A 9.6-g (0.031 mole) sample of the crude unsaturated ester was hydrogenated in ethyl alcohol using platinum oxide catalyst. Saponification and acidification produced 4.5 g. (56.5%) of C_{14}-isomeric acids, m.p. 123–125°. After two recrystallizations from ethyl acetate, tetradecanedioic acid,[11] m.p. 125–126°, was obtained.

Anal. Calcd. for $C_{14}H_{26}O_4$: neut. equiv., 129.2. Found: neut. equiv., 132.

IV. **Generation of Acetylethyl Radicals (CH_3COCH_2-CH_2·).**—An aqueous mixture of 57.1 g. (0.5 mole) of acetonyl acetone and 63 g. of 30% aqueous hydrogen peroxide was reductively cleaved in the usual fashion in the presence of 1,3-butadiene (54 g. or 1 mole) in 150 ml. of nitrogen-saturated methanol. The crude unsaturated diketones (25 g., 40%) were distilled through a 6-inch Vigreux column.

Fraction	B.p. °C.	B.p. Mm.	Weight, g.	n^{25}_D
1	40–95	0.5	6.5	1.4362
2	130–133	.5	3.2	1.4729
3	129–139	.5	1.5	1.4722
4	145	.55	4.9	1.4728
5	145–150	.55	5.1	1.4700
6	152–154	.58	2.0	....
7	Residue		4.8	

Analysis of fractions 2–6 showed that as the distillation proceeded, the composition of the distillate approached that of a C_{16}-unsaturated diketone.

Anal. Calcd. for $C_{16}H_{38}O_2$: C, 76.76; H, 10.46; quant. hydrog., 0.0159 g. H_2/g. Found for fraction 3: C, 73.95; H, 10.52. Found for fraction 6: C, 75.42; H, 10.23; quant. hydrog., 0.0171 g. H_2/g.

A sample (4.2 g., 0.17 mole) of fraction 5 was hydrogenated in ethyl alcohol (25 ml.) using platinum oxide catalyst. The sample absorbed about the theoretical amount of hydrogen. The hydrogenation mixture was diluted with 25 ml. of ethyl alcohol, warmed to dissolve the precipitated solid product, and filtered to remove the catalyst. After dilution with 10 ml. of water, the solution deposited 2.38 g. (57%) of isomeric diketones, m.p. 76–80.5°. Recrystallization from 25 ml. of methanol gave 1.25 g. (30%) of diketone (white plates, m.p. 85–87.5°) that was identified as 2,15-hexadecanedione.[12,13] The semicarbazone melted at 204.5–205.5°.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.55; H, 11.88; mol. wt., 254.4. Found: C, 75.38; H, 11.67; mol. wt., 248.

WILMINGTON, DELAWARE

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[11] P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1926), reported m.p. 125.8°.

[12] M. Stoll, *Helv. Chim. Acta*, **34**, 1817 (1951), reported m.p. 83–84° for the ketone and m.p. 214–216° for the semicarbazone.

[13] L. Canonica and T. Bacchetti, *Atti. accad. nazl. Lincei, Rend. Sci. fis., mat. e. nat.*, **10**, 479 (1951), (*C. A.*, **48**, 6377 (1954)), reported m.p. 83° for 2,15-hexadecanedione.

[CONTRIBUTION NO. 433 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Syntheses by Free-radical Reactions. V. A New Synthesis of Carboxylic Acids

BY D. D. COFFMAN, RICHARD CRAMER AND W. E. MOCHEL

RECEIVED NOVEMBER 25, 1957

A new method of carboxylation has been discovered in which the hydrogen atom in the compound RH is replaced by a carboxyl group through reaction with hydrogen peroxide, ferrous sulfate and carbon monoxide at atmospheric pressure. In addition to the carboxylic acid, RCOOH, a coupled product R–R is formed. The acid synthesis appears to include as one step the fast reaction $R\cdot + CO \longrightarrow RC{=}O$.

The action of hydroxyl radicals from ferrous sulfate and hydrogen peroxide (Fenton reagent) on organic compounds in aqueous solution is known[1] to bring about hydrogen abstraction, forming radicals which dimerize in high yields.

$$RH + HO\cdot \longrightarrow R\cdot + H_2O \qquad (1)$$

$$2R\cdot \longrightarrow R\text{–}R \qquad (2)$$

Since carbon monoxide can add to alkyl radicals to yield acyl radicals,[2–5] it seemed likely that carbon monoxide might react with alkyl radicals generated by Fenton reagent to give carboxylic acids. Formally, the reaction might be represented by equation 3. Carboxylation did occur when carbon monoxide at atmospheric pressure was bubbled

$$RH + CO + H_2O_2 \xrightarrow{Fe^{2+}} RCOOH + H_2O \qquad (3)$$

through an aqueous reaction mixture containing an organic reactant, RH, ferrous sulfate and hydrogen peroxide. The acid synthesis was accompanied by dimerization of the radicals R· to yield the coupled product R–R. This novel method of carboxylation has been employed in the synthesis of hydroxy-, amino- and cyanocarboxylic acids from the corresponding alcohol, amine or nitrile, and in the conversion of a monocarboxylic acid to a dicarboxylic acid. Table I lists the organic reactants used in conjunction with the Fenton reagent and carbon monoxide, the products formed, and the conversions per mole of hydrogen peroxide used.

