Oxidation of Terpene Compounds with *t*-Butyl Chromate. VIII.[1] The Oxidation of α-Terpinene[2]

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Received May 21, 1964

The oxidation of α-terpinene with *t*-butyl chromate affords 1-hydroxy-*p*-menth-3-en-2-one (II), 4-hydroxy-*p*-menth-1-en-3-one (III), carvacrol (IV), thymol (V), *p*-cymene (VIII), *p*-isopropenyltoluene (X), *p*-methylacetophenone (XI), *p*-mentha-1,3-dien-7-al (VI), cuminaldehyde (VII), and possibly trace amounts of 8-hydroxy-*p*-cymene (IX) and *p*-menth-3-ene-1,2-diol (XIII).

Previous work[3-12] on the *t*-butyl chromate oxidation of monocyclic terpene compounds containing an endocyclic ethylenic bond has shown that an active methylene group adjacent to the double bond was preferentially oxidized to an α,β-unsaturated ketone group. Among diene terpene hydrocarbons, only (+)-limonene[5] and terpinolene[10] have been subjected to this oxidation. In the latter case aromatization occurred in addition to the oxidation of the active methylene situated between two double bonds. The oxidation of α-terpinene has now been examined in order to further establish the oxidative behavior of *t*-butyl chromate.

α-Terpinene (I) was prepared by isomerization of (+)-limonene with dilute sulfuric acid and was contaminated with 6% of *p*-cymene. The oxidation of I with *t*-butyl chromate was conducted at 15° for 20 hr. in benzene containing glacial acetic acid and acetic anhydride. The neutral product obtained from the reaction mixture by the usual treatment[8,10] was shaken with sodium hydrogen sulfite to remove aldehydes, and then a combination of fractional distillation, column chromatography, and gas chromatography indicated the presence of 1-hydroxy-*p*-menth-3-en-2-one (II, 18% yield based on the sample taken), 4-hydroxy-*p*-menth-1-en-3-one (III, 3%), carvacrol (IV, 8%), thymol (V, 0.7%), *p*-cymene (VIII, 31%), *p*-isopropenyltoluene (X, 0.8%), *p*-methylacetophenone (XI, 0.6%), and possibly traces of 8-hydroxy-*p*-cymene (IX) and *p*-menth-3-ene-1,2-diol (XIII). Chromatographic separation of the aldehyde fraction gave cuminaldehyde (VII, 0.3%) and what appeared to be *p*-mentha-1,3-dien-7-al (VI, 0.4%). This assignment is based on the appearance of infrared absorption bands at 1673 and 2750 cm.$^{-1}$ attributable to an α,β:γ,δ-unsaturated aldehyde. The presence of this chromophore was further indicated by maximum absorption at 305 mμ (ε 4500)[13] in the ultraviolet spectrum.

Hydroxy ketones II and III were identified on the basis of the following considerations. Compound II, $C_{10}H_{16}O_2$, exhibited an infrared band at 1673 cm.$^{-1}$ and maximum absorption at 236 and 318 mμ (ε 13,270 and 80 respectively) which demonstrated the presence of an α,β-unsaturated ketone. A hydroxyl group was indicated by absorption at 3479 and 1147 cm.$^{-1}$ in the infrared spectrum and the formation of a monoacetate derivative XII on treatment with acetic anhydride and sodium acetate. Digestion of the acetate XII with palladium on charcoal gave carvacrol and acetic acid and established the fact that the keto alcohol II has a *p*-menthane skeleton and carries a ketone group at C-2.

Reduction of II with lithium aluminum hydride gave an unsaturated diol XIII which was almost quantitatively reconverted to II by oxidation with chromium trioxide–pyridine complex. The unsaturated diol absorbed 1 mole of hydrogen to give the saturated diol XIV. This diol XIV was confirmed to be *p*-menthane-1,2-diol by conversion into β-isopropyladipic acid *via* oxidation with lead tetraacetate followed by sodium hypobromite and by conversion to (±)-carvomenthone on pinacolic dehydration. These observations leave no doubt that the hydroxyl group in II is tertiary and is located at C-1.

