of an oil. This oil was treated with thionyl chloride and ammonium hydroxide as described above and gave 0.11 g. (67%) of a crude amide, m.p. 171.0–178.5°. Three recrystallizations from water brought the melting point to 177.8–178.9°, undepressed on admixture with the *exo*-amide. The infrared spectrum was also identical with the spectrum of the *exo*-amide.

Phenyl *exo-cis*-Bicyclo[3.3.0]oct-2-yl Ketone (V).—*exo-cis*-Bicyclo[3.3.0]octane-2-carboxylic acid (1.8 g.) was allowed to stand overnight with 3.5 g. of thionyl chloride. The excess thionyl chloride was removed under reduced pressure, and the residual crude acid chloride was dissolved in 10 ml. of dry benzene and used directly in the following preparation.

To an ethereal solution of phenylmagnesium bromide prepared from 0.485 g. of magnesium turnings and 3.3 g. of bromobenzene was added in small portions 2.37 g. of anhydrous cadmium chloride. When the addition was completed, the mixture was heated under reflux for 1 hr., at which time a negative Gilman test for phenylmagnesium bromide was obtained. The ether was then distilled and replaced by dry benzene; the benzene solution of the crude acid chloride described above was added dropwise with cooling in ice. After the addition was complete, the mixture was heated under reflux for 30 min. and then poured over 50 g. of ice and 10 ml. of 6 *N* sulfuric acid. The aqueous layer was separated and extracted with two 50-ml. portions of benzene, which were combined with the original benzene layer, washed with saturated sodium bicarbonate and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. Distillation of the residue through a semimicro column afforded 1.9 g. (75%) of liquid phenyl *exo-cis*-bicyclo[3.3.0]oct-2-yl ketone, b.p. 119–122° (0.55 mm.), $n^{25}\text{D}$ 1.5515–1.5555. An analytical sample had b.p. 121° (0.55 mm.), $n^{25}\text{D}$ 1.5530. The infrared spectrum of this ketone showed carbonyl absorption at 1675 cm.$^{-1}$, while the ultraviolet spectrum showed a maximum at 243 mμ ($\epsilon_{\max}$ 12,600, ethanol).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H, 8.47. Found: C, 84.17; H, 8.35.

Phenyl *exo-cis*-bicyclo[3.3.0]oct-2-yl ketone 2,4-dinitrophenylhydrazone was prepared by treatment of 0.2 g. of the ketone with a hot ethanolic sulfuric acid solution of 2,4-dinitrophenylhydrazine. The crude product, 0.28 g. (76%), had a melting point of 108.0–114.8°. Three recrystallizations from ethanol afforded fine orange needles, m.p. 121.6–122.4°. The ultraviolet spectrum of this compound shows a maximum at 368 mμ ($\epsilon_{\max}$ 19,500, chloroform).

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.21. Found: C, 64.21; H, 5.75; N, 14.34.

Phenyl *endo-cis*-Bicyclo[3.3.0]oct-2-yl Ketone (IV).—Under the conditions used in the above reaction for preparation of the *exo* isomer, the acid chloride prepared from 0.98 g. of *endo-cis*-bicyclo[3.3.0]octane-2-carboxylic acid gave 0.98 g. (72%) of liquid phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone, b.p. 114–117° (0.2 mm.), $n^{25}\text{D}$ 1.5550–1.5580. An analytical sample had b.p. 116–117° (0.2 mm.), $n^{25}\text{D}$ 1.5550. The ultraviolet spectrum of this ketone shows a maximum at 243 mμ ($\epsilon_{\max}$ 12,400, ethanol).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H, 8.47. Found: C, 84.07; H, 8.20.

Phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone 2,4-dinitrophenylhydrazone was prepared by the method described above; m.p. 150.2–152.9°. Three recrystallizations from ethanol afforded orange plates, m.p. 153.2–154.3°, undepressed by admixture with the 2,4-dinitrophenylhydrazone isolated from the product of reaction of methyl cycloöctene-1-carboxylate with phenylmagnesium bromide. Infrared spectra of the two samples (in potassium bromide pellets and chloroform solution) also were identical.

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.21. Found: C, 64.11; H, 5.72; N, 14.11.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION NO. 429 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Syntheses by Free-radical Reactions. I. Oxidative Coupling Effected by Hydroxyl Radicals

BY D. D. COFFMAN, E. L. JENNER AND R. D. LIPSCOMB

RECEIVED NOVEMBER 25, 1957

A new synthesis of difunctional compounds has been brought about by the dimerization of free radicals formed by the action of hydroxyl radicals on monofunctional compounds in aqueous systems at room temperature. The synthesis has been accomplished with lower straight- and branched-chain carboxylic acids, nitriles, amines, amides, alcohols and ketones. Isomeric products were obtained except when symmetrical reactants containing only equivalent hydrogen atoms were used.