Generally, for best yields, the compound to be carboxylated should be appreciably soluble in the aqueous medium and should not be susceptible to oxidative degradation by hydrogen peroxide. Furthermore, since attack by hydroxyl radicals is not selective, any carbon–hydrogen bond may be broken to yield the radical which is carboxylated. Therefore, isomeric products will be formed unless symmetrical reactants containing only equivalent carbon–hydrogen bonds are employed. The deactivating effect of a carboxyl group attached to a substituted methyl radical was apparent in unsuccessful attempts to carboxylate acetic acid and propionic acid, which did not yield malonic acid or methylmalonic acid, respectively.

Synthesis Conditions.—Carboxylation was accomplished at room temperature by introducing hydrogen peroxide, ferrous sulfate and carbon

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[1] D. D. Coffman, E. L. Jenner and R. D. Lipscomb, THIS JOURNAL, **80**, 2864 (1958).

[2] M. M. Brubaker, D. D. Coffman and H. H. Hoehn, *ibid.*, **74**, 1509 (1952); D. D. Coffman, P. S. Pinkney, F. T. Wall, W. H. Wood and H. S. Young, *ibid.*, **74**, 3391 (1952).

[3] T. L. Cairns, D. D. Coffman, Richard Cramer, A. W. Larchar and B. C. McKusick, *ibid.*, **76**, 3024 (1954).

[4] R. E. Foster, A. W. Larchar, R. D. Lipscomb and B. C. McKusick, *ibid.*, **78**, 5606 (1956).

[5] K. Faltings, *Ber.*, **72B**, 1207 (1939).

TABLE I

CARBOXYLATIONS ACCOMPLISHED BY REACTIONS OF HYDROXYL RADICALS, CARBON MONOXIDE, AND AN ORGANIC REACTANT

Organic reactant, RH	Product	Conversion, mole/mole of H_2O_2
$HOC(CH_3)_3$	$HOC(CH_3)_2CH_2COOH$	0.23[a]
	$[HOC(CH_3)_2CH_2]_2$	.33[a]
$H_2NC(CH_3)_3$	$H_2NC(CH_3)_2CH_2COOH$	.1
$NCC(CH_3)_3$	$NCC(CH_3)_2CH_2COOH$	.2[b]
	$[NCC(CH_3)_2CH_2]_2$	.07
$HOOCCH_2CH_3$	$HOOCCH_2CH_2COOH$	.05[c]
	$HOOCCH(CH_3)CH(CH_3)COOH$	.02
	$HOOC(CH_2)_4COOH$	.02
$HOOCCH_3$	$HOOCCH_2CH_2COOH$	.01[c]

Except as noted in *a* and *c*, the carbon monoxide was at atmospheric pressure. [a] In batch synthesis at 150–200 lb./sq. in., the conversions were 0.48 mole of acid and 0.1 mole of coupled product; constant environment synthesis at 750 lb./sq. in. gave 0.37 mole and 0.2 mole, respectively. [b] *unsym*-Dimethylsuccinimide and *unsym*-dimethylsuccinic acid were also formed. [c] This carboxylation was effected at 150 lb./sq. in.

monoxide simultaneously into a vigorously stirred aqueous solution containing an excess of the organic reactant. The preferred hydrogen peroxide–ferrous sulfate mole ratio varied with the carbon monoxide pressure and with the organic compound to be carboxylated. In the carboxylation of *t*-butyl alcohol, which was studied in detail, the preferred hydrogen peroxide–ferrous sulfate ratio was 1:0.6 for reactions at atmospheric pressure. In such syntheses the ferrous sulfate and hydrogen peroxide were completely consumed, and the yields of acid and coupled product were, respectively, 0.23 mole and 0.33 mole per mole of hydrogen peroxide. In many experiments, a 1:1 ratio was used giving maximum yields of 0.16 and 0.28 mole, respectively. At 750 lb./sq. in., the preferred ratio was 1:0.50. Reactants should be added in these ratios throughout the synthesis.

The yield of carboxylic acid was found sensitive to an excess of ferrous sulfate or of hydrogen peroxide (Fig. 1), while the yield of coupled product formed concurrently was scarcely affected. Thus, carboxylation of *t*-butyl alcohol under balanced conditions gave 0.17 mole of acid, but with excess ferrous sulfate or hydrogen peroxide the yield of acid decreased to less than 0.03 mole. The yield of tetramethyltetramethylene glycol (product of the coupling reaction), however, remained at 0.25 ± 0.04 mole throughout.

Variations in reaction time (15 min. to 3 hr.) or in temperature (0 to 30°) did not affect the yield of acid or coupled product. In the presence of oxygen, neither carboxylic acid nor coupled product was formed.

Carboxylation also has been accomplished through use of hydroxyl radicals generated by photolysis of hydrogen peroxide. Under these circumstances, 0.24 mole of β-hydroxyisovaleric acid was obtained from *t*-butyl alcohol per mole of hydrogen peroxide consumed.

