

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON, SEATTLE, WASH.]

The Mechanisms of Permanganate Oxidation. Oxidation of Tertiary Hydrogens¹BY KENNETH B. WIBERG^{2a} AND ADRIAN S. FOX^{2b}

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The mechanism of the permanganate oxidation of alkanes has been studied in neutral and basic solution by examining the stereochemistry of the oxidation of *p*-*sec*-butylbenzoic acid and 4-methylhexanoic acid and by the use of oxygen-18 as a tracer. Some preliminary kinetic data on the oxidations have also been obtained. The mechanism appears to be similar to that previously proposed for the chromic acid oxidation of hydrocarbons which involves an initial hydrogen atom abstraction.

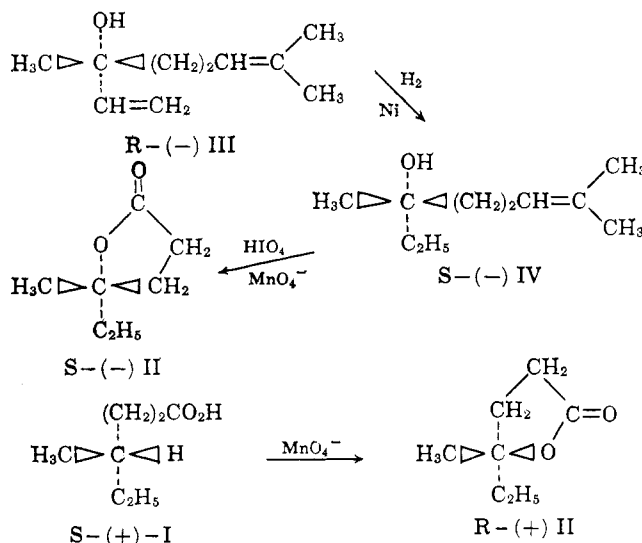
We have previously investigated the chromic acid oxidation of hydrocarbons.³ The effect of substituents and of structural change, and the stereochemistry of the reaction suggested that the initial step was a hydrogen atom abstraction by chromic acid leading to a radical and chromium(V). The latter species combined in the solvent cage to give a chromium(IV) ester with retention of configuration. Hydrolysis with chromium-oxygen bond cleavage then led to the observed tertiary alcohol, formed with retention of configuration. We have now examined the permanganate oxidation of hydrocarbons in order to see if a similar mechanism is found here.

Two interesting results have been reported previously. Kenyon and Symons⁴ have observed that the permanganate oxidation of 4-methylhexanoic acid (I) in dilute alkaline solution led to 4-hydroxy-4-methylhexanoate lactone (II) which was optically active. The compound was assumed to have been formed with inversion of configuration, and the mechanism was thought to involve the abstraction of the tertiary hydrogen as a hydride ion with participation of a carboxyl group leading to the lactone. This would be analogous to the behavior of the 4-chloro-4-methylhexanoic acid which in a solvolytic reaction led to inversion of configuration, presumably by participation of the carboxyl group.⁵ In strongly basic solution, the oxidation led to a lactone formed with complete racemization.

In contrast to this report, Eastman and Quinn⁶ found that the oxidation of dihydro- α -terpineol with alkaline permanganate led to a diol formed with retention of configuration. In this case the reaction was reported to have high stereospecificity. It appeared from the above that the stereochemistry of the permanganate oxidation of 4-methylheptanoic acid was in question, and we have reinvestigated this oxidation. (+)-4-Methylhexanoic acid was prepared from optically pure (-)-2-methyl-1-butanol. The absolute configuration of the latter has been established⁷ and the (+)-acid is thereby shown to be in the R-series.⁸

In order to determine the configuration of the product lactone R-(-)-linalool (III) ($\alpha_D^{25} -15.33^\circ$, $l = 1$, neat, 82% optically pure) was reduced with Raney nickel in absolute ethanol to give S-(-)-dihydrolinalool (IV) ($\alpha_D^{25} -1.15^\circ$, $l = 1$, neat). The latter was oxidized by sodium metaperiodate and lithium permanganate according to the procedure of

Lemieux and Rudloff⁹ to give S-(-)-4-hydroxy-4-methylhexanoate lactone ($\alpha_D^{25} -9.43^\circ$, $l = 1$, neat).¹⁰ The lactone was purified by vapor phase chromatography, saponified, and the hydroxy acid reconverted to the lactone. After repurification, the lactone was found to possess the same rotation as before, showing that no racemization had occurred on ring closure. Since the configuration of linalool has been determined,¹¹ the relative configuration of the acid and the lactone are now known.