The action of ferrous sulfate on hydrogen peroxide in acidic aqueous solution brings about the formation of hydroxyl radicals.[1]

$$\text{HOOH} + \text{Fe}^{++} \longrightarrow \text{HO}\cdot + \text{OH}^{-} + \text{Fe}^{+++} \qquad (\text{A})$$

The combination of hydrogen peroxide and a ferrous salt is frequently referred to as Fenton reagent because of his extensive studies[2] with this powerful oxidizing system. Hydroxyl radicals generated by this single electron transfer have been used in the initiation of vinyl polymerization,[3] in the oxidation of acids, alcohols, amines and other types of aliphatic organic compounds[4] and in the hydroxylation of aromatic compounds to obtain phenols.[5]

It has now been found that, under appropriate conditions of dilution and *p*H, a wide variety of aliphatic compounds undergo oxidative coupling by hydroxyl radicals at ordinary temperatures. In this process a hydroxyl radical attacks the aliphatic compound to remove a hydrogen atom bonded to carbon, and the free radicals thus formed dimerize.

$$\text{RH} + \text{HO}\cdot \longrightarrow \text{R}\cdot + \text{H}_2\text{O} \qquad (\text{B})$$

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

The hydrogen atom removed does not require activation by a carbonyl group, carbon–carbon unsaturation, etc., and the hydrogen atoms of *t*-butyl alcohol, for example, react readily. This synthesis is a non-chain radical reaction, and a mole of hydroxyl radical must be generated for each mole of organic reactant consumed. The coupling is accomplished by simply adding equimolar quantities of hydrogen peroxide and ferrous sulfate to an aqueous solution of the organic reactant.

---

[1] F. Haber and J. Weiss, *Proc. Roy. Soc.* (*London*), **A147**, 332 (1934); F. Haber and R. Willstätter, *Ber.*, **64**, 2844 (1931).

[2] H. J. H. Fenton, *J. Chem. Soc.*, **65**, 899 (1894).

[3] J. H. Baxendale, M. G. Evans and G. S. Park, *Trans. Faraday Soc.*, **42**, 155 (1946).

[4] J. H. Merz and W. A. Waters, *J. Chem. Soc.*, S-15 (1949).

[5] G. Stein and J. Weiss, *Nature*, **166**, 1104 (1950).

In previous studies of the oxidation of aliphatic compounds by hydroxyl radicals generated by chemical reactions, there was no evidence for the formation of coupled products, and it was not recognized that hydroxyl radicals would readily attack unactivated hydrogen atoms.[4] Only in the formation of bibenzyl from the reaction of hydroxyl radicals with the activated methyl group of toluene had evidence been obtained for coupling.[6] The literature contains many examples of the coupling of aliphatic compounds by free radicals generated by thermal decomposition. Thus, diacetyl peroxide at elevated temperatures has brought about the coupling of acids,[7] of esters and acyl chlorides[8] and of *t*-butyl alcohol.[9] Analogous couplings have been effected by the thermal decomposition of peroxydicarbonate[10] and of *t*-butyl hydroperoxide.[11]

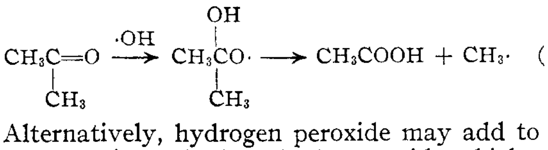
Scope.—This new synthesis of difunctional compounds by hydroxyl radical coupling has been accomplished with certain saturated lower, straight- and branched-chain aliphatic carboxylic acids, nitriles, amides, amines, alcohols and ketones. Table I lists the reactants used and the products obtained. The applicability of the synthesis is limited by the requirements that the compound to be coupled must be appreciably soluble in an aqueous medium and must not be susceptible to oxidative degradation. Since the attack of hydroxyl radicals on aliphatic compounds is not highly selective, isomeric products were obtained except when symmetrical reactants containing only equivalent hydrogens were used. For example, the coupling of pivalic acid and of pivalonitrile gave, in 37 and 52% yields, respectively, $\alpha,\alpha,\alpha',\alpha'$-tetramethyladipic acid and $\alpha,\alpha,\alpha',\alpha'$-tetramethyladiponitrile free of isomers. In contrast, *n*-butyric acid formed a mixture comprised of at least six of the C_8-dibasic acids, while propionitrile coupled to give about equal proportions of α,α'-dimethylsuccinonitrile, α-methylglutaronitrile and adiponitrile.

TABLE I

COUPLINGS EFFECTED BY THE HYDROXYL RADICAL

Reactant coupled	Products identified	Yield, %
Acetic acid	Succinic acid	4
Propionic acid	Adipic and dimethylsuccinic acids	
Isobutyric acid	α,α'-Dimethyladipic acids	
n-Butyric acid	Six C_8-isomeric acids: *e.g.*, β,β'-dimethyladipic, β-methylpimelic	
Pivalic acid	$\alpha,\alpha,\alpha',\alpha'$-Tetramethyladipic acid	37
Acetonitrile	Succinonitrile	18
Propionitrile	Adiponitrile, the α,α'-dimethylsuccinonitriles and α-methyl glutaronitrile	60
Pivalonitrile	$\alpha,\alpha,\alpha',\alpha'$-Tetramethyladiponitrile	52
Adiponitrile	A tetranitrile, $C_8H_{14}(CN)_4$	53
Propionamide	Adipamide (and isomers)	
Propylamine	Hexamethylenediamine	
t-Butylamine	$\alpha,\alpha,\alpha',\alpha'$-Tetramethyltetramethylenediamine	10
t-Butyl alcohol	$\alpha,\alpha,\alpha',\alpha'$-Tetramethyltetramethylene glycol	36
Acetone	Acetonylacetone, acetic acid	
Cyclopentanone	Valeric acid, a diketone	