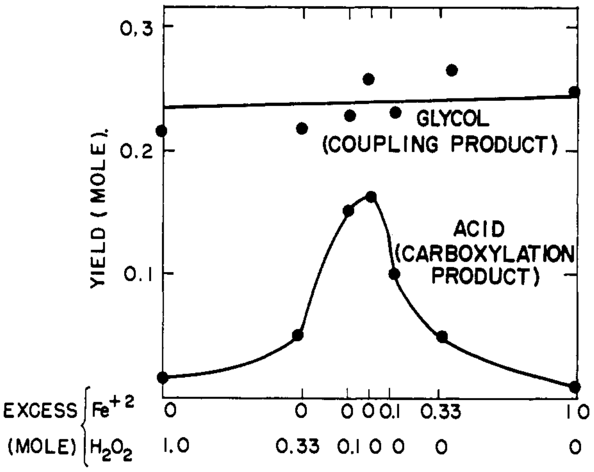
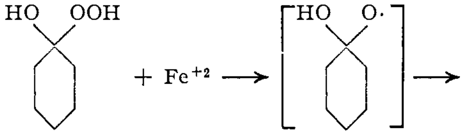


Fig. 1.—Effect of excess hydrogen peroxide or ferrous ion upon carboxylation and coupling. The experiments summarized in this figure relate to the carboxylation of *t*-butyl alcohol at atmospheric pressure. A mole each of hydrogen peroxide and ferrous sulfate were added concurrently and equivalently as aqueous solutions to an aqueous solution of 10 moles of *t*-butyl alcohol and up to one mole of either hydrogen peroxide or ferrous sulfate while carbon monoxide was bubbled through the reaction mixture.

In another modification of this synthesis, alkyl radicals obtained by reductive cleavage of a hydroxyhydroperoxide have been carboxylated. Thus, 1-hydroxycyclohexyl hydroperoxide was converted to pimelic acid when reductively cleaved with aqueous ferrous sulfate in the presence of carbon monoxide.



$$HOOC(CH_2)_4CH_2\cdot + Fe^{+2}(OH) \quad (4)$$

$$HOOC(CH_2)_4CH_2\cdot + CO \longrightarrow HOOC(CH_2)_5COOH \quad (5)$$

Mechanism.—A synthesis mechanism essentially in accord with the experimental results is summarized in equations 6 through 10.

$$H_2O_2 + Fe^{2+} \longrightarrow HO\cdot + HO^- + Fe^{3+} \quad (6)$$

$$HO\cdot + RH \longrightarrow R\cdot + H_2O \quad (7)$$

$$R\cdot + CO \longrightarrow R\overset{\overset{O}{\|}}{C}\cdot \quad (8)$$

$$R\overset{\overset{O}{\|}}{C}\cdot + Fe^{3+} \longrightarrow R\overset{+}{C}O + Fe^{2+} \quad (9)$$

$$R\overset{+}{C}O + \overset{-}{O}H \longrightarrow RCOOH \quad (10)$$

The chemistry of equations 9 and 10 may possibly be represented more accurately by equation 11.

$$R\overset{\overset{O}{\|}}{C}\cdot + Fe(OH)^{2+} \longrightarrow RCOOH + Fe^{2+} \quad (11)$$

The formation of alkyl radicals by hydrogen abstraction with hydroxyl radicals (equation 7) is borne out by the isolation of coupled products (R–R) which are formed in the absence[1] or in the presence of carbon monoxide.

The addition of carbon monoxide to allyl radicals to form acyl radicals (equation 8) has been reported in the copolymerization of ethylene with carbon monoxide.[2,3] Walling[6] has pointed out that the change in composition of ethylene–carbon monoxide copolymers as total pressure on the polymerization system is changed can be explained on the assumption that during copolymerization equilibrium is attained in the reaction

$$\mathrm{RCH_2CH_2\cdot + CO \rightleftarrows RCH_2CH_2C{=}O}$$

Since equilibrium is approached from the left and is reached in spite of competition with ethylene for alkyl radicals, it must be a fast reaction. In the carboxylic acid synthesis, the addition of carbon monoxide to alkyl radicals must be exceedingly fast, since, even at low concentrations of carbon monoxide, carboxylic acid is formed in spite of the competitive consumption of alkyl radicals by dimerization. Although the equilibrium concentration of carbon monoxide in the acid synthesis was less than 0.007 molar, the acid was synthesized easily at a rate greater than 0.3 mole per liter per hour at 20°.

Oxidation of acyl radicals to carbonium ions and neutralization (equations 9 and 10) complete the carboxylation reaction. The basis for these steps is reduction in the yield of carboxylic acid when ferric ion (equation 6) was complexed by the addition of fluoride ion to the reaction mixture (see Table II).

Table II

Effect of Fluoride Ion on the Carboxylation of *t*-Butyl Alcohol[a]

Salt added (moles)	β-Hydroxyisovaleric acid formed, moles
None	0.17
Sodium fluoride (6.5)	.07
Sodium perchlorate (10)	.14
Ferric sulfate	.19

[a] One mole each of ferrous sulfate and hydrogen peroxide were employed in these carboxylations.

Although reduction in the yield of acid accompanied a reduction in ferric ion concentration, the acid synthesis still proceeded at very low levels of ferric ion. Thus, when the concentration of ferric ion was reduced to 10^{-2} *M* (determined colorimetrically) by addition of fluoride ion, 0.07 mole of acid or 40% of the normal yield was obtained. The addition of sodium perchlorate, a salt which does not form a complex with ferric ion, did not affect the yield significantly. Also, the addition of excess ferric ion was without significant effect.

Other mechanisms including (a) the addition of a carboxyl to an alkyl radical, (b) the addition of hydroxyl radical to an acyl radical and (c) the cleavage of hydrogen peroxide by an acyl radical have been considered to be unsatisfactory.