At pH 7, S-(+)-4-methylhexanoic acid ($\alpha_D^{26} +10.36^\circ$, $l = 1$, neat) reduced two-thirds of an equivalent of potassium permanganate in 20 min. at 60° . From this reaction mixture 78% of the carboxylic acid having unchanged rotation was recovered and a 4.8% yield of R-(+)-4-hydroxy-4-methylhexanoate lactone ($\alpha_D^{26} +4.76^\circ$, $l = 1$, neat) was obtained. At pH 13, the acid reduced two equivalents of potassium permanganate in 30 min. at 60° and gave 53% recovery of carboxylic acid with unchanged rotation and a 4.6% yield of lactone ($\alpha_D^{25} +3.95^\circ$, $l = 1$, neat). Since the previously given data indicate the lactone to have a maximum rotation $\alpha_D = 11.4^\circ$, the permanganate oxidation of S-(+)-4-methylhexanoic acid to R-(+)-4-hydroxy-4-methylhexanoate lactone at pH 7 and 13 occurred with 42 and 35% retention of configuration, respectively. It is clear from this result that the permanganate oxidation occurs with the same stereochemical result as reported by Eastman and Quinn for the oxidation of dihydro- α -terpineol.

Another compound of interest was *p*-*sec*-butylbenzoic acid, the oxidation of which would permit the determination of the effect of changing from an alkyl

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(3) K. B. Wiberg and R. J. Evans, *Tetrahedron*, **8**, 313 (1960); K. B. Wiberg and G. Foster, *Chem. Ind. (London)*, 108 (1961); K. B. Wiberg and G. Foster, *J. Am. Chem. Soc.*, **83**, 423 (1961).

(4) J. Kenyon and M. C. R. Symons, *J. Chem. Soc.*, 3580 (1953).

(5) E. D. Hughes, *Quart. Rev. (London)*, **5**, 255 (1951).

(6) R. H. Eastman and R. A. Quinn, *J. Am. Chem. Soc.*, **82**, 4249 (1960).

(7) K. Freudenberg and J. Geiger, *Ann.*, **575**, 145 (1952); K. Freudenberg and W. Hohmann, *ibid.*, **584**, 54 (1953).

(8) The notation is that of R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(9) R. U. Lemieux and E. V. Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(10) After the completion of this work, this transformation, using another method of oxidation, was reported by P. Vlad and M. Soucek, *Collection Czech. Chem. Comm.*, **27**, 1726 (1962).

(11) R. H. Cornforth, J. W. Cornforth, and V. Prelog, *Ann.*, **634**, 197 (1960).

group to a phenyl on the degree of retention of configuration. The carboxyl group would not be expected to have much of an effect on the magnitude of rotation and would not change the sign of rotation. For example, the maximum rotation of $(-)$ -2-phenylbutane is -24.2° and that of $(-)$ -*p*-sec-butylbenzoic acid is -23.4° . The absolute configuration of $(-)$ -2-phenylbutane has been determined by Kenyon, Phillips, and Pittman,¹² and Cram and his co-workers¹³ have determined the absolute configuration of $(-)$ -2-phenyl-2-butanol.

The stereochemistry of the permanganate oxidation of *p*-sec-butylbenzoic acid was investigated at pH 7 and 13. At pH 7, one equivalent of the acid ($[\alpha]^{26}_D -23.42^\circ$, c 3.55, $l = 1$, methanol) was allowed to react with two-thirds of an equivalent of potassium permanganate at 60° for 20 min. The mixture of organic acids which was isolated from the reaction mixture was separated into two fractions with refluxing carbon tetrachloride-*n*-hexane (3:1). The insoluble fraction was shown to be *p*-acetylbenzoic acid and was obtained in 14.5% yield. The soluble fraction was separated into two components by a 100-cycle automatic Craig countercurrent distribution apparatus with a methanol-*n*-pentane-water (10:10:1) solvent system. The first component, unreacted *p*-sec-butylbenzoic acid with unchanged rotation, was obtained in 62.5% yield. The second component was $(-)$ - α -hydroxy-*p*-sec-butylbenzoic acid ($[\alpha]^{26}_D -0.034 \pm 0.13^\circ$, c 15.2, $l = 1$, methanol) and was obtained in 10.3% yield.

At pH 13, one equivalent of the acid ($[\alpha]^{26}_D -23.42^\circ$, c 3.55, $l = 1$, methanol) was allowed to react with two equivalents of potassium permanganate at 60° for 30 min. The mixture of organic acids which was isolated from the reaction mixture was separated as before. The insoluble fraction was found to be a mixture of terephthalic acid (3.5%) and *p*-acetylbenzoic acid (0.3%). The soluble fraction was separated using the Craig apparatus. The first fraction was unreacted acid with unchanged rotation and was obtained in 4.8% yield. The second fraction, obtained in 79% yield was found to be pure $(-)$ - α -hydroxy-*p*-sec-butylbenzoic acid ($[\alpha]^{26}_D -1.33 \pm 0.1^\circ$, c 21.9, $l = 1$, methanol). Recrystallization from ether-hexane and an additional 100 cycles of the Craig apparatus did not alter the melting point nor the optical rotation of the hydroxy acid. Therefore the reaction proceeded with virtually 100% racemization at pH 7 and with 6% retention of configuration at pH 13. The stereochemical results are summarized in Table I.

