Oxidation of Terpene Compounds with tert-Butyl Chromate. VII[1]. *Oxidation of d-p-Menthene-3*

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On the oxidation of monocyclic terpene compounds of *p*-menthane type, such as *d*-carvomenthene[2], *dl*-α-terpineol[3], *dl*-α-terpinyl acetate[4], *d*-limonene[5] and terpinolene[1], with *tert*-butyl chromate, it has been previously stated in this series that, in general, an active methylene adjacent to an endocyclic double bond was preferentially oxidized to an α,β-unsaturated carbonyl. This fact has also been reported by Dupont et al.[6] on the oxidation of carvomenthene by this oxidant. All these communications concerned the oxidation of the terpene compounds which have an endocyclic double bond between $C_{(1)}$ and $C_{(2)}$ in the skeleton of *p*-menthane type.

The present investigation deals with the oxidation of *d*-*p*-menthene-3 (I), which has an endocyclic double bond between $C_{(3)}$ and $C_{(4)}$, on purpose to compare the oxidative action of *tert*-butyl chromate with that in the previous experiments.

Results

d-*p*-Menthene-3 employed was prepared by pyrolysis of *l*-menthyl xanthate[7], but it was accompanied by a by-product, *d*-*p*-menthene-2, in the yield of 30%.

The oxidant, of type C presented by Oppenauer et al.[8], was prepared in the manner similar to that in the previous reports[1-4] from chromic anhydride and *tert*-butyl alcohol; also glacial acetic acid and acetic anhydride were added. The mole ratio of the sample to *tert*-butyl chromate was 1 to 3.

The oxidation reaction was carried out at 50°C during 36 hr. After the reaction was over, an excess of the oxidant was decomposed and then the reaction mixture was separated into an aqueous solution and a benzene solution.

In the aqueous solution, a trace of the unchanged starting material and a small quantity of acetone were found. From the benzene solution was obtained a crude neutral oil, which was fractionally distilled, whereas no acidic product was isolated. The fractions thus obtained were separated into their constituents by elution-chromatography. The constituent in the low-boiling fractions (b. p.$_{40}$ 51~77°C) was identified with the starting material, which accounted for 7.9% of the initial quantity, while those in the high-boiling fractions (b. p.$_{7}$ 75~150°C) consisted of *d*-carvenone (II), *dl*-*p*-menthen-3-one-5 (III) and an unidentified carbonyl compound in the yields of 49.6, 15.6 and 4.2%, respectively.

Besides, there was no identification of any compound which seemed to come from the oxidation of *d*-*p*-menthene-2 admixed in the starting sample.

Discussion

On the above oxidation of *d*-*p*-menthene-3 with *tert*-butyl chromate, it was clarified that an active methylene adjacent to the double bond is selectively oxidized to a carbonyl without an oxidative cleavage of the double bond or an attack at the side chains. Between *d*-carvenone and *dl*-*p*-menthen-3-one-5 obtained by this oxidation, it would be considered that *d*-carvenone is also produced from *d*-*p*-menthene-2 admixed in the starting sample. Now, on the assumption that *d*-*p*-menthene-2

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[1] Part VI: T. Matsuura, K. Saito and Y. Shimakawa, This Bulletin, 33, 1151 (1960).

[2] K. Fujita and T. Matsuura, *J. Sci. Hiroshima Univ.*, **A18**, 455 (1955).

[3] T. Matsuura and T. Suga, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **78**, 1117 (1957).

[4] T. Matsuura, T. Suga and K. Suga, ibid., **78**, 1122 (1957).

