axial bromine. These are accommodated by structure (24).

Further bromination of the dibromide using Wallach's procedure leads to a crystalline tribromide. The third bromine atom attached to C_3 is apparently axial as evidenced by the PMR spectrum. It seems that the dibromide gets brominated to form 1,3,8-tribromo-p-menthan-2-one (25) in the more stable conformation (35). The treatment of (25) with sodium bromohydride gives chiefly the alcohol (26); the latter results in ring closure to give by reaction with sodium methoxide the epoxide (34).

Similarly the hydrochlorination and chlorination of dihydrocarvone gives 1,8-dichloro-p-menthan-2-one (27). The bromination of (27) gives excellent yield of



the bromo dichloride with a boat conformation (36).

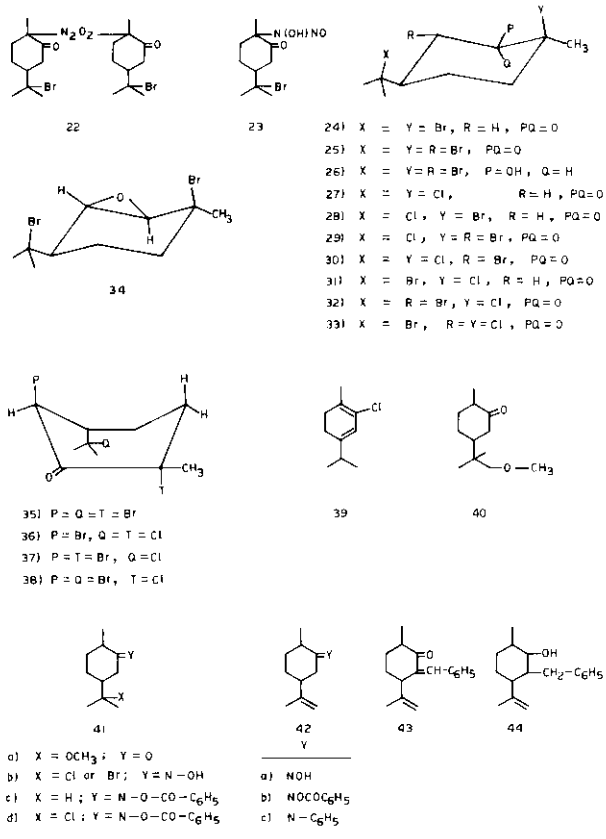
When subjected to hydrochlorination and bromination, dihydrocarvone furnishes 1-bromo-8-chloro-p-menthan-2-one (28), this is further brominated to give the trihalide (29) in the boat form (37). Chlorination of compound (28) affords (30) in the chair conformation with C_3 chlorine positioned equatorially. 8-Bromo-1-chloro-p-menthan-2-one (31) is obtained by hydrobromination and chlorination of dihydrocarvone and this on bromination gives the trihalide (32) in the boat form (38). Finally chlorination of (31) affords (33) in the chair conformation with an equatorial C_3 chlorine.

The action of PCl_5 on dihydrocarvone results in 2-chloro-p-mentha-1,3-diene (39), the formation of which implies prior rearrangement of the title compound to carvenone (12).[50]

Treibs[51] apparently prepared the novel derivative (40) by refluxing dihydrocarvone with CH_3OH/H_2SO_4 and this necessarily demands the addition of the elements of dimethyl ether across the isopropenyl double bond. Later investigation has shown that the products produced are 8-methoxycarvomenthone (41a) and carvenone (12).[30]

Reference has been made to dihydrocarvoxime (42a). This oxime adds HBr or HCl to give the halogen compounds (41b).[52,53] By comparison of the PMR characteristics of (42a) and (41b) with benzoyl esters (42b) and (41c) respectively the parent oximes have been assigned Z-stereochemistry.[53,54,cf.32]

Promoted by sodium ethoxide, dihydrocarvone



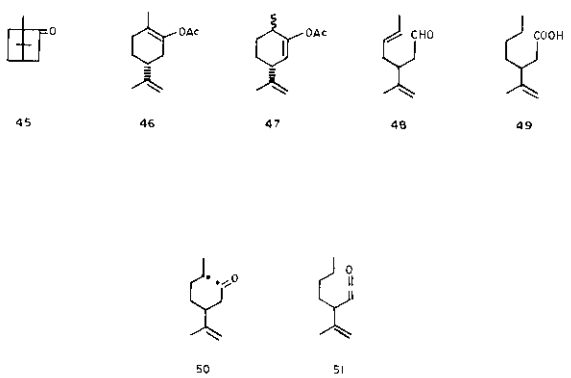
condenses with benzaldehyde to give the benzylidene derivative (43), b.p. 187-190° (10 mm), oxime, m.p.