The hydroxy ketone III, $C_{10}H_{16}O_2$, exhibited infrared absorption at 1674 cm.$^{-1}$ and λ_{max} 234 and 310 mμ (ε 11,000 and 100, respectively) which are characteristic of an α,β-unsaturated ketone. Heating the ketone with palladium on charcoal gave thymol and established that III is a *p*-menthane derivative with a carbonyl group at C-3. Hydroxyl bands were observed at 3511 and 1136 cm.$^{-1}$ in the infrared spectrum. The latter band is likely to indicate the hydroxyl group to be tertiary, and the 3511-cm.$^{-1}$ sharp band (in carbon tetrachloride) attributable to an intramolecular $O \cdots HO{=}C$ hydrogen bond seems to show that the tertiary hydroxyl group is located at C-4 adjacent to the C-3 carbonyl group.

From the varied products isolated it is clear that the oxidation of α-terpinene with *t*-butyl chromate has involved (see Scheme I) (a) hydroxylation of either of two carbon–carbon double bonds in conjugation and subsequent oxidation of the diols thus produced to keto alcohols II and III, (b) oxidation of an allylic carbon atom and enolization to phenols IV and V, and (c) aromatization followed by subsequent oxidation of benzillic position. The first phenomenon, *i.e.*, the formation of hydroxy ketones, and also the third reaction, *i.e.*, aromatization, have not been found in the *t*-butyl chromate oxidation of other mono-

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[1] Paper VII of this series: K. Fujita, *Bull. Chem. Soc. Japan*, **34**, 968 (1961).

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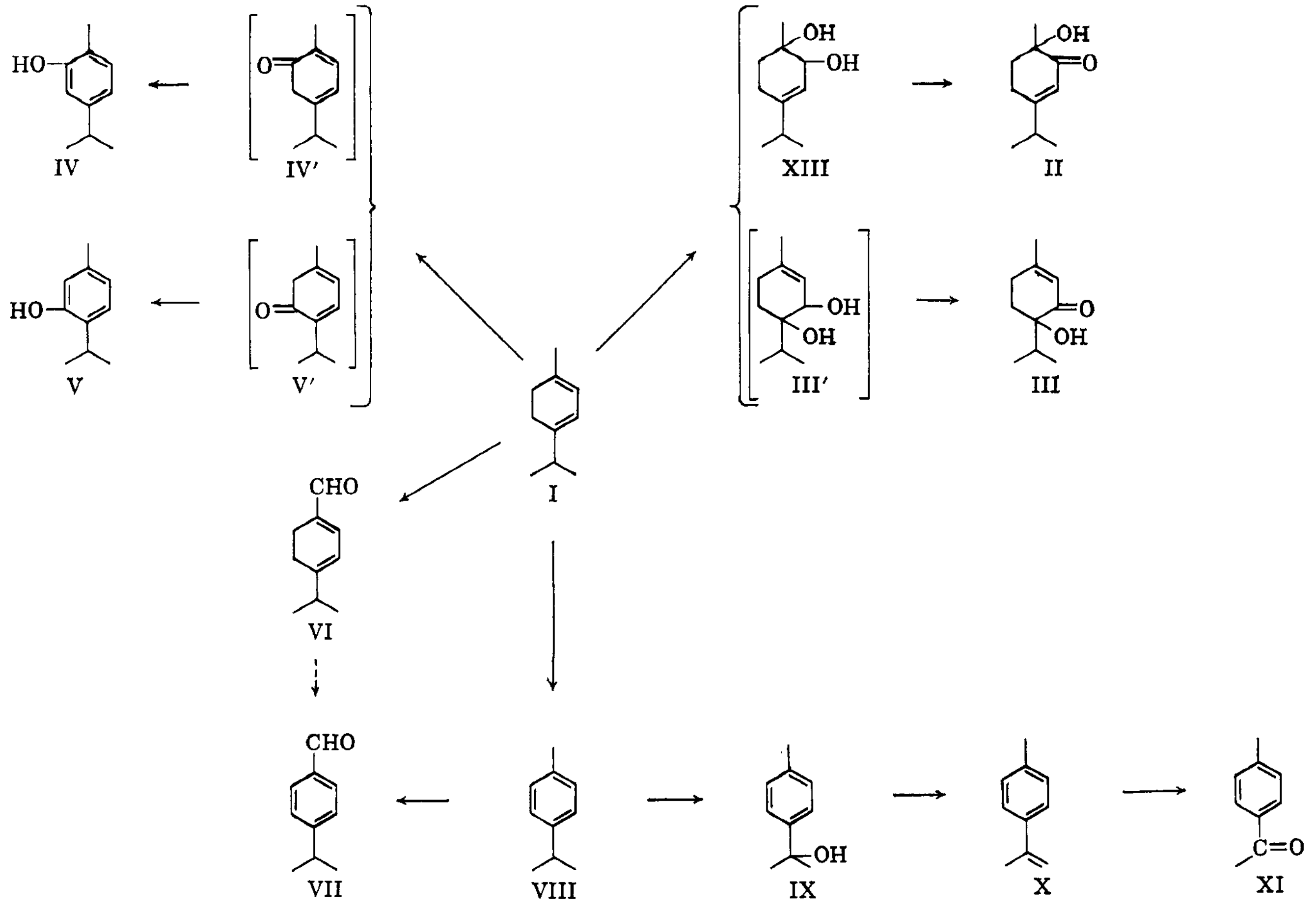
Scheme I