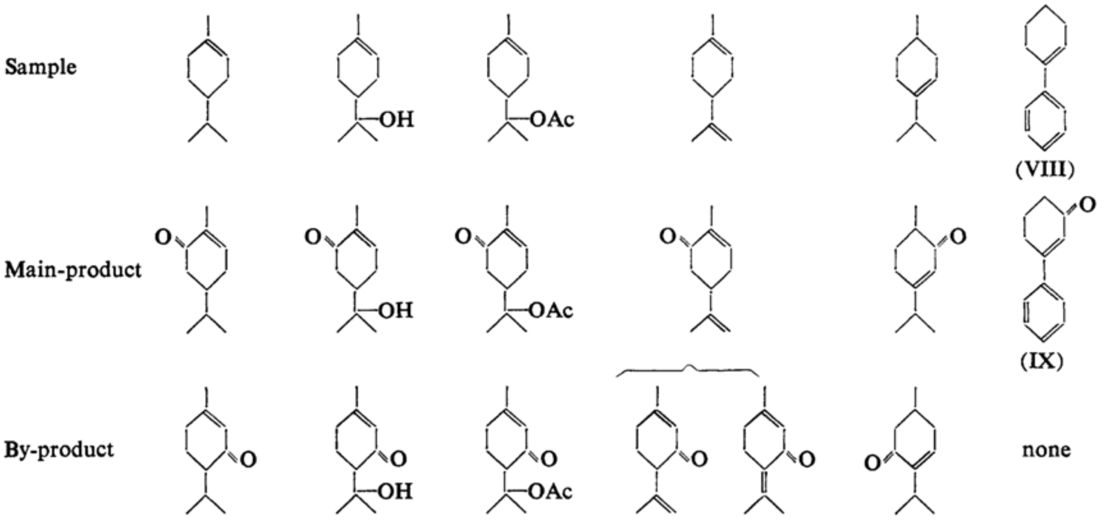
[5] K. Fujita, ibid., **78**, 1112 (1957).

[6] G. Dupont, R. Dulou and O. Mondou, *Bull. soc. chim. France*, **1953**, 60.

[7] L. Tschugaeff, *Ber.*, **32**, 3332 (1899).

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

TABLE I



is oxidized entirely to *d*-carvenone, the amount of *d*-carvenone calculated from *d*-*p*-menthene-2 is subtracted from the total amount of *d*-carvenone. Even in this case, the remaining amount of *d*-carvenone is larger than the yield of *dl*-*p*-menthen-3-one-5. Therefore, it may be said that, between the two active methylenes in the molecule of *d*-*p*-menthene-3, the oxidation of the $C_{(2)}$ active methylene to a carbonyl (to give II) proceeds predominantly in comparison with that of the $C_{(5)}$ active methylene (to III). On the other hand, it has been previously made clear on the oxidation of *d*-carvomenthene (*d*-*p*-menthene-1, IV)[2,6),*1] with the same oxidant under conditions similar to those of the present work that the $C_{(6)}$ methylene activated by the vicinal double bond between $C_{(1)}$ and $C_{(2)}$ is predominantly oxidized to a carbonyl (to give V as a main product) accompanying the oxidation at the $C_{(3)}$ active methylene (with the formation of small amounts of VI and VII). These are shown in Fig. 1.

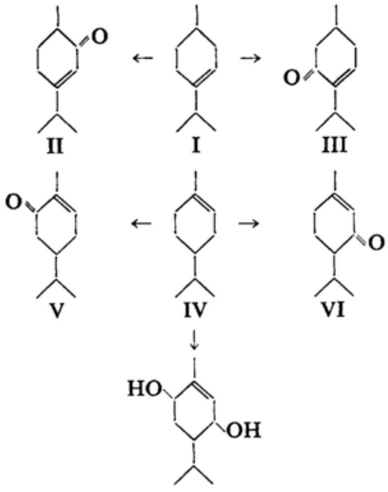


Fig. 1

It is interesting to consider why one of the two characteristic methylenes is predominantly oxidized by this oxidant. On the oxidation of *d*-carvomenthene, an active methylene adjacent to $\overset{*}{C}$-position in $-\overset{*}{C}(R)=CH-$ linkage is predominantly oxidized to a carbonyl, yielding *dl*-carvotanacetone (V). If the oxidation reaction of *d*-*p*-menthene-3 proceeds in a manner analogous to that in the case of *d*-carvomenthene, the $C_{(5)}$ methylene should be preferentially attacked. But this is not the case; the result of the present work shows, contrary to expectation, that the $C_{(2)}$ methylene remote from the $\overset{*}{C}$-position in $-\overset{*}{C}(R)=CH-$ linkage is oxidized preferentially to a carbonyl yielding *d*-carvenone (II). It may therefore be considered that an active methylene which is predominantly attacked is not always located at the position adjacent to the $\overset{*}{C}$-atom in $-\overset{*}{C}(R)=CH-$ linkage.