145-146° (methanol), which by reduction with Na/C_2H_5OH yields benzyldihydrocarveol (44).[55] Another condensation product is the anil (42c) obtained by heating dihydrocarvone and aniline in the presence of $ZnCl_2$.[56]

Throwing light on the biogenetic pathway is cyclization of (+)-dihydrocarvone to camphor (45).[12,15] In one method, (+)-dihydrocarvone is reacted with isopropenyl acetate in the presence of toluene-p-sulphonic acid monohydrate to give a mixture (ca 4:1) of (+)-2-acetoxy-p-mentha-1,8-diene (46) and 2-acetoxy-p-mentha-2,8-diene (47) and these are separated by preparative GLC.[12] Passage of BF_3 gas into a 0.1% solution of (46) in wet methylene chloride for 10 min provides (±)-camphor. (+)-Camphor does not racemise under these conditions and it is believed that the chiral centre at C_4 in (46) is disrupted by either double bond migration or 1,2-hydride shift.

On the other hand, a facile synthesis of (+)-camphor in 55% yield and 90% optical purity has been accomplished by thermolysis of (+)-dihydrocarvone at 400° for 20 hr.[15]

Exposure of dihydrocarvone to sunlight apparently leads to the unsaturated aldehyde (48) and the acid (49).[57] Here, dihydrocarvone splits at the carbonyl group on the more substituted side to give diradical (50) of which each radical centre can trap a favourably placed hydrogen to give the aldehyde (48) or a ketene (51) trapped by a hydroxylic solvent to give the acid (49).[58]