(a) **Carboxylation by Addition of Carboxyl and Alkyl Radicals.**—This is not in agreement with the

$$\mathrm{HO\cdot + CO \longrightarrow \cdot COOH} \qquad (12)$$

$$\mathrm{R\cdot + \cdot COOH \longrightarrow RCOOH} \qquad (13)$$

stoichiometry observed. The formation of a mole of carboxylic acid by this mechanism requires two moles of hydroxyl radical, hence two moles of ferrous ion. Two moles of ferrous ions are also consumed in giving a mole of coupled product. Hence, each mole of product, whether acid or coupled product, requires two moles of ferrous ion. Actually, more than a mole of product has been obtained from as little as 1.2 moles of ferrous sulfate; specifically, 0.6 mole of ferrous sulfate produced 0.23 mole of acid and 0.33 mole of coupled product.

Also the relative availability of carboxyl and alkyl radicals is not favorable. The formation of carboxylic acid in good yields by combination of alkyl and carboxyl radicals requires that both species be present in about equal concentrations. If one species is in great preponderance, that species will react principally by dimerization. Merz and Waters[7] reported the ratio of reaction rate constants for the reaction of hydroxyl radical with *t*-butyl alcohol and ferrous ion to be 0.65. Dainton and Hardwick[8] found the ratio of reaction rate constants for hydroxyl radical with carbon monoxide and ferrous ion to be 2.6. Consequently, the rate constant ratio for the reaction of hydroxyl radicals with carbon monoxide and *t*-butyl alcohol is 4. However, since the concentration ratio is less than 1:500, carbon monoxide can scarcely compete with *t*-butyl alcohol for hydroxyl radicals, and it does not appear likely that sufficient carboxyl radical would be formed to serve as an intermediate in the carboxylation.

A further consideration is the effect of concentration of the organic reactant RH upon the ratio of coupled product to carboxylic acid formed. In the competition of RH and carbon monoxide for hydroxyl radicals, reduction in the concentration of RH would favor a higher concentration of ·COOH radicals relative to R· radicals and should result in the formation of more carboxylic acid relative to coupled product. Instead, as is shown in Table III, reduction in the concentration of RH had little effect upon the ratio of coupled product to acid.

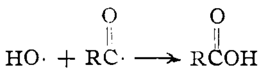
Table III

Effect of *t*-Butyl Alcohol Concentration Upon Relative Amounts of β-Hydroxyisovaleric Acid and Tetramethyltetramethylene Glycol[a]

Concn. of *t*-butyl alcohol, *M*	$\frac{\text{Moles glycol}}{\text{Moles acid}}$
4	1.8
0.4	2.0

[a] These experiments were made according to the procedure summarized in the Experimental section for Carboxylation of *t*-Butyl Alcohol at Atmospheric Pressure. The charge of *t*-butyl alcohol was reduced to 90 ml. in the second experiment, and the amount of water was increased correspondingly.

(b) **Carboxylation by Addition of Hydroxyl Radical to an Acyl Radical.**—Here also the stoi-



$$\mathrm{HO\cdot + R\overset{O}{\overset{\|}{C}}\cdot \longrightarrow R\overset{O}{\overset{\|}{C}}OH} \qquad (14)$$

chiometric requirements are the same as for carboxylation by combination of alkyl and carboxyl radicals and are not satisfied by experiment. Also, if the combination of acyl radicals with hydroxyl radical is involved in the carboxylation, it would be expected that dimerization of acyl radicals or

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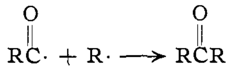
(6) C. Walling, *J. Polymer Sci.*, **16**, 315 (1955).

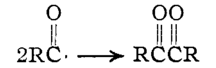
(7) J. H. Merz and W. A. Waters, *J. Chem. Soc.*, S15 (1949).

(8) F. S. Dainton and T. J. Hardwick, *Trans. Faraday Soc.*, **53**, 333 (1957).

combination of acyl radicals with alkyl radicals (equations 15 and 16) would be competitive. Ketonic products were not found.

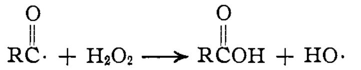


$$\mathrm{R\overset{O}{\overset{\|}{C}}\cdot + R\cdot \longrightarrow R\overset{O}{\overset{\|}{C}}R} \tag{15}$$



$$\mathrm{2R\overset{O}{\overset{\|}{C}}\cdot \longrightarrow R\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}R} \tag{16}$$

(c) Carboxylation by Reaction of Acyl Radicals with Hydrogen Peroxide to Give Carboxylic Acid and Regenerate Hydroxyl Radicals.—This reaction does not appear to be a step of the mechanism because higher hydrogen peroxide concentrations, instead of providing higher yields of acid as might be expected from equation 17, actually result in greatly reduced yields of acid (Fig. 1). Since the yield of coupled product was nearly unaltered (Fig. 1), excess hydrogen peroxide apparently did not interfere with the formation of hydroxyl or alkyl radicals.



$$\mathrm{R\overset{O}{\overset{\|}{C}}\cdot + H_2O_2 \longrightarrow R\overset{O}{\overset{\|}{C}}OH + HO\cdot} \tag{17}$$

It should be noted that the preferred mechanism (equations 6 to 10 inclusive) does not account for the effect of excess hydrogen peroxide or ferrous sulfate on the yield of acid (Fig. 1). Several explanations of this effect can be offered, but they have been omitted in the absence of experimental verification. To reconcile the photochemical carboxylation with the preferred mechanism it must be assumed that the trace of iron (0.04 p.p.m.) in the system was sufficient for oxidation of acyl radicals (equation 9).