The Reaction Course of α-Terpinene with *t*-Butyl Chromate



cyclic terpene hydrocarbons$^{3-12}$; only terpinolene[10] suffers aromatization.

Experimental

All melting points reported are uncorrected.

α-**Terpinene** (I).—Following the literature method,[14] (+)-limonene, b.p. 86–88° (44 mm.), $[\alpha]^{25}\text{D}$ +111.5°, was treated with a 4 *N* alcoholic solution of sulfuric acid, and the crude product was purified by distillation. The fraction used had b.p. 79° (33 mm.), $n^{25}\text{D}$ 1.4757, $d^{25}{}_4$ 0.8336, $\lambda_{\text{max}}^{\text{EtOH}}$ 265 mμ (ε 7190), and diene number[15] 175.4 corresponding to 94% of the theoretical value. Gas chromatographic as well as ultraviolet spectroscopic[15,16] analysis indicated the hydrocarbon to be contaminated with 6% of *p*-cymene.

Oxidation and Treatment of Reaction Mixture.—A *t*-butyl chromate solution was prepared from 191 g. of chromium trioxide, 352 g. of *t*-butyl alcohol, 1500 g. of benzene, 30 g. of glacial acetic acid, and 30 g. of acetic anhydride in the same manner as in the previous report[8]; the molar ratio of *t*-butyl chromate to *α*-terpinene was 1:2. This oxidant solution was added dropwise to a solution of 130 g. of *α*-terpinene in 130 g. of benzene during a period of 2 hr. with agitation at 3°, and then the mixture was maintained at 15° for 20 hr. with occasional stirring in an atmosphere of nitrogen. Then the whole reaction mixture was separated into a neutral benzene solution and an aqueous one,[8,10] and 116.3 g. of a neutral oily product was obtained. The distillation of the product gave 87.9 g. of a distillate, b.p. 69° (19 mm.) to 155° (3 mm.), and 20.6 g. of a residue (a resinous substance). The distillate was diluted with petroleum ether and shaken with 35% sodium hydrogen sulfite solution. The treatment of the separated sodium hydrogen sulfite solution with sodium carbonate gave 4.5 g. of a mixture (product A) of aldehydes and ketones, while the removal of the solvent from the petroleum solution gave 81.7 g. of the major neutral product (product B) free from aldehydes.

