[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, BECCO CHEMICAL DIVISION, FOOD MACHINERY AND CHEMICAL CORP.]

Reactions of Limonene Monoxide. The Synthesis of Carvone

SEYMOUR M. LINDER AND FRANK P. GREENSPAN[1]

Received March 29, 1956

An extensive study was made of the conversion of D-limonene into L-carvone. Two successful methods were developed, one by the pyrolysis of limonene glycol diacetate, and the other the oxidation of limonene glycol with *tert*-butyl chromate.

The first step in each synthesis was the same, the epoxidation of limonene, which proceeded in 90% yield. The basic approach involved the dehydration and oxidation of the ring-opened epoxide. In the first group of syntheses attempted the oxidation was performed before the dehydration.

On oxidation with *tert*-butyl chromate, limonene glycol could be converted to the keto alcohol. The keto alcohol could not be dehydrated directly. When the oxime or semicarbazone of the keto alcohol was steam distilled with acid, simultaneous hydrolysis and dehydration took place. The yield of carvone from limonene glycol was 9.2%.

In the second group of syntheses, the dehydration (alternately the dehydrochlorination or deacylation of ester) was performed before the oxidation. Pyrolysis of the glycol diacetate (deacylation) gave carveol acetate which was then saponified to carveol, and in turn oxidized to carvone. The overall yield of carvone from limonene epoxide was 7%.

Attempts to dehydrate limonene glycol to carveol led generally to dihydrocarvone. Limonene chlorohydrin formed by the ring opening of limonene oxide with hydrogen chloride could not be dehydrated. Limonene chlorohydrin, formed by the reaction of limonene glycol with thionyl chloride, dehydrochlorinated in the wrong direction, forming dihydrocarvone rather than the desired carveol.

The synthesis of L-carvone from D-limonene has been previously studied[2] but in each case limonene nitrosochloride was involved as the intermediate. The synthesis involved the conversion of D-limonene into the nitrosochloride which was then dehydrochlorinated to L-carvoxime and hydrolyzed to L-carvone. It was of interest to develop a method of synthesis which did not involve the use of nitrosyl chloride.

The basic approach used involved the conversion of limonene to limonene monoxide, ring opening to the glycol (alternately the acetate or chlorohydrin), followed by dehydration and oxidation of the ring-opened intermediate. The various attempted syntheses can be divided into two groups, (A) in which the oxidation was performed first, and (B) in which the dehydration (or dehydrochlorination) of the ring-opened intermediate was performed first.

Two successful syntheses were accomplished. One proceeded from the epoxide which was ring-opened to the glycol, then oxidized to the keto alcohol and dehydrated to carvone. In the other synthesis, the epoxide was converted to the glycol diacetate, which was pyrolyzed to carveol acetate, saponified to carveol, then oxidized to carvone.

While the yields are low in comparison to the previously reported syntheses of carvone, the reactions studied are of interest since they shed considerable light on the chemistry of terpene epoxides and their derivatives.

Limonene oxide for all the reactions described was prepared using a solution of peracetic acid in chloroform as the epoxidizing reagent. The yields were 90%, substantially greater than that previously reported for perbenzoic acid,[3,4] monoperphthalic acid[5] (71%), and peracetic acid.[6]

Synthesis through the oxidation of limonene glycol. One of the syntheses attempted involved the hydrolysis of limonene oxide to limonene glycol, followed by the oxidation of the glycol to the ketol, which was then to be dehydrated to carvone. Limonene glycol was prepared by the hydrolysis of the oxide with 1% sulfuric acid at 0°C.[3,4,7]

An extensive study was made of the oxidation of limonene glycol to the corresponding keto alcohol. The results in all cases except one were unsuccessful, probably due to glycol cleavage and oxidation of the exocyclic double bond. Tertiary butyl chromate,[8] a selective oxidizing agent which does not attack double bonds, has been found to accomplish the desired oxidation, although only in 44% yield. This represents the first successful synthesis of 1-hydroxydihydrocarvone to be reported.

As in the case of 1-methyl-1-cyclohexene-6-one,[9] the dehydration of the keto alcohol presented difficulties due to the interaction of the hydroxyl and carbonyl groups. The direct dehydration of the ketol could not be accomplished. It was necessary first to convert it into the oxime or semicarbazone and then simultaneously dehydrate and hydrolyze

---

[1] New Address: FMC Organic Chemicals Division, Food Machinery and Chemical Corporation, New York 17, New York.