Although acetic acid and acetone have been reported as "not noticeably attacked" by hydroxyl radicals,[4] conditions favorable for hydroxyl radical coupling have now been found to give low conversions of succinic acid from acetic acid, and of acetonylacetone and also acetic acid from acetone. The acetic acid most probably originated by cleavage of the hydroxyisopropoxy radical formed by hydroxyl radical attack at the carbonyl group of acetone.



$$\mathrm{CH_3\underset{CH_3}{\underset{|}{C}}{=}O \xrightarrow{\cdot OH} CH_3\overset{OH}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}O\cdot \longrightarrow CH_3COOH + CH_3\cdot} \qquad \text{(D)}$$

Alternatively, hydrogen peroxide may add to acetone to give a hydroxyhydroperoxide which could be reductively cleaved by ferrous ion to the same hydroxyisopropoxy radical. The fate of the methyl radical formed is uncertain, but it, like the hydroxyl radical, may have abstracted a hydrogen atom from acetone to yield the transitory acetonyl radical which dimerized.

The reaction of cyclopentanone with hydroxyl radicals resulted in the formation of some valeric acid in addition to the expected diketone. This acid may also have originated from an α-hydroxyalkoxy radical.[12–14] In this case, however, the intermediate radical was reduced and gave the saturated monocarboxylic acid. Under other conditions, radicals of this type have been found to dimerize and give dicarboxylic acids.[14] *t*-Butyl alcohol, which has been reported to be oxidized[4] to acetone and formaldehyde, readily coupled in reactions with hydroxyl radicals to yield $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylene glycol.

Conditions.—The coupling by hydroxyl radicals was accomplished at room temperature by introducing hydrogen peroxide and ferrous sulfate simultaneously and equivalently into an aqueous medium containing the organic reactant. The presence of excess organic reactant and efficient agitation favored reaction of the hydroxyl radical with the organic compound rather than with ferrous ion or hydrogen peroxide. The concentrations of hydroxyl radical and of organic substrates had important effects on the yield. For example, a 30% yield of isomeric C_6-dinitriles from propionitrile was increased to 58% by 3-fold dilution of the reaction mixture with respect to the radical-generating solutions; further dilution decreased the yield (see Fig. 1). The concentration of the hydroxyl radical was largely dependent upon the volume of water used and upon the rate of addition of the reactants. The concentration of the organic reactant could be varied up to the concentration of a saturated solution in water. At the

---

[6] J. H. Merz and W. A. Waters, *J. Chem. Soc.*, 2427 (1949).

[7] M. S. Kharasch and M. T. Gladstone, THIS JOURNAL, **65**, 15 (1943).

[8] M. S. Kharasch, E. U. Jensen and W. H. Urry, *J. Org. Chem.*, **10**, 386 (1945).

[9] M. S. Kharasch, J. L. Rowe and W. H. Urry, *ibid.*, **16**, 905 (1951).

[10] H. C. McBay and O. Tucker, *ibid.*, **19**, 869 (1954).

[11] E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 149 (1951).

[12] W. Cooper and W. H. T. Davidson, *ibid.*, 1180 (1952).

[13] E. G. E. Hawkins and D. P. Young, *ibid.*, 2805 (1950).

[14] N. Brown, M. J. Hartig, M. J. Roedel, A. W. Anderson and C. E. Schweitzer, THIS JOURNAL, **77**, 1756 (1955); and N. Brown, A. W. Anderson and C. E. Schweitzer, *ibid.*, **77**, 1760 (1955).

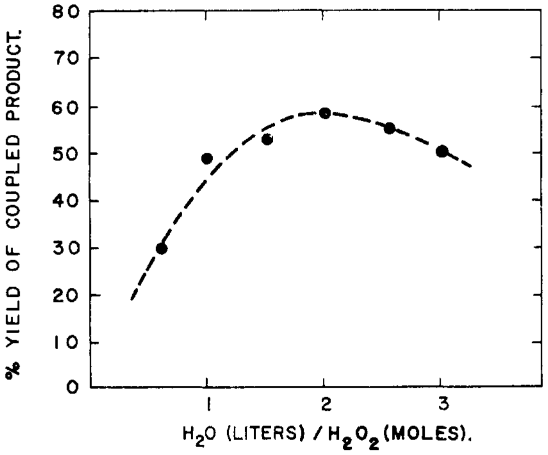


Fig. 1.—Yield *vs.* dilution in the hydroxyl radical coupling of propionitrile in saturated aqueous solution.