TABLE I
STEREOCHEMICAL RESULTS OF PERMANGANATE OXIDATIONS

Substrate acid	α_D	Optical purity, %	pH	α_D of oxid. prod.	Retention of config., %
4-Methylhexanoic	+10.36°	100	7	+4.76°	42
hexanoic	+10.36	100	13	+3.95	35
<i>p</i> -sec-Butylbenzoic	-23.4	99.6	7	0.0	0
	-23.4	99.6	13	-1.33	6

Another approach which might lead to information on the nature of the reaction involves the use of O^{18} as a tracer. Both the carboxyl group of the acid, and the permanganate ion, may be labeled, and the amount of O^{18} in the oxygen introduced during the reaction may

(12) J. Kenyon, H. Phillips, and V. P. Pittman, *J. Chem. Soc.*, 1072 (1935).

(13) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2149 (1952); D. J. Cram and J. Allinger, *ibid.*, **76**, 4518 (1954); D. J. Cram and J. Tadanier, *ibid.*, **81**, 2137 (1959).¹⁴

(14) The maximum rotation of 2-phenyl-2-butanol was reported as α_D 17.7° leading to an assumed value of α_D 17.2° for α -hydroxy-*p*-sec-butylbenzoic acid

be determined. The lactone was analyzed by reduction with lithium aluminum hydride to 4-methylhexane-1,4-diol, dehydration of the tertiary alcohol grouping, equilibration of the water formed with carbon dioxide, and mass spectral analysis of the latter. The α -hydroxy-*p*-sec-butylbenzoic acid was analyzed in the same fashion, except that the reduction step was not needed. The results of this investigation are shown in Table II.

TABLE II
OXYGEN TRANSFER IN PERMANGANATE OXIDATIONS

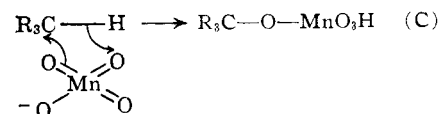
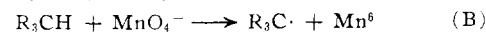
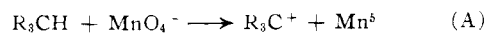
Substrate acid	pH	% O^{18} per oxygen RCO ₂ H	MnO ₄ ⁻	Product	% O^{18} in 3° position	% Oxygen transfer
4-Methylhexanoic	7	...	1.366	4-Hydroxy-4-methylhexanoate	0.585	24.7
Same	7	1.473	...	lactone	.325	8.7
Same	13	1.473	...	lactone	.305	7.4
<i>p</i> -sec-Butylbenzoic	7	...	1.366	α -Hydroxy- <i>p</i> -sec-butylbenzoic acid	.211	0.6

Finally, a preliminary kinetic study was performed. The oxidation was investigated at pH 7 and 13 using phosphate buffers, and the reaction was followed by noting the rate of disappearance of permanganate spectrophotometrically at 510 m μ . At pH 13, plots of $\log (A - A_\infty)$ against time gave a plot with some curvature, but which could be roughly approximated by a straight line. At pH 7, there was an initial rapid reaction corresponding to the oxidation of about 1% of the substrate followed by a plot similar to that found at pH 13. The initial rapid reaction (~ 20 times as fast as the following reaction) may have been due to an impurity, but it was observed with both acids discussed above and also for 5-methylheptanesulfonic acid.

The concentration of acid in the reaction solutions was $1-4 \times 10^{-2} M$, and of permanganate was $4-6 \times 10^{-4} M$. At pH 13 the rate constants (l. mole⁻¹ sec.⁻¹) were: 4-methylhexanoic acid, 7.0×10^{-3} ; 5-methylheptanesulfonic, 3.0×10^{-3} ; and *p*-sec-butylbenzoic, $49. \times 10^{-3}$. Using manganate instead of permanganate at pH 13, the rate constants were: 4-methylhexanoic, 0.4×10^{-3} ; and *p*-sec-butylbenzoic, 1.8×10^{-3} . At pH 7 with permanganate, the rate constants for the slower reaction were: 4-methylhexanoic acid, 1.3×10^{-3} ; 5-methylheptanesulfonic, 0.7×10^{-3} ; and *p*-sec-butylbenzoic, 7.7×10^{-3} . No significance should be attached to the small difference in rate between pH 7 and 13 since the stoichiometry of the reactions differ, and rates refer to both the initial step and the amount of permanganate consumed in subsequent steps (such as oxidation of alkene formed).

Discussion

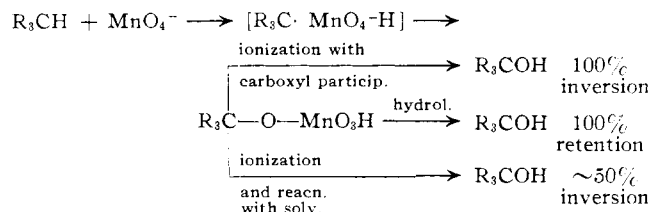
There are relatively few mechanisms which need be considered for the first step of the reaction, which must necessarily involve the abstraction of the tertiary hydrogen. The latter may be removed as a hydride ion or a hydrogen atom (or their equivalents, a proton plus two or one electron), or it may be removed in a cyclic process which effects oxygen insertion.