Identification of Reaction Products. A.—Product A (4.5 g.) was eluted on a silica gel column with 20 vol. % ethyl acetate in *n*-hexane and separated into four eluates. The third and fourth eluates were confirmed to be III (0.32 g.) and II (1.38 g.), respectively, by infrared spectrum comparison.

Cuminaldehyde (VII).—The first eluate, 0.30 g., gave cuminaldehyde 2,4-dinitrophenylhydrazone, m.p. and m.m.p. 241–242°.

p-**Mentha-1,3-dien-7-al** (VI).—The second eluate, 0.47 g., showed bands at 2750, 1673 (CHO), and 1375 and 1357 cm.$^{-1}$ (isopropyl) in the infrared spectrum, and an absorption maximum at 305 mμ (ε 4500, in ethanol)[13] (calcd.[17] 291 mμ) in the ultraviolet, and gave 2,4-dinitrophenylhydrazone, m.p. 230–231°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 409 mμ[18] (ε 28,200) (calcd.[19] 405 mμ).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 57.96; H, 5.75; N, 17.02.

B.—Product B (see above) was distilled into six fractions: (1) b.p. 69–70° (18.5 mm.), 35.79 g., (2) b.p. 70–75° (18.5 mm.), 1.14 g., (3) b.p. 38–100° (5.5 mm.), 5.12 g., (4) b.p. 100–104° (5.5 mm.), 33.42 g., (5) b.p. 104–140° (5.5 mm.), 0.75 g., and (6) residue, 3.96 g. By column chromatography on silica gel with 20 vol. % ethyl acetate in *n*-hexane, fraction 4 was further fractionated into three fractions: (4-1) $R_f{}^{20}$ 0.54, 9.46 g., (4-2) R_f 0.38, 3.01 g., and (4-3) R_f 0.28, 17.81 g.

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[20] R_f shows the value on the chromatostrip chromatogram [J. G. Kirchner, J. M. Miller, and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951)] which was developed with 20 vol. % ethyl acetate in *n*-hexane.

1-Hydroxy-*p*-menth-3-en-2-one (II).—Fraction 4-3, b.p. 99–100° (4 mm.), $n^{25}{}_D$ 1.4928, $d^{25}{}_4$ 1.0074, showed bands at 3479, 1147 (OH), 1673 (α,β-unsaturated C=O), 1387 and 1372 (isopropyl), 3044, 1627, 878 (trisubstituted C=C), and 1430 cm.$^{-1}$ ($CH_2C{=}C$) in the infrared spectrum, and λ_{max}^{EtOH} 236 and 318 mμ (ϵ 13,270 and 80) in the ultraviolet.

Anal. Calcd. for $C_{10}H_{16}O_2$: mol. wt., 168.2. Found: mol. wt., 168.

The 2,4-dinitrophenylhydrazone had m.p. 208–209°, $\lambda_{max}^{CHCl_3}$ 392 mμ (ϵ 26,000).

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 55.12; H, 5.80; N, 15.89.

The phenylurethane had m.p. 132–132.5°.

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.33; H. 7.42; N, 4.70.

Acetylation of II.—A mixture of 3.0 g. of II, 7.5 g. of acetic anhydride, 1.0 g. of anhydrous sodium acetate, and 15 g. of xylene was refluxed for 5 hr. This treatment gave 3.4 g. of the acetylated compound XII: b.p. 128–131° (4.5 mm.); m.p. 41–42°; λ_{max}^{EtOH} 237 and 317 mμ (ϵ 14,600 and 90); ν_{max}^{KBr} 1737, 1256, 1222 (acetate), 1681 (α,β-unsaturated C=O), 1629, 821 (trisubstituted C=C), and 1443 cm.$^{-1}$ ($CH_2C{=}C$).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63; mol. wt., 210. Found: C, 68.62; H, 8.76; mol. wt., 202.

The 2,4-dinitrophenylhydrazone had m.p. 136–136.5°, $\lambda_{max}^{CHCl_3}$ 381 mμ (ϵ 29,500).