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References

1. O. Wallach, Chem.Ber., **28**, 2704, 1895
2. F. Tiemann and F. W. Semmler, Chem.Ber., **28**, 2141, 1895
3. O. Wallach, Annalen, **275**, 110, 1893
4. A. Baeyer, Chem.Ber., **26**, 823, 1893
5. A. R. Pinder, The Chemistry of the Terpenes, Chapman & Hill Ltd., London, 1960 (a) p. 74, (b) p. 72
6. L. R. Crymble, A. W. Stewart, R. Wright, and F. W. Rea, J.Chem.Soc., **99**, 1265, 1911
7. O. P. Vig, S. D. Sharma, S. Chander, and I. Raj, Indian J. Chem., **3**, 425, 1965
8. O. Wallach, Annalen, **279**, 377, 1894
9. T. G. Halsall, D. W. Theobald, and K. B. Walshaw, J.Chem.Soc., 1029, 1964
10. M. Joshida, Chem. & Pharm.Bull. (Japan), **3**, 215, 1955
11. D. C. Humber and A. R. Pinder, J.Org.Chem., **31**, 4188, 1966
12. J. C. Fairlie, G. L. Hodgson, and T. Money, J.Chem.Soc. Perkin I, 2109, 1973
13. O. Wallach, Annalen, **305**, 220, 1899
14. J. A. Marshall, W. I. Fanta, and H. Roebke, J.Org.Chem., **31**, 1016, 1966
15. J. M. Conia and G. L. Lange, J.Org.Chem., **43**, 564, 1978
16. W. J. Ehmann (to SCM Corp.), U.S. Patent 4,020,108 (1977) (Chem.Abstr., 1977, **87**, Abstr.136044w)
17. R. E. Ireland and P. Bey, Org.Synth., **53**, 63, 1973
18. E. E. Royals and L. L. Harrell Jr., J.Amer.Chem.Soc., **77**, 3405, 1955
19. R. L. Settine, G. L. Parks, and G. L. K. Hunter, J.Org.Chem., **29**, 616, 1964
20. K. Arata and K. Tanabe, Chem.Lett., 321, 1976
21. K. Arata, S. Akutagawa, and K. Tanabe, J.Catalysis, **41**, 173, 1976
22. K. Arata, H. Takahashi, and K. Tanabe, Roczniki Chem., **50**, 2101, 1976
23. N. E. Kologrivova, Z. V. Kamaeva, and L. A. Kheifits, Zh.Vses. Khim O-va, **22**(2), 223, 1977 (Chem.Abstr., 1977, **87**, Abstr. 135966m)
24. E. I. Klabunovskii, L. F. Godunova, and L. K. Maslova, Izvest.Akad.Nauk S.S.S.R., Ser.Khim., (5), 1063, 1972 (Chem.Abstr., 1972, **77**, Abstr. 75348t)
25. A. B. Booth (to The Glidden Co.), U.S.Patent 2,945,068 (1961) (Chem.Abstr., 1961, **55**, Abstr.22722)
26. J. C. Leffingell (to R. J. Reynolds Tobacco Co., Ger.Offen., 1,814,025 (1970) (Chem.Abstr., 1970, **72**, Abstr.133029z)
27. Wallach, O., Annalen, **300**, 290, 1898; **313**, 345, 1900
28. H. D. Law, J.Chem.Soc., **101**, 1549, 1912
29. H. Rupe and K. Loff, Chem.Ber., **47**, 2151, 1914
30. G. Buchi and R. E. Erickson, J.Amer.Chem.Soc., **76**, 3493, 1954
31. A. Baeyer, Chem.Ber., **27**, 1921, 1894
32. A. Zabza, C. Wawrzenczyk, and H. Kuczynski, Bull.Acad.polon. Sci., Ser.Sci.chim., **XX**, 631, 1972
33. O. Wallach, Annalen, **286**, 131, 1895
34. A. Klages, Chem.Ber., **32**, 1516, 1899
35. A. M. Magdeburg, J.prakt.Chem., **93**, 10, 1916
36. K. O. A. Michaelis and S. L. S. Thomas, J.Chem.Soc., 1139, 1940
37. O. Wallach, (a) Annalen, **279**, 377, 1894; (b) **279**, 389, 1894; (c) **286**, 127, 1895
38. A. Baeyer, Chem.Ber., **28**, 1589, 1895
39. A. Baeyer, Chem.Ber., **27**, 1915, 1894
40. T. Kurata, Yukagaku, Japan, **27**, 226, 1978
41. A. Baeyer, Chem.Ber., **27**, 1915, 1897
42. I. L. Kondakov and T. Gorbunov, J.prakt.Chem., **56**, 248, 1897
43. F. Richter, W. Wolff, and W. Presting, Chem.Ber., **84**, 871, 1931
44. I. M. Klotz, J.Amer.Chem.Soc., **66**, 88, 1944
45. T. Norin, Acta.Chem.Scand., **19**, 1915, 1965
46. W. G. Dauben, G. W. Shaffer, and E. J. Deviny, J.Amer. Chem.Soc., **92**, 6273, 1970
47. D. W. Theobald, Tetrahedron, **25**, 3139, 1969
48. R. M. Carman and B. N. Venzke, Austral.J.Chem., **26**, 1977, 1973
49. R. G. Johnston and J. Read, J.Chem.Soc., 233, 1934
50. A. Klages and A. Kraith, Chem.Ber., **32**, 2560, 1899
51. W. Treibs, Chem.Ber., **70**, 384, 1937
52. O. Wallach, Annalen, **279**, 381, 1894
53. B. Singaram and J. Verghese, unpublished results
54. B. Singaram and J. Verghese, J.Indian Chem.Soc., **15B**, 854, 1977
55. O. Wallach, Annalen, **305**, 261, 1899
56. G. Reddelien and O. Meyn, Chem.Ber., **53B**, 345, 1920
57. G. Ciamician and P. Silber, Chem.Ber., **41**, 1928, 1908
58. M. Pfau, Flavour Industry, **3**, 89, 1972
59. L. F. Godunova, E. I. Klabunovskii, A. A. Balandin, and E. A. Oger, Izvest.Akad.Nauk S.S.S.R., Ser.Khim., (7), 1593, 1968 (Chem.Abstr., 1968, **69**, Abstr. 106884f)