Experimental

Carboxylation of *t*-Butyl Alcohol at Atmospheric Pressure.[9]—The reaction vessel was a 5-l., 5-necked flask fitted with two graduated dropping funnels, a glass, propeller-type stirrer, a thermometer and a sintered glass tube for introduction of carbon monoxide beneath the surface of the reaction mixture. The neck through which the stirrer entered the flask was left open for exit of unreacted carbon monoxide. The flask was charged with 900 ml. (10 moles) of *t*-butyl alcohol, 1600 ml. of water and 27 ml. (0.5 mole) of concd. sulfuric acid. This solution was chilled to 15–20° by cooling with an ice-water-bath, and the flask was kept in this bath during the reaction. One of the dropping funnels contained a solution of 175 g. (0.63 mole) of ferrous sulfate heptahydrate and 35 ml. (0.63 mole) of concd. sulfuric acid in sufficient water to give 750 ml. of solution. The other funnel contained 1 mole of hydrogen peroxide in 150 ml. of aqueous solution. The reaction mixture was stirred vigorously, and the rates of addition of the ferrous sulfate and peroxide solutions were adjusted so that the funnels were emptied simultaneously in about 15 minutes while carbon monoxide was bubbled through the reaction mixture at the rate of 1.6 l./min. When the funnels were emptied, the reaction was complete, and the temperature had risen to about 25°.

The products were isolated by extraction. About 300 g. of anhydrous sodium sulfate was added to the reaction mixture, which resulted in separation of a *t*-butyl alcohol layer. The aqueous layer was extracted three times with methyl ethyl ketone using 5 lb. of ketone for each extraction.[10] The ketone extracts and *t*-butyl alcohol layer were combined and extracted with 200 ml. of water containing enough sodium hydroxide to maintain the *p*H at 10. The aqueous solution was acidified carefully with 50% sulfuric acid and extracted three times with an equal volume of methyl ethyl ketone. This extract was dried over calcium sulfate, and the solvent was distilled under reduced pressure (10–15 mm.) leaving 24 g. of crude product which contained more than 95% β-hydroxyisovaleric acid (0.20 mole). This acid distilled at 94–97° (2.5 mm.).

The methyl ethyl ketone solution from which the acid had been extracted was concentrated under reduced pressure (10–15 mm.), leaving a mass of crystalline α,α,α′,α′-tetramethyltetramethylene glycol (weight 49 g., 0.32 mole), which could be recrystallized from ethyl acetate or sublimed for further purification. The pure glycol melted at 85–87°. Its identity was proved by comparison of melting points with the product obtained by Coffman, Jenner and Lipscomb by the coupling of *t*-butyl alcohol.[1]

β-Hydroxyisovaleric acid has been described by Pressman and Lucas,[11] but it was incompletely characterized. For example, the boiling point was not recorded, nor was the melting point of a solid derivative given. The acid from the carboxylation of *t*-butyl alcohol was therefore characterized in sufficient detail to differentiate it from α-hydroxyisobutyric (which might have resulted through oxidation of *t*-butyl alcohol), and the acid was identified by comparison with an authentic sample of β-hydroxyisovaleric acid obtained by oxidation of diacetone alcohol (see Table IV).

TABLE IV

PROPERTIES OF HYDROXYCARBOXYLIC ACIDS

	Carboxylation product from *t*-butyl alcohol	Authentic β-hydroxyisovaleric acid	Authentic α-hydroxyisobutyric acid
Composition			
Carbon, %	50.52	50.8[a]	46.2[a]
Hydrogen, %	8.79	8.4[a]	7.7[a]
Neutral equiv.	121.5	118[a]	104[a]
Compn. of Ag salt, found			
Carbon, %	26.3	26.6[a]	22.8[a]
Hydrogen, %	3.87	4.00[a]	3.3[a]
Silver, %	46.75	48.0[a]	51.2[a]
M.p., °C. of *p*-bromophenacyl ester	66–67	68[b]	155–156
Infrared absorption	Same as authentic β-hydroxyisovaleric acid		
$n^{25}\mathrm{D}$	1.4396	1.4400	
M.p., °C.	Glass at −80	Glass at −80	79
pK_A	4.40	4.43	3.91

[a] Calculated values. [b] No depression on mixing.

Preparation of Authentic β-Hydroxyisovaleric Acid.—The method was similar to that used by Pressman and Lucas[11] modified according to the procedure of Smith, Prichard and Spillane[12] for oxidizing mesityl oxide.

A chilled (10°) alkaline solution of sodium hypochlorite prepared from 320 g. (8 moles) of sodium hydroxide, 230 g. (3.1 moles) of chlorine and 1500 ml. of water was placed in a 3-l. flask equipped with stirrer and reflux condenser, and 100 g. (0.85 mole) of diacetone alcohol in 200 ml. of dioxane was added. Reaction began immediately and within a few minutes the mixture was refluxing vigorously. The reaction was moderated by occasional immersion of the flask in an ice–water-bath, but the temperature was maintained at or near reflux. After 0.5 hr., cooling was no longer necessary. The mixture was stirred 2.5 hours longer and was allowed to stand overnight.

The product was extracted from the acidified reaction mixture with 4 l. of methyl ethyl ketone and was recovered by distillation. The yield of acid was 71 g. or 70%. β-Hydroxyisovaleric acid has a distribution ratio (ketone–water) of 1.2 with methyl ethyl ketone, while in ether the corresponding ratio (ether–water) is 0.3.

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[9] D. D. Coffman, U. S. Patent 2,687,432, August 24, 1954.

[10] In some experiments continuous extraction with diethyl ether was employed with equally good results.