[2] E. E. Royals and S. E. Horne, Jr., *J. Am. Chem. Soc.*, **73**, 5856 (1951). Other references to previous work will be found in the above reference.

[3] N. Prileschajew, *Ber.*, **42**, 4811 (1909) and German Patent **230,723**.

[4] H. Meerwein, A. Ogait, W. Prang, and A. Serini, *J. prakt. Chem.*, **113**, 9 (1926).

[5] E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955).

[6] B. A. Arbusow and B. M. Michailow, *J. prakt. Chem.*, **127**, 92 (1930).

[7] H. Schmidt, *Ber.*, **82**, 11 (1949).

[8] R. V. Oppenauer and H. Oberrauch, *Anales asoc. quim. argentina*, **37**, 246 (1949).

[9] L. W. Butz, B. L. Davis, and A. M. Gaddis, *J. Org. Chem.*, 12, 130 (1947).

the derivative. An interfering reaction is the acid-catalyzed isomerization of carvone to carvacrol.

Using a pH of 0.9 to 1.0, previously optimum for the hydrolysis of carvoxime,[10] we obtained a 21% yield of carvone. A 9% yield was obtained when oxalic acid was used as dehydrating agent. The best overall yield was 6%.

Attempted synthesis through dehydration of limonene glycol. An attempt was made to dehydrate limonene glycol to carveol, which could then be oxidized to carvone. The dehydrating agents used were iodine, anhydrous oxalic acid, sulfuric acid in formic acid, 10% sulfuric acid, and anhydrous zinc chloride. In all cases, dihydrocarvone was obtained rather than the desired carveol. After this work had been completed, Royals and Harrell similarly reported the formation of ketone, rather than carveol, for the dehydration of limonene glycol.[5]

Synthesis through pyrolysis of limonene glycol diacetate. An attempt was made to convert the glycol diacetate to carveol acetate which could be hydrolyzed to carveol and oxidized to carvone. This approach had previously been studied by Blumann and Wood,[11] who report that they obtained a material similar to carvone in chemical properties, but having a different odor. It was of interest, nevertheless, to study the reactions and to determine whether it was possible, by varying the conditions, to obtain the desired carvone.

The monoacetate was converted to the diacetate by treatment with acetic anhydride. The overall yield from the epoxide was 70%. The crude diacetate, which contained 17% dihydrocarvone, was pyrolyzed by dropping it through a column packed with glass helices. (Alumina caused isomerization to carvacrol and stainless steel caused reduction of the double bond.) The temperature proved to be very critical. If it were too low, no reaction took place; if too high, removal of both acetoxy groups took place, as evidenced by the high bromine number and low ester value. The hydrocarbon and the unreacted diacetate were separated from the carveol acetate by distillation. The conversion to carveol acetate in the pyrolysis was 25%.

The yield on the saponification of the carveol acetate was 55%. Infrared evidence indicated that the product contained a high concentration of carveol with dihydrocarvone as an impurity.

The carveol, so obtained, was oxidized with chromium trioxide in acetic acid at low temperatures.[11-13] The resultant carvone was separated from the unreacted carveol by extraction with neutral sodium sulfite. The yield of carvone was 75% on the basis of the carveol reacted. The material prepared from the pyrolysis had an off-odor, but had the correct bromine number, carbonyl content, and formed a crystalline hydrogen sulfide addition compound.[14]

The overall yield from limonene oxide to carvone for this synthesis was 7%.

Attempted synthesis through dehydration of limonene chlorohydrin. Limonene oxide was converted into the chlorohydrin by reaction with hydrogen chloride in ether. Limonene chlorohydrin, which has not previously been described, was found to be a mixture of two isomers, one of which, when dehydrated, would be expected to give carvyl chloride, which could then be hydrolyzed to carveol and oxidized to carvone.

The results of all dehydration experiments attempted were unsuccessful. In no case was there any appreciable increase in bromine number, indicating that little dehydration took place. The dehydrating agents used were aqueous oxalic acid, anhydrous oxalic acid, anhydrous formic acid, phosphorus pentoxide, acetic anhydride, potassium acid sulfate, aqueous sulfuric acid, and iodine.

Attempted synthesis through dehydrochlorination of limonene chlorohydrin. This synthesis was dependent on conversion of the tertiary hydroxyl to a chloro group and dehydrochlorination of the resultant limonene chlorohydrin to carveol. Treatment of the glycol with concentrated hydrochloric acid under mild conditions did not give the desired chloro compound. Addition to the double bond appeared to take place. Under more vigorous conditions, isomerization to dihydrocarvone was the dominant reaction. The tertiary hydroxyl group of limonene glycol appears to be fairly unreactive toward substitution by chlorine. Ethereal hydrogen chloride also appears to add to the double bond.