saturation point, propionitrile gave about a 50% yield of the isomeric C_6-dinitriles, and the yield decreased markedly at lower concentrations (see Fig. 2). At low concentrations of propionitrile, coupling was suppressed, and the available hydroxyl radical was increasingly consumed in competitive reactions with ferrous ion and hydrogen peroxide.[15]

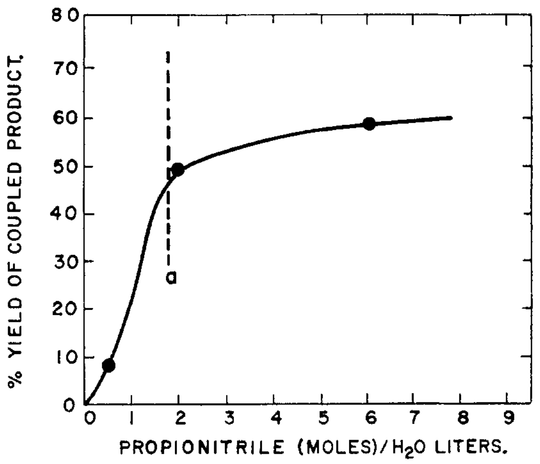


Fig. 2.—Yield *vs.* concentration of propionitrile in hydroxyl radical coupling; (a) concentration of propionitrile in a saturated aqueous solution at 25°.

Under the conditions used, the presence of ferric ion in excess did not appear deleterious. The *p*H had a very pronounced effect on the coupling, and this effect was operative over a broad range of dilutions (see Fig. 3). In general, the highest yields were obtained at a *p*H of 2 or less.

Reactivity of Hydroxyl Radicals.—Only qualitative comparisons of the susceptibilities of carbon–hydrogen bonds to attack by hydroxyl and other radicals and of the aptitudes of these radicals to abstract hydrogen are possible because of the diverse conditions in generating and utilizing the various radicals and because of lack of quantitative knowledge of the products. However, the nature of the products from propionic, *n*-butyric and isobutyric acids suggests that hydroxyl radicals and chlorine atoms have qualitatively similar preferences in attack on carbon–hydrogen bonds. Table II lists the net results after substitution by chlorination and after coupling by hydroxyl and methyl radicals. The sites listed are most probably those of initial free-radical attack. However, the possibility of preferential attack by hydroxyl radical at the β- or γ-carbon atoms to yield primary radicals which might have undergone exchanges[19] followed by α-coupling has not been excluded experimentally. Radical exchange has been investigated with inconclusive results in coupling by methyl radicals[18] and has been found unimportant in the free-radical chlorination[20] of aliphatic hydrocarbons.

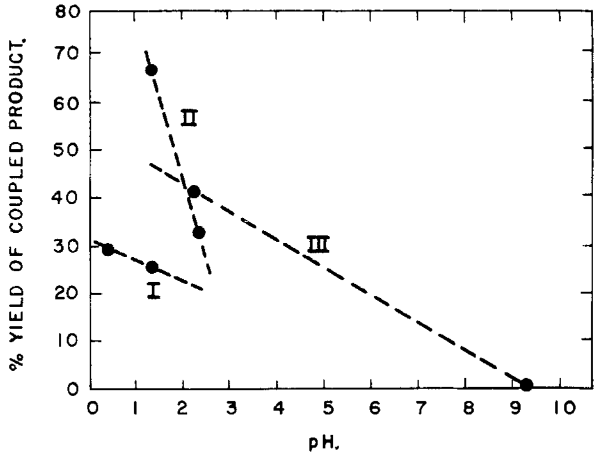


Fig. 3.—Yield *vs.* *p*H in the hydroxyl radical coupling of propionitrile in saturated aqueous solution at various dilutions of H_2O_2. Dilution H_2O (l.)/H_2O_2 (moles): I, 0.7; II, 2.1; III, 3.6.

Table II

Sites of Free Radical Attack

Radical	Propionic acid	*n*-Butyric acid	Isobutyric acid
Cl·	β, some α	Mostly β and γ, some α	β[16]
HO·	β, some α	Mostly β, some α and γ	β
CH_3·	α[16]	α[16]	α[17,18]

The deactivating effect of the carboxyl group, to which inhibition of α-substitution is attributed, is apparent from the products formed in competitive hydroxyl radical couplings of acetic and pivalic acids. A carbon–hydrogen bond in pivalic acid appeared to be about three times as sensitive to hydroxyl radical attack as was a carbon–hydrogen bond in acetic acid, or, pivalic acid appeared to be about nine times as reactive as acetic acid on a molar basis.

The aptitude of hydroxyl radicals relative to that of chlorine atoms and methyl radicals to abstract hydrogen is obscured by competitive reactions which consume hydroxyl radicals and lower the yields of coupled products. Other observa-

---

(15) W. G. Barb, J. H. Baxendale, P. George and K. R. Hargrave, *Trans. Faraday Soc.*, **47**, 462 (1951).

(16) M. S. Kharasch and H. C. Brown, This Journal, **62**, 926 (1940).

(17) M. S. Kharasch, U. S. Patent 2,426,224, August 26, 1947.