[11] D. Pressman and H. J. Lucas, THIS JOURNAL, **62**, 2069 (1940).

[12] L. I. Smith, W. W. Prichard and L. J. Spillane, *Org. Syntheses*, **23**, 27 (1943).

Carboxylation of *t*-Butyl Alcohol at 750 Lb./Sq. In. Pressure in a Constant Environment Reaction System.—A stainless steel autoclave of about 600-ml. capacity was employed as the reaction vessel. It was provided with a stirrer and had four valved openings at the top and two at the bottom.

Three solutions were fed into the autoclave. A 2:1 (by weight) water–*t*-butyl alcohol solution that contained 0.2 mole of sulfuric acid per liter was added from a Hills–McCanna pump adjusted to feed 800 ± 50 ml./hr. A 1.3 *M* aqueous solution of ferrous sulfate, which was 1.3 *M* in sulfuric acid, and a 1.3 *M* aqueous solution of hydrogen peroxide were displaced from separate cylinders at a rate of 300 ± 10 ml./hr. The ferrous sulfate and *t*-butyl alcohol solutions were mixed just prior to addition. Carbon monoxide was admitted at constant pressure at the top of the autoclave.[13]

The autoclave was charged with 400 ml. of *t*-butyl alcohol solution and was pressured to 750 lb./sq. in. with carbon monoxide. Addition of the three solutions at the specified rates was begun, and the product was withdrawn continuously through a valve into a graduated vessel at a rate which maintained 400 ml. of liquid in the autoclave. Gas was bled continuously from the autoclave at a rate of 20 ml./hr. in order to remove by-product oxygen.

β-Hydroxyisovaleric acid and $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylene glycol were isolated as in the experiments at atmospheric pressure. The yields were 0.37 mole of acid and 0.20 mole of glycol per mole of hydrogen peroxide.

Photochemical Carboxylation of *t*-Butyl Alcohol.—A 3-l. glass beaker was charged with 2.1 l. of an aqueous 30% *t*-butyl alcohol solution. This beaker was enclosed in a 5-l. stainless steel beaker and was covered with a loosely fitting aluminum lid that had holes in it to admit a Hanovia mercury lamp with quartz envelope (No. CH-3), a thermometer and sintered glass gas inlet tube for carbon monoxide. The temperature was maintained at 22 ± 3° by exterior cooling with ice-water, and the mixture was stirred magnetically.

Carbon monoxide generated from formic acid (by the action of sulfuric acid) to avoid contamination by iron carbonyl in cylinder carbon monoxide was bubbled continuously through the reaction mixture. Hydrogen peroxide was added intermittently; the concentration never exceeded 0.06 *M*. The course of the reaction was followed by periodically withdrawing samples and determining the iodine liberated from sodium iodide by titration with sodium thiosulfate. The rate of peroxide consumption was 0.015 ±0.005 mole/hr.

The products were isolated by extraction and distillation. The yield of β-hydroxyisovaleric acid was 0.24 mole/mole of hydrogen peroxide consumed.

Analysis of the extracted aqueous phase showed it contained 0.04 p.p.m. Fe^{3+} ion (about 10^{-6} *M*). Whether this amount of iron is necessary or sufficient to account for the formation of the carboxylic acid is uncertain.

Carboxylation of *t*-Butylamine.—The apparatus used in the carboxylation of *t*-butyl alcohol at atmospheric pressure was employed. The flask was charged with 146 g. (2 moles) of *t*-butylamine, 111 ml. (2 moles) of concd. sulfuric acid and 2 l. of water.

Two solutions, one containing a mole of ferrous sulfate and a mole of sulfuric acid with water to make 750 ml. of solution and the other containing a mole of hydrogen peroxide, diluted with water to 150 ml., were added as in the carboxylation of *t*-butyl alcohol.

The resulting reaction mixture contained ferric sulfate, sulfuric acid, unreacted *t*-butylamine and $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylenediamine, in addition to the carboxylation product, β-aminoisovaleric acid. Most of the iron was first removed by concentrating the reaction mixture under vacuum to a volume of 500 ml., adding gaseous hydrogen chloride until the concentration was 6 *M*, and extracting repeatedly with diethyl ether. The extracted solution was made alkaline with sodium hydroxide. *t*-Butylamine and $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylenediamine were removed by extraction with *n*-butyl alcohol. The extracted aqueous solution was neutralized with carbon dioxide and evaporated to dryness and β-aminoisovaleric acid was extracted from the residue with ethyl alcohol. The yield was 0.10 mole of crude amino acid.

Although a compound considered to be β-aminoisovaleric acid has been reported previously and several solid derivatives have been described,[14] the product from the carboxylation of *t*-butylamine did not crystallize nor did it yield any of the solid derivatives that had been described earlier.

Accordingly, crystalline β-aminoisovaleric acid was prepared by amination of β,β-dimethylacrylic acid following the procedure of Slimmer.[14] With 2,4-dinitrofluorobenzene, this amino acid gave a crystalline derivative which melted over the range 125–165° after repeated crystallization. The compound obtained by carboxylation of *t*-butylamine when treated with 2,4-dinitrofluorobenzene gave a solid derivative which melted over the same range with no depression on mixing. In spite of the wide melting range, identification of the compound as β-aminoisovaleric acid is considered satisfactory since X-ray diffraction patterns of the derivatives were identical. *Anal.* Calcd. for $C_{11}H_{14}N_3O_6$: N, 14.82. Found: N, 15.18.