Anal. Calcd. for $C_{18}H_{24}N_4O_6$: N, 14.28. Found: N, 14.09.

Dehydrogenation of the Acetylated Compound (XII).—Heating of 1.02 g. of XII with 0.25 g. of palladium–charcoal[21] (palladium content 10%) at 230–235° for 9 hr. in a current of nitrogen gave 0.50 g. of carvacrol (phenylurethane, m.p. and m.m.p. 134–135°) and acetic acid.

Reduction of II with Lithium Aluminum Hydride.—To a suspension of 0.35 g. of lithium aluminum hydride in 19 ml. of ether was added dropwise a solution of 2.00 g. of II in 4 ml. of ether, and then the mixture was refluxed for 4 hr. Thus, 1.96 g. of the crude diol was obtained. The purification by chromatography on a silica gel column with 40 vol. % ethyl acetate in isopropyl ether gave 1.21 g. of an unsaturated diol XIII: m.p. 57–58°; ν_{max}^{KBr} 3351, 1130, 1110 (OH), 3097, 1661, 845 (trisubstituted C=C), 1379 and 1362 (isopropyl), and 1431 cm.$^{-1}$ ($CH_2C{=}C$).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.74; H, 10.92.

When XIII in pyridine was oxidized with chromium trioxide–pyridine complex at room temperature for 2.5 days, it was reconverted to II.

Catalytic Hydrogenation of the Unsaturated Diol XIII.—XIII in ethyl alcohol was hydrogenated in the presence of prereduced palladium hydroxide on calcium carbonate under atmospheric pressure. The uptake of hydrogen amounted to 0.97 mole, and XIII was converted into the saturated diol XIV, m.p. 46–48°.

Proof of the Saturated Diol XIV Being *p*-Menthane-1,2-diol.—Oxidation of a benzene (10 ml.) solution of XIV (0.49 g.) with lead tetraacetate (1.8 g.) at 55°, followed by hydrogen peroxide, gave a keto acid XV: 0.46 g.; ν_{max}^{liq} 3000 (broad), 1715, 1415, 938 (COOH), and 1429 cm.$^{-1}$ (CH_2CO–); ν_{max}^{KBr} of the sodium salt, 1711 (keto group) and 1577 and 1420 cm.$^{-1}$ (COO^-). Oxidation of keto acid XV with sodium hypobromite at 35° afforded β-isopropyladipic acid: m.p. 75.5–76.5°, lit.[22] m.p. 75–76°; ν_{max}^{KBr} 3000 (broad), 1707, 1413, 949 (COOH), and 1390 and 1368 cm.$^{-1}$ (isopropyl). Also, sodium hypoiodite oxidation of XV gave iodoform, m.p. and m.m.p. 120–121°.

When a heterogeneous mixture of the saturated diol XIV and 10% sulfuric acid was refluxed for 2 hr., (±)-carvomenthone (semicarbazone, m.p. and m.m.p. 173–174°) was produced.

4-Hydroxy-*p*-menth-1-en-3-one (III).—Fraction 4-2, b.p. 89–90° (3 mm.), $n^{25}{}_D$ 1.4916, $d^{25}{}_4$ 1.0127, showed bands at 3490, 1136 (OH), 1674 (α,β-unsaturated C=O), 1380 and 1359 (isopropyl), 3026, 1631, 832 (trisubstituted C=C), and 1430 cm.$^{-1}$ ($CH_2C{=}C$) in the infrared spectrum (liquid film), and λ_{max}^{EtOH} 234 and 318 mμ (ϵ 11,000 and 100) in the ultraviolet. Also, the infrared spectrum in 0.005 *M* carbon tetrachloride solution exhibited the sharp hydroxyl and the carbonyl band only at 3511 and 1678 cm.$^{-1}$, respectively.

The 2,4-dinitrophenylhydrazone had m.p. 151–152°, $\lambda_{max}^{CHCl_3}$ 389 mμ (ϵ 28,860).