(18) C. C. Price and H. Morita, This Journal, **75**, 3686 (1953).

(19) A. B. Ash and H. C. Brown, *Rec. Chem. Progr.*, **9**, 81 (1948).

(20) H. C. Brown and G. A. Russell, This Journal, **74**, 3995 (1952).

tions not yet published suggest that hydroxyl radicals may be more active in abstracting hydrogen atoms than are chlorine atoms.

Experimental

Coupling of Nitriles.[21] **Acetonitrile.**—Into a solution of acetonitrile (8 moles) in 280 ml. of water at 30° were introduced simultaneously and equivalently hydrogen peroxide (2 moles) as a 30% aqueous solution, and ferrous sulfate (2 moles) and sulfuric acid (2 moles) in 620 ml. of water. The addition time was 15 minutes, and vigorous stirring was employed. Succinonitrile was isolated in 18% yield based on the hydrogen peroxide used. A sample of the distilled succinonitrile was hydrolyzed with aqueous hydrochloric acid. The succinic acid obtained was recrystallized from water, m.p. 184–185° alone and when mixed with an authentic sample.

Propionitrile.—The coupling of propionitrile was explored under a variety of conditions. A typical procedure is described.

The following radical-generating solutions were used: (a) 201 g. (0.72 mole) of ferrous sulfate heptahydrate and 75 g. (0.72 mole) of concd. sulfuric acid in 600 ml. of distilled water and (b) 75 ml. (82 g., 0.72 mole) of 30% hydrogen peroxide.

Into a 5-necked, indented, 3-liter flask fitted with 2 dropping funnels and a high-speed, Morton-type, stainless steel silver-plated stirrer were placed 600 ml. (465 g., 10.8 moles) of redistilled propionitrile and 600 ml. of distilled water. Stirring was started and solutions a and b were added dropwise through separate feeds, the addition being regulated so that the hydrogen peroxide and ferrous sulfate were present in equimolar proportions. The reaction mixture was maintained at 28° by means of an ice-bath. Total addition time was 30 minutes. The reaction was strongly exothermic and rapid, since cessation of the addition of either peroxide or ferrous sulfate resulted in an immediate decrease in temperature which was quickly restored to normal when addition was resumed. After the addition was complete, stirring was continued for 15 minutes, and the organic layer was separated. The aqueous phase was extracted 4 times with 75-ml. portions of benzene, and the extracts were combined with the principal organic portion and placed over calcium carbonate to remove traces of acid. Distillation was employed to remove benzene, water and unchanged propionitrile. The high-boiling residue was fractionated *in vacuo* to isolate the dinitriles. The yield of mixed dinitriles isolated was 23.4 g. or 60% based on hydrogen peroxide, one mole of which should yield, theoretically, one-half mole of coupled product.

Characterization of Dinitriles from Propionitrile.—The products obtained from four similar couplings of propionitrile were combined and fractionally distilled through a 14-inch, spinning-band column. Ten fractions were obtained, varying in size from about 5–20% of the whole sample. There was only a small residue. Each fraction (Table III) was subjected to elemental analysis, determination of refractive index, infrared examination and hydrolysis.

TABLE III

DISTILLATION OF COUPLED PRODUCTS FROM PROPIONITRILE

Fraction	Vol., ml.	B.p. (5 mm.),[22] °C.	Analyses,[a] % C	H	N	O	$n^{22}D$
1	5	66–85	59.59	7.21	20.48	12.22	1.4271
2	5	85–90	63.68	7.94	23.14	5.24	1.4261
3	5	90–100	66.63	8.00	24.53	0.84	1.4267
4	10	100–106	66.62	7.82	25.08	0.48	1.4283
5	5	106–108	66.91	7.81	25.34	...	1.4299
6	10	106–109	67.41	8.06	25.35	...	1.4318
7	10	109–108	67.19	8.08	25.61	...	1.4321
8	7	108–120	66.92	7.91	25.54	...	1.4331
9	6	120–131	65.57	8.06	25.23	1.14	1.4378
10	16	131–136	64.56	7.96	24.40	3.08	1.4401
Residue	2						

[a] Calcd. for $C_6H_8N_2$: C, 66.7; H, 7.41; N, 25.9 (oxygen determined by difference).

Although no well-defined flats were obtained in the distillation curve, at least 95% of the material distilled within the range defined by the boiling points of the isomeric 6-carbon dinitriles. The carbon, hydrogen and nitrogen analyses and the refractive indices also were near the values required for a 6-carbon dinitrile, with the exception of fraction 1 which contained the lowest boiling materials. Fractions 2, 9 and 10, and especially fraction 1, contained appreciable amounts of oxygen. From the infrared analysis, it was concluded that a substituted succinonitrile was present in fractions 1 through 5, chiefly in 2, 3 and 4, which constituted about 20% of the reaction mixture. A substituted glutaronitrile was detected in fractions 3 through 9, chiefly concentrated in fractions 6, 7 and 8, which constituted about 30% of the reaction mixture. Adiponitrile was found in fractions 8, 9 and 10, principally 9 and 10, which constituted about 25% of the reaction mixture. Among the impurities were found indications of $-NH_2$, $-NH$, $-OH$ and three different types of $C{=}O$, one of which is probably amide. All of the impurities detected were concentrated in the lowest boiling fractions except one type of carbonyl which occurred chiefly in the highest boiling fraction.