Carboxylation of Pivalonitrile.—A 2-gallon stainless steel autoclave was charged with 2 l. of water and 120 ml. (1 mole) of pivalonitrile. The autoclave was cooled to 20° and pressured to 200 lb./sq. in. with carbon monoxide. Solutions of 278 g. (1 mole) of ferrous sulfate heptahydrate in 55 ml. (1 mole) of sulfuric acid and 575 ml. of water, and of 86 ml. of 35% hydrogen peroxide in 664 ml. of water were added through Flowrators at equal rates.

Crystalline $\alpha,\alpha,\alpha',\alpha'$-tetramethyladiponitrile (m.p. 137–139°) was filtered from the reaction mixture. The yield was 11 g. (0.07 mole).

β-Cyanoisovaleric acid was isolated by extraction with methyl ethyl ketone by a procedure similar to that employed in the isolation of products from the carboxylation of *t*-butyl alcohol. The product (25 g.) was an oil from which crystals slowly separated on standing. The oil had a neutralization equivalent of 121 (calcd. for β-cyanoisovaleric acid, 127) and on hydrolysis in hydrochloric acid it gave unsymmetrical dimethylsuccinic acid, m.p. 138°, reported m.p. 140°. *Anal.* Calcd. for $C_6H_{10}O_4$: C, 49.3; H, 6.90; neut. equiv., 73. Found: C, 48.3; H, 6.90; neut. equiv., 76. The preparation of β-cyanoisovaleric acid has been described,[15] but the cyanoacid was not isolated. The crystalline material which separated from the crude β-cyanoisovaleric acid or sublimed from it when a sample was heated to 100° (1 mm.) was apparently unsymmetrical dimethylsuccinimide which has been prepared from the isomeric α,α-dimethyl-β-cyanopropionic acid.[16] The sublimate melted at 104°, reported m.p. 105°, and had a neutral equivalent of 121 (calcd. 127). Chromatography of the crude carboxylation product on a silica column[17] indicated the presence of 13.5% (by weight) of unsymmetrical dimethylsuccinimide, 41% unsymmetrical dimethylsuccinic acid and 45.5% β-cyanoisovaleric acid.

Carboxylation of Propionic Acid.—A 2-gallon stainless steel autoclave fitted with a paddle-type stirrer and a cooling coil through which tap water was circulated was charged with 500 g. (6.6 moles) of propionic acid and 1500 ml. of water. The autoclave was closed, and carbon monoxide was admitted until a pressure of 150 lb./sq. in. was reached. Two solutions, one containing one mole ferrous sulfate and one mole sulfuric acid in sufficient water to make 750 ml. and the other solution having one mole hydrogen peroxide in water to make 750 ml., were added through Flowrators at approximately equivalent rates during 30 minutes.

Most of the unreacted propionic acid was removed along with water by distillation under reduced pressure. The water which codistilled with the acid was replaced with fresh water and, after 5 l. had distilled, the distillate was nearly acid free. The aqueous solution of non-volatile acids was then extracted continuously with ether to recover 38.5 g. of a mixture of acids.

A sample of the acid was chromatographed on silica according to the method of Marvel and Rands[20] and was found to contain 60% C_6-dibasic acid (coupled product), 14% C_4-dibasic acid (carboxylation product), 7.5% propionic acid and 15% of a product that appeared to be lactic acid. The crude acid product was fractionated by crystallization from water, and the crude fractions were recrystallized from ethyl alcohol. The following were isolated: symmetrical

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[13] This equipment was assembled and its operation was supervised by Dr. Paul Mehne of this Laboratory.

[14] W. Heintz, *Ann.*, **198**, 48 (1879); M. D. Slimmer, *Ber.*, **35**, 408 (1902).

[15] C. Montemartini, *Chem. Zentr.*, **70, I**, 182 (1899).

[16] E. Blaise, *Compt. rend.*, **128**, 676 (1899).

[17] C. S. Marvel and R. D. Rands, Jr., This Journal, **72**, 2642 (1950).

dimethylsuccinic acid (3.8 g.), adipic acid (5.2 g.), succinic acid (4.5 g.), residue (15 g.). The acids were all identified by mixed-melting points with authentic samples of the corresponding acids.

Since chromatography of the residual acids indicated only a trace of C_4-dicarboxylic acid, it appeared that no methylmalonic acid, a product of carboxylation at the α-carbon atom, was formed.

Carboxylation of 1-Hydroxycyclohexyl Hydroperoxide.—A 3-l. flask, similar to that used in the carboxylation of *t*-butyl alcohol, was charged with 750 ml. of methanol and 750 ml. of water and was chilled to 10°. Two solutions, one consisting of 139 g. (0.5 mole) of ferrous sulfate heptahydrate and 28 ml. (0.5 mole) of concd. sulfuric acid in 288 ml. of water and the other solution containing 66 g. (0.5 mole) of 1-hydroxycyclohexyl hydroperoxide in sufficient methanol to make 375 ml., were added at equivalent rates to the vigorously stirred reactor during 0.3 hr. The temperature was maintained at 10–20°, and carbon monoxide was bubbled through the reaction mixture at the rate of 1.5 l./min.

The product was saturated with anhydrous sodium sulfate and extracted continuously with ether. The ether solution was extracted with aqueous alkali to recover organic acids. Methanol was distilled from the alkaline extract which was then acidified and steam distilled to remove volatile monocarboxylic acid. The procedure for separation of pimelic (carboxylation product) and dodecanedioic (coupled product) acids[18] in the steam distillation residue was based on their distribution ratios between ether and water (approximately 1 for pimelic acid and 1000 for dodecanedioic acid). The acids were extracted from the residue with ether, and the ether solution was extracted four times with an equal volume of water to obtain an ether-soluble acid fraction (19 g.), mainly dodecanedioic acid, and a water-soluble acid fraction (9 g.) believed to be mostly pimelic acid.