The abstraction of a hydride ion would lead to a carbonium ion, and for this process one would expect a large difference in rate between an ordinary tertiary hydrogen and a benzylic tertiary hydrogen. The small observed rate factor (~ 6 – 8) suggests that this process is not operative.¹⁵ Either mechanism B or C would accommodate the small difference in rate. We have previously concluded that a process like B is more likely than one like C for the oxidation of tertiary hydrogens by chromic acid,³ and we shall assume that this holds for the permanganate oxidation also. However, it must be stated that all of our data on the permanganate oxidation may be accommodated by mechanism C as well as with B.

If the first step is the removal of a hydrogen atom, the observed stereochemistry and the observation of oxygen transfer indicates that carbon–oxygen–manganese bond formation must follow while the products of the original reaction are still within the solvent cage. Hydrolysis of the manganese ester with manganese–oxygen bond cleavage will give the tertiary alcohol with retention of configuration and with oxygen transfer.

One does not find complete oxygen transfer and one does not observe complete retention of configuration. Thus, it is necessary to try to estimate the part of the reaction which proceeds *via* each of the possible paths. With 4-methylhexanoic acid, 7–9% oxygen transfer from the carboxyl group to the tertiary center is observed. This must involve carboxyl participation in a process forming a carbonium ion. The latter could be formed either by an electron transfer reaction between the initially formed radical and Mn(VI) or by ionization of the manganese ester formed *via* the combination reaction. Since there is no way in which to distinguish between these, for convenience we shall assume that the latter is correct. The net process may then be schematically represented by



If we assume, in analogy with the work of Streitwieser,¹⁶ that an $\text{S}_{\text{N}}1$ reaction of the intermediate ester will give about 50% inversion, the proportion of each of the reactions may be roughly estimated. About 8% of the reaction proceeds with 100% inversion, $x\%$ with 100% retention, and $y\%$ with 50% inversion. The net retention was 40%. Thus

$$0.08(-1.0) + x(+1.0) + y(-0.5) = 0.4$$

and

$$0.08 + x + y = 1.0$$

therefore $x = 0.63$ and $y = 0.29$.

It would appear that 60–65% of the reaction leading to alcohol proceeded *via* hydrolysis of the ester, and this is in accord with the oxygen transfer data. About 25% oxygen-18 was transferred from the permanganate, but it is known¹⁷ that the percentage of oxygen transfer decreases as the extent of reaction increases, presumably *via* induced exchange of the permanganate oxygens with the solvent. With benzaldehyde, for example, there is an apparent 54% transfer through 90% reaction, whereas there appears to be essentially complete trans-

fer at 0% reaction. The amount of induced exchange of the permanganate would be expected to increase with increasing reaction times, and the hydrocarbon oxidation is considerably slower than the aldehyde oxidation. The amount of the *total* reaction which proceeds *via* carbonium ion formation is probably considerably higher than 29%, since a reasonable proportion of the reaction probably involves elimination to an alkene and further oxidation to products which are not isolated. This would account for the relatively low yield of alcohol and low conversion.

With *p*-sec-butylbenzoic acid, if the same mechanism applied, one would expect a much lower degree of retention of configuration since the ionization of the intermediate manganese ester leading to a carbonium ion would be more favored than in the case of 4-methylhexanoic acid, and since there should be little difference in the hydrolysis rates of the two intermediate esters. The retention of configuration is decreased to 0–6% in accord with this expectation, and the amount of oxygen transfer from permanganate is also reduced.

The most interesting aspect of the oxidation of *p*-sec-butylbenzoic acid is the difference in yield between pH 7 and 13. At the former pH, the products were 15% *p*-acetylbenzoic acid, 10% α -hydroxy-*p*-sec-butylbenzoic acid, and 63% recovered starting acid. At the latter pH, the products were 3.5% terephthalic acid, 0.3% *p*-acetylbenzoic acid, 79% α -hydroxy-*p*-sec-butylbenzoic acid, and 5% recovered starting acid. Thus, at the lower pH, more elimination occurred than hydroxy acid formation, whereas at pH 13, elimination was negligible.

In the solvolysis of 2-phenyl-2-butyl chloride in 80% ethanol, the ratio of elimination to substitution was found to be 1.9:1¹⁸ which is in good accord with the oxidation results at pH 7. The higher degree of substitution at pH 13 may arise from the greater stability of the *t*-benzyl radical as compared to the tertiary paraffin radical. If the former had a higher activation energy for combination with manganate ion than the latter, it might diffuse out of the solvent cage and then be oxidized by permanganate to $\text{R}_3\text{C}-\text{O}-\text{MnO}_3^-$. This might undergo hydrolysis with manganese–oxygen bond cleavage more readily than $\text{R}_3\text{C}-\text{O}-\text{MnO}_3\text{H}^-$ and might lead largely to alcohol formation. In principle, this idea could be tested by examining the degree of oxygen transfer at pH 13. However, conditions of high basicity, under which manganate is stable, are those which should be particularly favorable for induced oxygen exchange of permanganate and therefore this experiment does not appear promising. The details of the later steps of the oxidation of *p*-sec-butylbenzoic acid at pH 13 are still in question.