Samples of fractions 1, 3, 7 and 10 were hydrolyzed with concd. hydrochloric acid at 100°, and the hydrolysates were isolated and examined. Acids obtained from fractions 1, 3 and 10 melted at 190°, 192° and 150°, respectively. The acid from fraction 7 was an oil which slowly crystallized to a solid, m.p. 75°. The literature melting points for *meso*-α,α'-dimethylsuccinic acid, adipic acid and α-methylglutaric acid are 195,[23] 153[24] and 78–80°,[25] respectively. Thus, the products of the reaction of hydroxyl radicals with propionitrile consist principally of α,α'-dimethylsuccinonitrile, α-methylglutaronitrile and adiponitrile in approximately equal amounts.

The aqueous portion of the hydrolysate from fraction 1, which contained most of the oxygenated impurities, was made basic with sodium hydroxide and evaporated to dryness. The residue was acidified with sulfuric acid and extracted with ether. The small amount of the organic material obtained after evaporation of the ether was placed on a silicic acid column saturated with water, and the column was developed with chloroform–butanol mixtures. The chromatogram thus obtained indicated, in addition to propionic and 6-carbon dicarboxylic acids, the presence of formic acid and three other acidic substances, among which may be the α- and β-hydroxypropionic acids.

Variables in the Coupling of Propionitrile.—Variations from the described coupling procedure were made, and the yields of coupled product were noted as an indication of the effect of the variable. Qualitatively, as judged from examination of the distillation curves, there were no important differences in the composition of the product as a result of the variations. Infrared spectra of the distilled products indicated that all three possible isomeric six-carbon dinitriles were obtained, *viz.*, α,α'-dimethylsuccinonitrile, α-methylglutaronitrile and adiponitrile. The distillation data indicated that the three isomers were present in approximately equal proportions and their combined amounts comprised at least 70% of the distillate.

Concentration of Reactants.—The concentrations of the organic substrate and of the hydroxyl radical were regulated separately. Since ferrous ion and hydrogen peroxide react practically instantaneously[3] to yield hydroxyl radical, the concentration of this radical was varied by changing the volume of water present while keeping the addition time constant. The yield of dinitriles was found to increase to an optimum value by diluting the reaction mixture with water. Figure 1 plots the yield of coupled product against the concentration of hydroxyl radicals, expressed as a function of dilution in terms of liters of water per mole of hydrogen peroxide used. *In these experiments, propionitrile was in excess so that the concentration of propionitrile in the aqueous phase remained constant at saturation.*

The concentration of the organic substrate was controllable within the range up to the saturation point in water. Figure 2 indicates the effect on yield when the amount of propionitrile was reduced so that less than a saturated solu-

---

[21] E. L. Jenner, U. S. Patent 2,700,051, Jan. 18, 1955.

[22] A. Franke and M. Kohn, *Monatsh. Chem.*, **23**, 744 (1902), report a b.p. of 136–137° (13 mm.) for α-methylglutaronitrile. W. A. Lazier and G. W. Rigby, U. S. Patent 2,242,309 (1941), report b.p. 154° (10 mm.) and $n^{25}D$ 1.4369 for adiponitrile.

[23] E. H. Farmer and A. T. Healey, *J. Chem. Soc.*, 1067 (1927).

[24] P. E. Verkade, H. Hartman and J. Coops, *Rec. trav. chim.*, **45**, 379 (1926).

[25] H. Wieland and F. Vocke, *Z. physiol. Chem. Hoppe-Seyler's* **177**, 74 (1928).

tion prevailed. *As long as a saturated solution was maintained, the yield was essentially unaffected by variation in the quantity of propionitrile.* When the concentration of propionitrile was below the saturation point, the yield of coupled product decreased sharply, presumably because the propionitrile was able to compete less effectively with ferrous ions, hydrogen peroxide and even with other hydroxyl radicals for the available free hydroxyls.

***p*H.**—An important relation between *p*H and the yield of coupled product was observed. As the *p*H was increased by decreasing the amount of sulfuric acid and by adding phosphate buffers, the yield decreased. This is illustrated in Fig. 3 in which three sets of experiments are plotted. The *p*H plotted was that measured by a Beckman *p*H meter at the end of the reaction. Since the *p*H decreased during the reaction, the *p*H value shown was the minimum attained. A sharply downward slope of the yield lines with increasing *p*H was observed at three different dilutions.

Temperature.—The coupling of propionitrile was investigated at 75° instead of room temperature since the solubility, and therefore the concentration, of propionitrile in the aqueous phase is greater at higher temperatures, and an increase in the yield of coupled product should have resulted. The yield of coupled product was 52.8%, which is slightly lower than that obtained in the control experiment at room temperature. This suggests that at the higher temperatures either competitive reactions were accelerated or extensive hydrolysis of the nitrile occurred.