When the glycol was treated with thionyl chloride, substitution by chlorine took place. The hydrogen chloride was removed only on prolonged refluxing with pyridine and large amounts of dihydrocarvone were formed, indicating that the dehydration took place in the wrong direction.

EXPERIMENTAL

Oxidation of limonene glycol to the keto alcohol. tert-Butyl chromate was prepared by adding 59 g. of chromium trioxide in small portions to 168 ml. of *tert*-butyl alcohol with slight cooling.[15] The solution was diluted with 220 ml. of dry benzene and dried over anhydrous magnesium sulfate. To the above solution was added a solution of 100 g. of anhydrous limonene glycol in 800 ml. of dry benzene, keeping the temperature between 25° and 30°. Infrared evidence indicated that the reaction was complete in 2 hr. The complex was hydrolyzed by the addition in succession of 600 ml. of water, 120 g. of hydrated oxalic acid, then 600 ml. of 20% sulfuric acid with stirring, keeping the temperature below 25°. After 3 hr., the mixture was separated and the organic layer washed with alkali and dried. A 44% yield of oil was obtained.

---

(10) C. Bordenca, R. K. Allison, and P. H. Dirstine, *Ind. Eng. Chem.*, **43**, 1196 (1951).

(11) A. Blumann and W. R. Wood, *J. Chem. Soc.*, 4420 (1952).

(12) R. H. Reitsema, *J. Am. Chem. Soc.*, **75**, 1996 (1953).

(13) A. Blumann and O. Zeitschel, *Ber.*, **47**, 2623 (1914).

(14) O. Wallach, *Ann.*, **305**, 224 (1899).

(15) It is stated[7] that *tert*-butyl chromate explodes violently when heated above 60°.

Anal. Calcd. for $C_{10}H_{16}O_2$: Carbonyl oxygen, 9.5%, bromine number, 94; hydroxyl, 10.10. Found: Carbonyl oxygen, 8.6; bromine number, 102.8; hydroxyl, 10.25%.

Infrared evidence indicated the presence of an α-hydroxy ketone.

Dehydration of the keto alcohol. The keto alcohol was converted to the semicarbazone which could not be crystallized. The semicarbazone was steam-distilled, the *p*H being kept at 0.9 to 1.0 by the addition of 25% sulfuric acid. The product was isolated from the distillate and purified by conversion to the sodium sulfite derivative. A 15% yield of oil having a spearmint-like odor was obtained.

Anal. Calcd. for $C_{10}H_{14}O$: Carbonyl oxygen, 10.7%; bromine number, 211. Found: Carbonyl oxygen, 10.3%; bromine number, 210.8.

The keto alcohol was converted to the oxime which could not be crystallized. The oxime was refluxed for an hour with 5% oxalic acid, then the mixture was steam-distilled. The product which was isolated from the distillate in 20% yield was shown by infrared analysis to consist of approximately 50% carvone.

Preparation of limonene glycol monoacetate. A solution of 463.7 g. of limonene monoxide in 1400 ml. of acetic acid was refluxed for 4 hr. and allowed to stand at room temperature for 72 hr. On removal of the acetic acid, 561.5 g. (93%) of oil was obtained which had an ester value of 275.2. A sample was steam-distilled.

Anal. Calcd. for $C_{12}H_{20}O_3$: Ester value, 264; bromine number, 75.5; carbonyl, 0. Found: Ester value, 274.9; bromine number, 76.8; carbonyl, 17.4% as dihydrocarvone.

Preparation of limonene glycol diacetate. A solution of 633.8 g. of limonene glycol monoacetate in 1265 ml. of acetic anhydride was refluxed for 7 hr. and allowed to stand at room temperature for 50 hr. On removal of the acetic anhydride and acetic acid, 688 g. (88.4%) of oil was obtained. A steam-distilled sample was submitted for analysis.

Anal. Calcd. for $C_{14}H_{22}O_4$: Ester value, 442; bromine number, 63; carbonyl, 0. Found: Ester value, 413.4; bromine number, 64.7; carbonyl, 6.6% as dihydrocarvone.