Experimental

(+)-4-Methylhexanoic Acid.—To a cooled, stirred solution of 35.6 g. (1.55 mg.-atoms) of sodium metal in 1.5 l. of anhydrous ethanol was added dropwise 264 g. (1.65 moles) of redistilled diethyl malonate. To this was slowly added 159 g. (1.5 moles) of optically pure (+)-2-methyl-1-chlorobutane¹⁹ ($\alpha_{\text{D}}^{25} + 1.47^\circ$, $l = 1$, neat, derived from (–)-2-methyl-1-butanol, $\alpha_{\text{D}}^{25} - 4.65^\circ$, $l = 1$, neat). After heating to reflux for 48 hr., 950 ml. of a mixture of ethanol and (+)-2-methyl-1-chlorobutane was distilled directly from the reaction mixture. After cooling, 930 ml. of 20% methanolic potassium hydroxide (3.3 moles) was added, and the mixture was heated to reflux for an additional 24 hr. The alkaline solution was distilled under reduced pressure to remove most of the solvent, and an equal volume of water (about 700 ml.) was added. The aqueous solution was washed with ether (2 \times 100 ml.), acidified to pH 1.5 with concentrated hydrochloric acid, and extracted with ether (4 \times 400 ml.). The combined ether solution was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated by dis-

(15) The relative rates of solvolysis of *t*-butyl chloride and cumyl chloride in 90% acetone are 1:620.¹⁶

(16) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

(17) K. B. Wiberg and R. Stewart, *J. Am. Chem. Soc.*, **77**, 1786 (1955).

(18) Private communication from Prof. Y. Pocker.

(19) S. F. Velick and J. English, Jr., *J. Biol. Chem.*, **160**, 473 (1945). The 2-methyl-1-butanol was kindly supplied by the Dow Chemical Co.

tillation through a 12-in. Vigreux column. The residue was heated under reflux at 140° for 36 hr. After cooling, the crude acid was taken up in 300 ml. of ether and was extracted into 200 ml. of cold, saturated sodium bicarbonate solution. The alkaline solution was carefully acidified to pH 1.5 with concentrated hydrochloric acid and was extracted with 400 ml. of ether. The ether solution was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated by distillation through a short column. The residue was distilled giving 80.3 g. (63%) of 4-methylhexanoic acid, b.p. 69–70° at 1 mm., $\alpha_D^{25} + 10.36^\circ$ ($l = 1$, neat), $n_D^{25} 1.4215$.

Sodium (+)-5-Methyl-1-heptanesulfonate.—A mixture of 40.8 g. (0.21 mole) of (+)-5-methyl-1-bromoheptane¹⁹ ($\alpha_D^{25} + 9.22^\circ$, $l = 1$, neat) and 29.0 g. (0.23 mole) of anhydrous sodium sulfite in 300 ml. of water was heated to reflux until the reaction mixture became homogeneous (about 48 hr.). The mixture was cooled to 0° in an ice-salt bath, and the white, crystalline solid which precipitated from the solution was filtered and recrystallized four times from 75% ethanol. After drying under vacuum for 24 hr. at 60° and 0.5 mm., the yield was 26.5 g. (60%) of sodium (+)-5-methyl-1-heptanesulfonate, $[\alpha]_D^{25} + 6.50^\circ$ (c 19.3, $l = 2$).

Anal. Calcd. for $C_8H_{17}SO_3Na \cdot H_2O$: C, 41.0; H, 8.2; S, 13.7. Found: C, 41.0; H, 8.3; S, 13.6.

(-)-4-Hydroxy-4-methylhexanoate Lactone from (-)-Dihydrolinalool.—A mixture of 10.1 g. (96 mmoles) of anhydrous sodium carbonate, 54.9 g. (0.26 mole) of sodium metaperiodate, 0.76 g. (4.3 mmoles) of lithium permanganate trihydrate, and 5.0 g. (30 mmoles) of (-)-dihydrolinalool ($\alpha_D^{25} - 1.15^\circ$, $l = 1$, neat) in 4 l. of distilled water was stirred continuously for 48 hr. Sulfur dioxide was bubbled into the reaction mixture until only a pale yellow color remained. The solution was acidified to pH 1 with concentrated hydrochloric acid and was extracted with ether (5 × 100 ml.). The combined ether solution was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated by distillation through a short column. The residue was washed with 20 ml. of cold 5% sodium carbonate solution and distilled under reduced pressure, giving 2.06 g. (50%) of (-)-4-hydroxy-4-methylhexanoate lactone, $n_D^{25} 1.4389$, $\alpha_D^{25} - 9.43^\circ$ ($l = 1$, neat). The infrared spectrum was identical with that of a known sample of the lactone.

Stability of the Lactone to Hydrolysis and Ring Closure.—A solution of 0.5 g. of (-)-4-hydroxy-4-methylhexanoate lactone ($\alpha_D^{25} - 9.32^\circ$, $l = 1$, neat) in 10 ml. of 10% potassium hydroxide solution was prepared. It was washed with 20 ml. of ether, acidified to pH 1 with concentrated hydrochloric acid, and extracted with 40 ml. of ether. The ether extract was washed with 10 ml. of a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated by distillation. The residue was distilled giving 0.46 g. (92%) of (-)-4-hydroxy-4-methylhexanoate lactone, b.p. 88° at 9 mm., $\alpha_D^{25} - 9.30^\circ$ ($l = 1$, neat).