However, there is an analogy between the oxidation of the two isomers, when attention is paid to the distance from an easily oxidizable methylene to the two side chains. That is, whether a double bond may be located between $C_{(3)}$ and $C_{(4)}$ or between $C_{(1)}$ and $C_{(2)}$, the active methylene remote from the isopropyl group is predominantly attacked. This may be tentatively explained on the assumption that the steric inhibition of the isopropyl group to the oxidizability of an active methylene is reduced with the increase of the distance between the two groups, isopropyl and active methylene, while the effect of the methyl group is small.

[*1] Kozo Fujita, to be published.

This assumption may be supported by the results obtained from the oxidations of the *p*-menthane-type terpene compounds with *tert*-butyl chromate[3-5], which are shown in Table I, omitting the oxidative fission product, homoterpenyl methyl ketone. Moreover, it has been reported that 1-phenylcyclohexene (VIII) yields exclusively 3-phenylcyclohex-2-enone (IX)[9] by this oxidant. There is also a predominance of oxidizability of an active methylene remote from the phenyl group in the molecule.

In the present work, when the *p*-menthene-3 (I) employed was dextrorotatory, among the reaction products, carvenone (II) showed the dextrorotation, whereas *p*-menthen-3-one-5 (III) was optically inactive. Similarly among the oxidation products of *d*-carvomenthene (IV)[2],[*1], carvotanacetone V was optically inactive, whereas piperitone VI was dextrorotatory.

In these cases, such optically inactive products as *p*-menthen-3-one-5 and carvotanacetone result from the oxidation of an active methylene adjacent to the $\overset{*}{C}$-atom in $-\overset{*}{C}(R)=CH-$ linkage ($C_{(4)}$ in I or $C_{(1)}$ in IV). It may be assumed that, on the oxidation of *d*-*p*-menthene-3 with *tert*-butyl chromate as well as in the case of *d*-carvomenthene, an optically inactive product is given by the formation of a *dl*-form via tautomeric intermediate radicals. This is also confirmed by the fact that, on the oxidation of *d*-limonene[5], *dl*-carvone is given as the result of the attack on an active methylene at the similar relative position.

It may be furthermore considered that acetone found in the aqueous solution is formed by the oxidation of surviving *tert*-butyl alcohol in the concentrated oxidant[10].

Experimental

Oxidation of *d*-*p*-Menthene-3.—*d*-*p*-*Menthene-3.*—The material (b. p. 164.5~165°C, n_D^{25} 1.4498, d_4^{25} 0.8116, $[\alpha]_D^{20}$ +111.9°, nitrosochloride m. p. 127~127.5°C) was prepared by the method of Tschugaeff[7], which consists in treating *l*-menthol (m. p. 42.5~43.5°C) with metallic sodium and carbon disulfide in toluene successively, methylating the resulting sodium menthylxanthate with methyl iodide on dilution with ether, pyrolyzing the methyl menthylxanthate thus obtained (m. p. 39~40°C) at 210°C, and rectifying the crude product.

The hydrocarbon obtained as above was analyzed according to the racemization procedure of Hückel et al.[11,12] by refluxing with toluene-*p*-sulfonic acid in ethanol solution, and it was shown that this contained 70.1% of *d*-*p*-menthene-3 and 29.9% of *d*-*p*-menthene-2. Because of the difficulty of isolating the two components, this material was used as the sample without further separation.

Oxidant.—*tert*-Butyl chromate used as an oxidant was prepared by adding 120 g. of chromic anhydride in small portions to 266 g. of *tert*-butyl alcohol under ice-cooling, diluting the resultant with 600 cc. of benzene, drying the resulting benzene solution over anhydrous sodium sulfate, and concentrating it to 75 vol. % under reduced pressure. To the concentrated solution were added 80 g. of glacial acetic acid and 110 g. of acetic anhydride just prior to the oxidation.