A solution of 50 g. of anhydrous limonene glycol in 250 ml. of acetic anhydride was refluxed for 2.5 hr., then poured into water. After the acetic anhydride had hydrolyzed, the product was isolated by extraction with ether. On removal of the ether, a residue of 69 g. (92.5%) of oil was obtained.

Anal. Found: Ester value, 420.7; bromine number, 65.2.

Pyrolysis of limonene glycol diacetate. The pyrolysis was conducted by dropping 544 g. of limonene glycol diacetate (77% pure by ester value, 10% dihydrocarvone) through an electrically-heated column packed with glass helices. It was run at 347–361° over a period of 2.5 hr., being preheated to 190°. The material which came through the column was treated with sodium bicarbonate solution to remove the acid, a yield of 318 g. of oil being obtained.

Anal. Calcd. for $C_{12}H_{18}O_2$: Ester value, 290; bromine number, 164; carbonyl, 0. Found: Ester value, 244.2; bromine number, 118.1; carbonyl, 16.4% as dihydrocarvone.

After two treatments with sodium bisulfite, 257.2 g. of material, which was free of carbonyl was obtained.

Anal. Found: Ester value, 249.0; bromine number, 117.0; glycol, 9.12% as limonene glycol.

The product resulting was distilled *in vacuo*, the main fraction, 92 g., boiling at 83–90°/3.5 mm.

Anal. Found: Ester value, 275.3; bromine number, 145.1; glycol, 5.48% as limonene glycol; carbonyl, 2.45% as dihydrocarvone.

Saponification of carveol acetate to carveol. A solution of 29.1 g. (0.15 mole) of carveol acetate (distilled) in a solution of 20 g. potassium hydroxide (100% excess) in 300 ml. of methanol was refluxed for 1.5 hr. After neutralization of the excess alkali and removal of the solvents and salts, 12 g. of oil was obtained. Infrared evidence indicated that it contained a high concentration of carveol. It contained 32% of dihydrocarvone as an impurity.

Preparation of limonene chlorohydrin. To 550 ml. of 1.9*N* hydrogen chloride in ether was added slowly 150 g. of limonene monoxide (92% pure) and the mixture allowed to stand at room temperature for 3 hr. The solution was then washed with water and dried over anhydrous magnesium sulfate. After removal of the ether, 170 g. (91%) of oil was obtained.

Anal. Calcd. for $C_{10}H_{17}OCl$: Cl, 18.83; bromine number, 85; sapon. number, 282; glycol, 0; oxirane oxygen, 0. Found: Cl, 17.81; bromine number, 80.5; sapon. number, 274; glycol, 0; oxirane oxygen, 0.

Analytical methods. 1. Bromine number: W. W. Scott and N. H. Furman, *Standard Methods of Chemical Analysis*, Fifth Edition, Vol. 2, p. 1770, Van Nostrand Co., Inc., New York, 1944. 2. Epoxy (ether HCl Method): D. Swern, T. W. Findley, G. N. Billen, and J. T. Scanlan, *Anal. Chem.*, **19**, 414 (1947). 3. Hydroxyl (acetic anhydride-pyridine): C. L. Ogg, W. L. Porter, and C. O. Willits, *Ind. Eng. Chem., Anal. Ed.*, **17**, 394 (1945). 4. Carbonyl (hydroxylamine hydrochloride-pyridine): W. M. D. Bryant and D. M. Smith, *J. Am. Chem. Soc.*, **57**, 57 (1935). 5. Glycol (periodic acid): W. D. Pohle, V. C. Mehlenbacher, and J. H. Cook, *Oil and Soap*, **22**, 115 (1945), or S. Siggia, *Quantitative Organic Analysis via Functional Groups*, First Edition, John Wiley & Sons, New York, 1949, p. 8.

BUFFALO 7, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE HEYDEN NEWPORT CHEMICAL CORP.]

Local Anesthetics. I. Dialkylaminoalkyl Ethers of Benzaldoximes and Benzophenone Oximes

GEORGE M. SIEGER[1] AND DAVID X. KLEIN

Received July 23, 1956

A number of dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes have been prepared and characterized. In preliminary physiological screening studies the β-diethylaminoethyl ether of α-benzaldoxime (as the hydrochloride) appeared to be the most interesting of all the compounds tested for local anesthetic activity; it offered good anesthetic action and was the least irritating.

As part of a synthetic medicinals program started in these laboratories several years ago a search was made for new and improved local anesthetics. In these studies attention was focused on the dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes, two previously unreported types

---

[1] Present address: Research Division, American Cyanamid Co., Pearl River, N. Y.