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 54.87; H, 5.79; N, 16.17.

Digestion of the keto alcohol III (0.22 g.) with 0.03 g. of palladium–charcoal[21] (palladium content 10%) at 230–240° for 15 hr. in a current of nitrogen gave thymol (0.11 g.), which was identified as thymoxyacetic acid, m.p. and m.m.p. 148–149°.

***p*-Menth-3-ene-1,2-diol (XIII).**—This compound was not obtained in a pure state. However, the gas chromatogram [3-m. column of 3% Thermol-1 (Shimadzu Seisakusho Ltd., Kyoto) on quartz (150–200 mesh) at 140° and 50 ml. of helium/min.] of fraction 6 showed a small peak having the same retention time as that of *p*-menth-3-ene-1,2-diol, in addition to the peaks of IV and II.

Carvacrol (IV) and Thymol (V).—The infrared spectrum of fraction 4-1, b.p. 85–88° (3 mm.), $n^{25}{}_D$ 1.5186, $d^{25}{}_4$ 0.9697, λ_{max}^{EtOH} 275 and 282 mμ (ϵ 2320 and 2110), coincided with that of the authentic carvacrol, and this fraction gave only carvacryl phenylurethane, m.p. and m.m.p. 134–135°. However, its gas chromatogram (3-m. column of silicone DC-550 on Celite at 150° and 60 ml. of helium/min.) showed a small peak, t_R 36.08 min., corresponding to that of thymol, in addition to a large peak, t_R 38.31 min., of carvacrol, indicating the presence of thymol in 8%.

Treatment of the fraction 5 with 5% potassium hydroxide solution gave 0.72 g. of a phenolic substance which consisted of carvacrol (96%) and thymol (4%).

***p*-Cymene (VIII) and *p*-Isopropenyltoluene (X).**—The gas chromatogram (4.5-m. column of Thermol-1 on Celite at 135° and 60 ml. of helium/min.; 3-m. column of P.E.G.-6000 on Celite at 80° and 60 ml. of helium/min.) of fraction 1 did not show any peak of unchanged α-terpinene, but only a peak corresponding to *p*-cymene. This hydrocarbon was confirmed by infrared and ultraviolet spectra comparison.

The gas chromatogram of fraction 2 indicated this fraction to consist of VIII (68%) and X (31%). The latter hydrocarbon, isolated by means of gas chromatography (Thermol-1 on Celite), was identified by infrared and ultraviolet spectra comparison and by degradation into *p*-methylacetophenone and formaldehyde on ozonolysis.

***p*-Methylacetophenone (XI) and 8-Hydroxy-*p*-cymene (IX).**—Fraction 3 was further separated into four fractions by column chromatography on silica gel with 20 vol. % ethyl acetate in *n*-hexane. The first fraction, 1.18 g., consisted of VIII (51%) and X (49%). The fourth fraction, 2.05 g., was II. The second fraction, 0.72 g., λ_{max}^{EtOH} 247 mμ, ν_{max}^{liq} 1677 cm.$^{-1}$ (C=O), gave *p*-methylacetophenone 2,4-dinitrophenylhydrazone, m.p. and m.m.p. 262–263°. The third fraction, 0.67 g., was mainly III, but the gas chromatogram (6-m. column of silicone DC-550 on Celite at 180° and 100-ml. of helium/min.) showed a small peak having the same retention time, t_R 15.2 min., as that of 8-hydroxy-*p*-cymene. Also, the chromatostrip chromatogram showed a spot corresponding to this alcohol.

Acknowledgment.—The authors wish to express their hearty thanks to Messrs. A. Ogawa, K. Saito, H. Ôtani, and A. Kinozaki, and to the late Mr. S. Hoshika, who assisted in a part of this research, and the late Miss K. Iwata of the Faculty of Pharmacy of Kyoto University for microanalysis. This research was aided by a grant from the Ministry of Education in Japan.

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