Oxidation Process.—The acidified oxidant was added dropwise with stirring at 50±1°C to 55 g. of the starting material during 2 hr., and continuously stirred at the same temperature for a further 34 hr., under an atmosphere of carbon dioxide.

The reaction mixture was then left to stand at room temperature for 12 hr. and treated with water and oxalic acid to decompose the excess of the oxidant. The resulting mixture was separated into two layers, an aqueous solution and a benzene solution, and the former was repeatedly extracted with benzene. The benzene extract was then combined with the benzene solution.

Identification of Oxidation Products.—*Benzene Solution.*—The combined benzene solution mentioned above was washed with water and was treated with a saturated aqueous solution of sodium bicarbonate to extract acidic products. After further washing with water, drying over anhydrous sodium sulfate and removing the solvent, the resulting benzene solution gave a neutral brown oil which amounted to 56.8 g.

Neutral Oil.—The crude neutral oil obtained above was fractionated to 13 fractions and left a resinous residue in an amount of 7.67 g. The yield and physical properties of these fractions were given as in Fig. 2.

(1) Low-boiling Fractions (b. p.$_{40}$ 51~77°C).—The total yield of fractions 1 and 2 amounted to 10.3% of the neutral oil[*2] or to 7.9% of the starting material. On the strip-chromatogram[13], sprayed

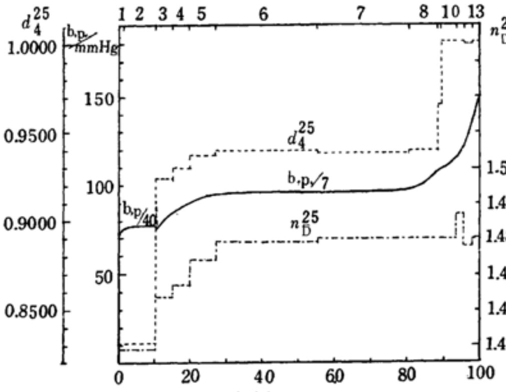


Fig. 2

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9) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, **1951**, 516.

10) T. Suga, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 948 (1959).

11) W. Hückel and W. Tappe, *Ann.*, **537**, 113 (1939).

12) W. Hückel, W. Tappe and G. Legutke, ibid., **543**, 197 (1940).

[*2] It shows hereafter the neutral oil free from distillation residue.

13) J. G. Kirchner, J. M. Miller and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951); J. M. Miller and J. G. Kirchner, ibid., **25**, 1107 (1953); T. Furukawa, *J. Sci. Hiroshima Univ.*, **A21**, 285 (1958).

with 5 vol.% concentrated nitric acid in concentrated sulfuric acid, these two fractions showed only one spot of R_f[*3] value 0.89 agreeing with that of the starting material. Furthermore, these fractions gave *d-p*-menthene-3 nitrosochloride, m. p. 127~128°C, showing no depression by mixing with the known sample. From the estimation by the racemization procedure mentioned above[11,12], it was found that the combined low-boiling fraction consisted of 98% of *p*-menthene-3 and 2% of *p*-menthene-2.

It was thus confirmed that the low-boiling fractions were virtually unchanged *p*-menthene-3.

(2) High-boiling Fractions (b. p.$_7$ 75~150°C).—The total yield of high-boiling fractions, from fraction 3 to fraction 13, amounted to 89.7% of the neutral oil or to 69.3% of the starting material. The strip-chromatograms of these fractions, sprayed with 2,4-dinitrophenylhydrazine–hydrochloric acid, gave two notable spots, R_f values of which were 0.47 and 0.35, respectively, and a faint spot of R_f value 0.20. Every fraction was then eluted through a silica gel column with 15~20 vol.% ethyl acetate in *n*-hexane, giving the following constituents.

(a) *dl-p*-Menthen-3-one-5.—The component which gave a spot of R_f value 0.47 (yield: 20.1% to the neutral oil or 15.6% to the starting material) showed the optical rotation $[\alpha]^{17}_{D}$ 0° (c 8.73 in ethanol, l 0.947). An absorption maximum λ^{alc}_{max} 235 mμ (a[*4]=56.2) in the ultraviolet spectrum and an absorption band at 1675 cm^{-1} (liquid film) in the infrared spectrum indicated the presence of an α,β-unsaturated carbonyl group. In the infrared absorption spectrum, two special wave numbers 1360 and 809 cm^{-1}, characteristic of the isopropyl group and of the linkage of type $R_1R_2C{=}CHR_3$, respectively, were also observed.