Samples of the fractions were separated on a silica gel column. The ether-soluble fraction contained 95% dodecanedioic acid. The water-soluble fraction contained four acids of which the two principal components appeared to be pimelic acid (50%) and dodecanedioic acid (35%).

A 2-g. sample of the water-soluble acids was separated into ten fractions by counter-current extraction using five 100-ml. portions of water and of ether. A comparison of a calculated distribution of pimelic acid among the various fractions with the actual acid content as determined by titration indicated that the four middle fractions (two ether and two water) contained nearly pure pimelic acid. The crude acid from these fractions weighed 0.5 g. After recrystallization, the acid melted at 94–96° (compared with 103° reported for pimelic acid); the melting point was not depressed by mixing with authentic pimelic acid. *Anal.* Calcd. for $C_7H_{12}O_4$: C, 52.5; H, 7.5; neut. equiv., 80. Found: C, 53.1; H, 7.67; neut. equiv., 82.

The yield of pimelic acid calculated from the chromatographic separation of the water-soluble acid fraction was 2.8 g. (0.02 mole) from 0.5 mole of 1-hydroxycyclohexyl hydroperoxide.

WILMINGTON, DELAWARE

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[18] W. Cooper and W. H. T. Davison, *J. Chem. Soc.*, 1180 (1952); N. Brown, M. J. Hartig, M. J. Roedel, A. W. Anderson and C. E. Schweitzer, THIS JOURNAL, **77**, 1756 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Base-catalyzed Isomerization of 5,8-Dihydro-1-naphthol and Its Methyl Ether

BY JEROME F. EASTHAM AND DONALD R. LARKIN

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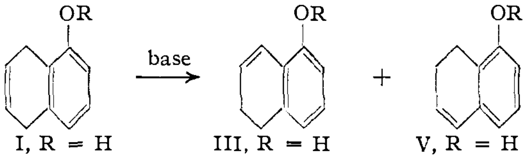
5,8-Dihydro-1-naphthol (I) is isomerized by base to produce primarily 5,6-dihydro-1-naphthol and some 7,8-dihydro-1-naphthol. Isomerization of the methyl ether of I proceeds in a similar manner. The structure of 5,6-dihydro-1-naphthol has been shown by degradation and of 7,8-dihydro-1-naphthol by degradation and synthesis. The rates of these base-catalyzed isomerizations of I and its methyl ether have been compared. The ultraviolet spectra of isomeric pairs such as 5,6- and 7,8-dihydro-1-naphthol are discussed.

The base-catalyzed isomerization of an allylphenol to a propenylphenol is a well known reaction.[1] In connection with other work[2] it was necessary to prepare a quantity of 5,8-dihydro-1-naphthol (I), a cyclic analog of an allylphenol. The present paper reports our findings on the course and the rate of base-catalyzed isomerization of I.

Potassium and alcohol in liquid ammonia efficiently reduce 1-naphthol to 5,8-dihydro-1-naphthol (I).[3] The unconjugated dihydronaphthol (I) produced is isomerized (equation 1) by alkali to a conjugated isomer[4] whose structure had never been determined. Isomerization of the methyl ether[5] II of the reduction product proceeds in a similar manner. It has now been shown that the base-catalyzed isomerization of 5,8-dihydro-1-naphthol or its methyl ether yields predominantly the 5,6-dihydroisomer (III or IV) along with some of the 7,8-dihydroisomer (V or VI). The chemical evidence for the position of the double bond in 5,6-dihydro-1-naphthol is shown in Chart I.



(1)

I, R = H   III, R = H   V, R = H
II, R = CH_3 IV, R = CH_3 VI, R = CH_3

The crystalline product from alkali-isomerization of 5,8-dihydro-1-naphthol was methylated[6] and

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[1] As leading references see D. S. Tarbell in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 19; and A. R. Bader, THIS JOURNAL, **78**, 1708 (1956).

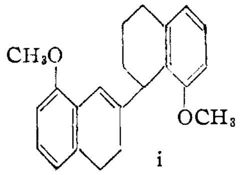
[2] J. F. Eastham and D. R. Larkin, Abstracts, 7th Annual Southeastern Regional Meeting of the American Chemical Society, Columbia, S. C., 1955. Details of this work, which concerned the effect of variables on the rate of the reduction in ref. 3, will be reported later.

[3] A. J. Birch, *J. Chem. Soc.*, 430 (1944).

[4] F. M. Rowe and E. Levin, *ibid.*, **119**, 2021 (1921).

[5] The 5,8-dihydro ether II, a liquid, did not form a crystalline adduct with mercuric acetate as does the parent hydrocarbon, 1,4-dihydronaphthalene (J. Sand and O. Grenssler, *Ber.*, **36**, 3699 (1903)). An acetate, also a liquid, could be prepared from the dihydronaphthol I by treatment with acetic anhydride.

[6] Initially some attempts were made to show the position of the double bond in III through a crystalline acetate prepared from it. However, work with the methyl ether IV proved more fruitful. Purification by distillation of the ether IV always left a dimer, $C_{22}H_{24}O_2$, m.p. 148°, probably with the structure indicated by i.



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