4-Methylhexanoic Acid-O¹⁸.—A mixture of 89 g. of 4-methylhexanoic acid, 80 ml. of water-O¹⁸ (1.70 atom %), and 5 ml. of concentrated hydrochloric acid was heated to reflux for 36 hr. The reaction mixture was cooled to room temperature and extracted with ether (3 × 75 ml.). The ether solution was washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated by distillation. Distillation of the residue gave 88.5 g. of 4-methylhexanoic acid-O¹⁸, b.p. 70° at 1 mm.

The oxygen-18 content was determined from the mass spectrometer m/e 60 and 62 peaks. These are due to the rearrangement ions $[CH_3CO^{18}O^{16}H_2]^+$ and $[CH_3CO^{16}CO^{18}H_2]^+$, respectively, and are common for most aliphatic carboxylic acids having β -hydrogens.²⁰ The acid was found to have 1.43 atom % oxygen-18.

Permanganate-O¹⁸ Oxidation of (+)-4-Methylhexanoic Acid at pH 7.—To a stirred solution of 25 g. (0.19 mmole) of (+)-4-methylhexanoic acid ($\alpha_D^{25} + 10.36^\circ$, $l = 1$, neat) and 12.6 g. (0.19 mole) of potassium hydroxide in 2 l. of 0.3 M phosphate buffer (0.171 M potassium dihydrogen phosphate and 0.129 M dipotassium hydrogen phosphate) heated on a steam cone to 60°, was added 20.2 g. (0.13 mole, 0.67 equiv.) of solid potassium permanganate (1.366% O¹⁸ per oxygen¹⁷). After approximately 20 min., when the color of the solution had changed to red, the solution was cooled rapidly with an ice-salt bath to 0°. Enough sodium sulfite and concentrated sulfuric acid were added to the cold, stirred solution to decolorize it completely and bring it to pH 2.5. The cold solution was extracted with ether (2 × 850 ml.), and the ether solution was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated by distillation. The concentrate was extracted with cold 10% sodium bicarbonate solution and with 3% sodium carbonate solution, dried over anhydrous sodium sulfate, and distilled giving 1.27 g. (4.8%) of (+)-4-hydroxy-4-methylhexanoate lactone, b.p. 67–68.5° at 1.0 mm. Further purification was effected by vapor phase chromatography at 150° on Carbowax-20M, and it then had $\alpha_D^{25} + 4.76^\circ$ ($l = 1$, neat). The unreacted

acid was isolated from the alkaline solution in the usual fashion giving 19.5 g. (78%) of the acid, $\alpha_D^{25} + 10.36^\circ$ ($l = 1$, neat).

Permanganate Oxidation of 4-Methylhexanoic Acid-O¹⁸ at pH 7.—The above procedure was repeated using 43 g. (0.33 mole) of 4-methylhexanoic acid (1.47% O¹⁸) giving 4.3% pure lactone (by vapor phase chromatography) and 67% 4-methylhexanoic acid.

Permanganate Oxidation of (+)-4-Methylhexanoic Acid-O¹⁸ at pH 13.—A stirred solution of 30 g. (0.23 mole) of (+)-4-methylhexanoic acid-O¹⁸ ($\alpha_D^{25} + 10.36^\circ$, $l = 1$, neat; 1.47% O¹⁸ per oxygen) and 15.2 g. (0.23 mole) of potassium hydroxide in 1 l. of 0.1 N potassium hydroxide containing 0.0166 mole of tripotassium phosphate was allowed to react with 73 g. (0.46 mole, 2 equiv.) of potassium permanganate at 60°. After 30 min. the color of the solution was deep green. The reaction mixture was worked up as described above giving 4.6% (+)-4-hydroxy-4-methylhexanoate lactone ($\alpha_D^{25} + 3.95^\circ$, $l = 1$, neat) and 53% of unchanged (+)-4-methylhexanoic acid.

Permanganate Oxidation of *p*-Isopropylbenzoic Acid at pH 13.

—To 5 g. (0.03 mole) of *p*-isopropylbenzoic acid in 10 ml. of water, was added sufficient 10% potassium hydroxide solution to convert it to the anion. The solution was diluted to 500 ml. with 0.2 N potassium hydroxide solution, and 9.65 g. (0.06 mole, 2 equiv.) of potassium permanganate dissolved in 500 ml. of water was added. The solution was heated at 60° until it became green (about 40 min.). A few drops of glycerol was added, and the reaction mixture was rapidly cooled to 0° in an ice-salt bath. After filtering, the solution was acidified to pH 1 with concentrated hydrochloric acid and extracted with ether (4 × 200 ml.). The combined ether solution was washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness using a rotary evaporator without heating. The residue was washed with 80 ml. of cold carbon tetrachloride to remove unchanged starting material (0.4 g., m.p. 115–117°), and was recrystallized from 200 ml. of boiling water to give 3.2 g. (50%) of α -hydroxy-*p*-isopropylbenzoic acid, m.p. 149–151° (reported²¹ m.p. 155–156°).