The component gave the following derivatives, agreeing with those of *dl-p*-menthen-3-one-5, respectively.

Semicarbazone, m. p. 142~142.5°C (lit., 142°C[14], 141~142°C[15]).

Oxime, m. p., 66°C (lit., 66°C[14,15]).

2,4-Dinitrophenylhydrazone, m. p. 143~143.5°C (lit., 145~146°C[16]).

These showed that this component consisted of *dl-p*-menthen-3-one-5.

(b) *d*-Carvenone.—The component which gave a spot of R_f 0.35 (yield: 71.5% to the neutral oil or 49.6% to the starting material) exhibited the optical rotation $[\alpha]^{21}_{D}$ +45.4° (c 10.16 in ethanol, l 0.947). The ultraviolet spectrum of the component showed the absorption maximum λ^{alc}_{max} 234 mμ (a=96.5), which corresponded to that of α,β-unsaturated ketone.

The following derivatives, prepared from the component, agreed well with those of *d*-carvenone respectively.

Semicarbazone, m. p. 200~201°C (lit., 199~201°C[17]).

2,4-Dinitrophenylhydrazone, m. p. 165°C (lit., 164°C[18]).

Thus, it was established that this component consisted of *d*-carvenone.

(c) Unidentified Carbonyl Compound.—The component gave a spot of R_f value 0.20. Its yield amounted to 5.5% of the neutral oil or 4.2% of the starting material. The component was considered to be a carbonyl compound because of its positive reaction to the carbonyl reagents, sodium nitroprusside and 2,4-dinitrophenylhydrazine. But, owing to its small quantity, further investigation was given up.

The Extract with Sodium Bicarbonate Solution.—Acidified with 10% sulfuric acid and extracted with ether, the sodium bicarbonate extract gave a dark-brown viscous oil in the amount of 2.5 g., from which no reaction product was distilled out but the resinous residue remained behind.

Aqueous Solution.—The aqueous solution mentioned above was neutralized with sodium carbonate and extracted with chloroform and ether, successively, and the residual solution was distilled out. From both of the extracts and from the aqueous distillate, a trace of the starting sample was found on the strip-chromatogram and a small amount of acetone was isolated as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 125~126°C.

Summary

On oxidation with *tert*-butyl chromate, *d-p*-menthene-3 gave *d*-carvenone as a main product and *dl-p*-menthen-3-one-5 as a by-product.

In this oxidation, it is found that, when an endocyclic double bond is in the position between $C_{(3)}$ and $C_{(4)}$ in monocyclic terpenes of *p*-menthane type, two active methylenes adjacent to the endocyclic double bond are selectively oxidized to carbonyls as in the case of the terpenes containing an endocyclic double bond in the position between $C_{(1)}$ and $C_{(2)}$, and that, between the two active methylenes, the one remote from the isopropyl group attached to $C_{(4)}$ is preferentially attacked rather than the other which is close to the same group.

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[*3] R_f shows hereafter the value on chromatogram which was developed with 15 vol.% ethyl acetate in *n*-hexane on a silica-plaster of Paris (4:1) strip.

[*4] Absorptivity, using the concentration in g./l. and the cell length in cm.

14) Q. Wallach, *Ann.*, **397**, 213 (1913); A. Kötz and H. Steinhorst, "Beilstein", VII$_1$-66 (*Ann.*, **379**, 23 (1911)).

15) W. Treibs, G. Lucius, H. Kögler and H. Breslauer, *Ann.*, **581**, 59 (1953).

16) H. E. Eschinazi and H. Pines, *J. Am. Chem. Soc.*, **78**, 1176 (1956).

17) G. Büchi and R. E. Erickson, ibid., **76**, 3493 (1954).

18) J. K. Roy, *Chem. Abstr.*, **48**, 13660 (1954).