Ferric Ion Concentration.—Ferric ion under certain conditions causes the destruction of hydrogen peroxide.[15] Since in the reaction of hydrogen peroxide with ferrous sulfate, ferric ion is one of the products, it follows that the concentration of ferric ion steadily increases in the aqueous solution. In order to determine whether the presence of appreciable amounts of ferric ion was important, a solution of ferric sulfate (12%) was substituted for water in the reaction mixture, and the coupling of propionitrile was carried out. The yield of coupled product under these conditions was 62%, which is as high as that obtained when water alone is used as the medium. Therefore, the presence of ferric ions under the conditions used was not deleterious to the coupling.

Pivalonitrile.—The reaction vessel was charged with 1300 ml. of water and 112 ml. (83 g., 1 mole) of pivalonitrile. While the mixture was vigorously agitated, 150 ml. of 6.67 *M* hydrogen peroxide and 750 ml. of 1.33 *M* ferrous sulfate solution (prepared from 278 g. of ferrous sulfate heptahydrate, 55 ml. of sulfuric acid and 575 ml. of water) were added simultaneously and equivalently from calibrated burets. The temperature was kept at 30° by means of an ice-bath during the 15 minutes required for the addition. The solid product was isolated by filtration, washed with water, and dried; weight 42.5 g. (51.8% yield). It was recrystallized from 180 ml. of ethyl alcohol to obtain 34.5 g. (42.1% yield) of pale-yellow, crystalline $\alpha,\alpha,\alpha',\alpha'$-tetramethyladiponitrile, m.p. 138°.

$\alpha,\alpha,\alpha',\alpha'$-Tetramethyladipic acid was obtained by hydrolysis of the nitrile. A 1-liter Hastelloy bomb was charged with 32.8 g. (0.2 mole) of recrystallized tetramethyladiponitrile, 67 ml. of concd. hydrochloric acid and 200 ml. of glacial acetic acid. This mixture was rocked and heated at 140° for 8 hours. The bomb was cooled and emptied. The contents comprised a mixture of crystals and liquid. The liquid was concentrated to about 40% of its original volume. The solid was then returned to the liquid, and water was added to bring the total volume to about 500 ml. The mixture was digested for 15 minutes at the boiling point, cooled and filtered. The product was washed with water and dried. A theoretical yield (41 g.) of white crystals, m.p. 190–191°, was obtained; neut. equiv. calcd. 101.1, found 100.7.

Variables in the Coupling of Pivalonitrile.—The ratio of water to hydrogen peroxide was the most important variable found in a brief investigation of the coupling of pivalonitrile. The yield of dinitrile increased to 52 from 10% when the ratio of the liters of water per mole of hydrogen peroxide was increased to 2.1 from 0.8. Further dilution reduced the yield to 29% as shown in Table IV. It was further found that when the glass stirrer generally employed was replaced by a silver-plated stirrer a 6% decrease in yield resulted. Adequate agitation of the reaction mixture was very important. With mild agitation, approximately one-half the usual yield was obtained.

TABLE IV

EFFECT OF DILUTION IN THE COUPLING OF PIVALONITRILE

Pivalonitrile,[a] moles	H_2O_2,[b] mole	Liters of H_2O/ mole of H_2O_2	Yield, %, based on H_2O_2[c]
2.68	1	0.8	10
1.34	1	1.5	43
1	1	2.1	52
0.67	0.5	2.6	29

[a] In all experiments, the quantity of pivalonitrile employed was sufficient to maintain substantially a saturated solution. [b] Equimolar quantities of ferrous sulfate, sulfuric acid and hydrogen peroxide were used. [c] The yield is based on the assumption that one mole of hydrogen peroxide reacts with one mole of nitrile to give one-half mole of product.

Adiponitrile.—Solutions containing a mole of hydrogen peroxide in 120 ml. of water and a mole each of ferrous sulfate and of sulfuric acid in 575 ml. of water were added simultaneously and equivalently during 10 minutes to a vigorously stirred mixture of adiponitrile (4.1 moles) and sulfuric acid (1 mole) in 2000 ml. of water.

The product was distilled through a molecular still, b.p. 145–185° at 0.005 mm. The distillate crystallized for the most part. The crystals were isolated by digesting the mush in methanol and filtering the resulting mixture. The crude product was purified by digestion with hot ethyl alcohol whereupon white crystals, m.p. 128–132°, were obtained in 53% yield.

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.32; H, 6.68; N, 25.84.

A 2.8-g. sample of tetranitrile was heated at reflux in a solution of 15 ml. of acetic acid in 15 ml. of aqueous hydrochloric acid. Concentration of the hydrolysate brought about crystallization of the acid which was recrystallized from water to obtain a tetracarboxylic acid, m.p. 179–186°.

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; neut. equiv., 72.6. Found: C, 49.74; H, 6.29; neut. equiv., 72.

The structures of the tetranitrile and the tetracarboxylic acid were not demonstrated. However, it seems likely that β-coupling occurred to yield γ,γ'-bis-(cyanomethyl)-suberonitrile.