Permanganate Oxidation of (-)-*p*-sec-Butylbenzoic Acid at pH 13.—A stirred solution of 4.36 g. (24.5 mmoles) of (-)-*p*-sec-butylbenzoic acid ($[\alpha]_D^{25} - 23.4^\circ$, c 3.55, $l = 1$, methanol) which had been neutralized in 50 ml. of water with 40% potassium hydroxide solution and diluted to 500 ml. with 0.1 N potassium hydroxide, was allowed to react with 7.75 g. (49 mmoles, 2 equiv.) of potassium permanganate at 60°. The procedure given above was followed except that the crude mixed acids were extracted with 180 ml. of boiling carbon tetrachloride-*n*-hexane (1:3). The solution was evaporated to dryness with a rotary evaporator giving 3.9 g. of acid, m.p. 107–119°. The carbon tetrachloride-hexane-insoluble fraction, 0.24 g., was found from its ultraviolet absorption spectrum to be a mixture of 0.144 g. (3.5%) of terephthalic acid and 0.096 g. (2.5%) of *p*-acetylbenzoic acid. The carbon tetrachloride-hexane-soluble fraction, 3.9 g., was completely separated into two fractions using an automatic 100-cycle Craig countercurrent distribution apparatus with a methanol-*n*-pentane-water (10:10:1) solvent system. The first fraction, 0.212 g. (4.8%) was unchanged (-)-*p*-sec-butylbenzoic acid, m.p. 90–91°, $[\alpha]_D^{25} - 23.3^\circ$ (c 15.7, $l = 1$, methanol). The second fraction, 3.69 g. (79%), was pure (-)- α -hydroxy-*p*-sec-butylbenzoic acid, m.p. 122.5–123°, $[\alpha]_D^{25} - 1.33^\circ$ (c 21.9, $l = 1$, methanol).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3; neut. equiv., 194. Found: C, 68.5; H, 7.1; neut. equiv., 190.

Recrystallization from ether-*n*-hexane did not alter the melting point or the rotation.

Permanganate-O¹⁸ Oxidation of (-)-*p*-sec-Butylbenzoic Acid at pH 7.—To 3.27 g. (18 mmoles) of (-)-*p*-sec-butylbenzoic acid ($[\alpha]_D^{25} - 23.4^\circ$, c 3.55, $l = 1$, methanol), which had been neutralized with a 40% solution of potassium hydroxide in 60 ml. of water and diluted to 750 ml. with pH 7 phosphate buffer solution, was added 1.93 g. (12 mmoles, 0.67 equiv.) of potassium permanganate-O¹⁸ (1.366% O¹⁸ per oxygen¹⁷) at 60° with stirring. The reaction mixture was worked up as described above giving 0.45 g. of carbon tetrachloride-*n*-hexane-insoluble material and 3.09 g. of soluble material. The latter was separated by countercurrent distribution into 0.42 g. of (-)- α -hydroxy-*p*-sec-butylbenzoic acid, m.p. 122–123°, $[\alpha]_D^{25} - 0.03 \pm 0.13^\circ$ (c 15.2, $l = 1$, methanol), and 2.54 g. of unchanged starting material. The carbon tetrachloride-hexane-insoluble material was largely *p*-acetylbenzoic acid.

Oxygen-18 Analysis. a. α -Hydroxy-O¹⁸-*p*-sec-butylbenzoic Acid.—A small sample (about 0.15 g.) of the hydroxy acid and a small piece of iodine were placed in a 2.5-ml. gas bulb which was evacuated to 10^{-4} mm. About 40 mm. of carbon dioxide was admitted into the bulb, and the reaction mixture was heated for 1 hr. at 90°. The oxygen-18 content of the tertiary hydroxy group was calculated from the mass spectrometrically determined oxygen-18 content of the carbon dioxide.

(20) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier Press Co., New York, N. Y., 1960, p. 274.

(21) R. Meyer, *Ann.*, **220**, 1 (1883); **219**, 234 (1883).

b. **4-Hydroxy-O¹⁸-4-methylhexanoate Lactone.**—The labeled lactone (0.86 g.) in 5 ml. of ether was added to a slurry of 0.25 g. of lithium aluminum hydride in 25 ml. of anhydrous ether. The reaction mixture was stirred for 45 min., and was then decomposed with 10 ml. of 30% Rochelle salt solution. The ether layer was decanted, dried over anhydrous potassium carbonate, and concentrated by distillation. The viscous residue was distilled, giving 0.75 g. (85%) of 4-methylhexane-1,4-diol, b.p. 87–89° at 0.5 mm. n_D^{20} 1.4556. About 0.2 g. of the diol and a small piece of iodine were heated to 70° for 1 hr. in a 2.5-ml. gas bulb containing 15 mm. of carbon dioxide. Mass spectrometric analysis of the carbon dioxide permitted the calculation of O¹⁸ content of the tertiary hydroxy position. Absence of reaction at the primary hydroxy position was demonstrated by repeating the equilibration using 4-methyl-1-hexanol-O¹⁸. A negligible amount of exchange (0.9%) occurred under the reaction conditions given above.

Kinetic Studies.—The pH 7 buffer solution was prepared by dissolving 7.465 g. of potassium hydrogen phosphate and 7.776

g. of potassium dihydrogen phosphate in a small amount of boiled distilled water, and diluting this to 1 l. in a volumetric flask (ionic strength 0.243 *M*). The pH 13 solution was prepared by dissolving 3.06 g. of tripotassium phosphate in a small amount of 0.1 *N* potassium hydroxide solution and diluting to 1 l. with the latter.

The solutions of the acids were prepared by weighing out appropriate quantities of the acid, neutralizing with potassium hydroxide, and diluting to volume with the buffer solution. Permanganate solutions were freshly prepared in the same buffers. In one arm of a U-tube attached to a Beckman cell was placed 3 ml. of the acid solution, and in the other was placed 3 ml. of the permanganate solution (about 10⁻⁴ *M*). The solutions were brought to 25° and transferred to the Beckman cell by rapid inversion of the tube. The rate of reaction was determined from the rate of change of optical density at 510 μ (permanganate). During the run, the cell was maintained in a thermostated water bath placed in the light path of the spectrometer.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY, DURHAM, N. C.]

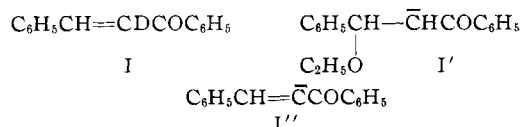
Base-Catalyzed Hydrogen-Deuterium Exchange at the α -Carbon of β -Phenylindenone¹

BY BERNARD W. ROCKETT, THOMAS M. HARRIS, AND CHARLES R. HAUSER

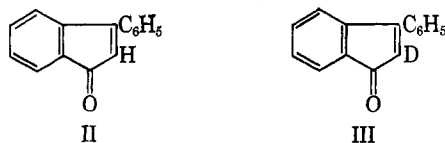
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Deuteration of β -phenylindenone (II) was effected with deuterioethanol by means of sodium ethoxide at 0° to form the α -deuterio derivative III. This result is in agreement with an addition-elimination exchange mechanism, but not with one involving ionization of the α -vinyl hydrogen.

Deuterations of ethyl cinnamate, chalcone, and certain related compounds have recently been effected with deuterioethanol by means of a catalytic amount of sodium ethoxide.² The reaction involved replacement of the α -vinyl hydrogen of the α,β -unsaturated compound by deuterium to form the corresponding α -deuterio derivative; for example, chalcone gave I. Some evidence was presented for an addition-elimination mechanism through carbanion I'. However, an alternative mechanism involving ionization of the α -vinyl hydrogen to form carbanion I'' as the reactive intermediate was not excluded.

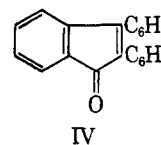


We have now observed a similar deuteration of β -phenylindenone (II), which may be regarded as a cyclic analog of chalcone. The deuteration was effected with deuterioethanol and sodium ethoxide at 0°. To facilitate the hydrogen-deuterium exchange at this temperature a molecular equivalent of sodium ethoxide and a large excess of deuterioethanol were used, although only a catalytic amount of the base should be required. The product III was isolated as its *p*-nitrophenylhydrazone since the free ketone (II or III) was obtained as a liquid which was sensitive to air oxidation. This derivative contained 1.0 deuterium atom per molecule.

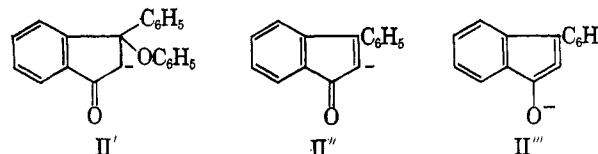


The deuteration of II produced appreciable changes in the infrared spectrum of the *p*-nitrophenylhydrazone. Some bands became weak or disappeared while other bands appeared (see Experimental). Similar spectral changes have been observed previously for other

deuterations.^{2,3} It should be pointed out that both the deuterated and undeuterated compounds showed similar infrared N–H stretching frequencies at 3295 cm^{-1} . This indicates that deuterium had not replaced substantially the hydrogen on nitrogen in the *p*-nitrophenylhydrazone during the work-up procedure. That deuteration had involved exchange of the α -hydrogen of ketone II, not one or more of the aromatic hydrogens, was supported by the failure of α,β -diphenylindenone (IV) to undergo a significant deuterium-hydrogen exchange (only 0.04 D atom/molecule) under conditions similar to those used for deuteration of II (see Experimental).



The deuteration of II to form III is considered to involve the addition-elimination mechanism through carbanion II', not ionization of the α -vinyl hydrogen to form carbanion II'', since stabilization of II'' would require the unlikely resonance structure II'''.⁴



During the course of this work the related deuteration of Δ^1 -5 α -androsten-3-one to form the compound indicated in V was reported.⁵ The exchange that occurred at the 2-position was considered to involve the addition-elimination mechanism.⁵ This, which resulted in a six-membered ring and ours in a five-membered ring, complement one another.

(1) Supported by the National Science Foundation, NSF-G14527.
(2) M. F. Zinn, T. M. Harris, D. G. Hill, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 71 (1963).

(4) See E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1959, p. 388.

(5) R. H. Shapiro, J. M. Wilson, and C. Djerassi, *Steroids*, **1**, 1 (1963).