Coupling of Carboxylic Acids. Acetic Acid.—To a solution of 200 ml. of acetic acid and 50 ml. of water was added simultaneously 41.6 ml. (0.4 mole) of 30% hydrogen peroxide and an aqueous solution containing 0.4 mole each of ferrous sulfate and sulfuric acid. The mixture was vigorously stirred at 25° during the 20-minute addition period. Iron salts were removed by passing the solution through a Nalcite HCR ion-exchange column. The sulfuric acid was largely neutralized by addition of 75 ml. of 20 *N* sodium hydroxide to bring the *p*H to 2.0. Water was removed by distillation at 50 mm. When the residue in the distillation flask had partially solidified, it was extracted 10 times with ether. From the ether extract there was obtained 1.1 g. (4%) of white crystalline material, m.p. 180–183° after washing with ether. The product, after recrystallization from water, was identified as succinic acid, m.p. 185–186°, neut. equiv. 59 (calcd. 59).

Propionic Acid.—The couplings of propionic and isobutyric acids were carried out by a procedure similar to that described under "Propionitrile." Generally, the acid to be coupled was employed in a 3- to 10-fold excess over the hydrogen peroxide–ferrous sulfate required. The addition usually required from 15 minutes to one hour. At the end of the addition, the mixture was separated if two phases were present, and the aqueous phase was extracted with a solvent such as ether, benzene or methyl ethyl ketone. After distillation of the solvent and unreacted starting material, the product was isolated by either distillation or crystallization.

From the coupling of propionic acid (500 ml. or 6.7 moles) in 100 ml. of water by reaction with 30% hydrogen peroxide (1.2 moles) and ferrous sulfate (1.2 moles) in 1200 ml. of 1 *M* sulfuric acid, 40 g. of a brown viscous liquid was obtained. A 0.83-g. sample was subjected to countercurrent partition (8 funnels) between water and 1:1 ethyl acetate–methyl ethyl ketone. The distribution obtained corresponded to that expected for adipic acid. Calcd. for adipic acid: neut. equiv., 73.1. Found: neut. equiv., 72.0.

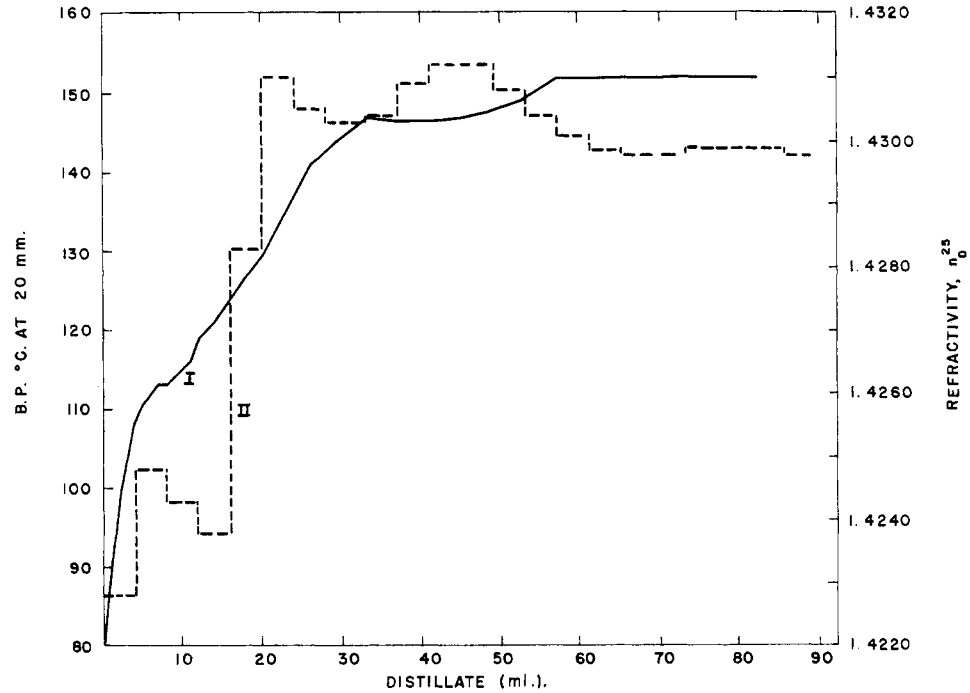


Fig. 4.—Fractionation of ethyl esters from the hydroxyl radical coupling of *n*-butyric acid: I, b.p., °C.; II, n^{25}D.

Water (10 ml.) was added to the 39 g. of product, and during 24 hours partial crystallization occurred. The filtered and washed crystals weighed 6.5 g. After recrystallization from water (charcoal was employed to remove the color), the product melted at 144–145°. The melting point of a mixture with adipic acid (m.p. 152–153°) was 144.5–146.5°. The product was recrystallized from 70% nitric acid and then 4 times from water, m.p. 143–145°. Calcd. for adipic acid: neut. equiv., 73.1. Found: neut. equiv., 73.4.

The low melting point indicated that the adipic acid was contaminated, and the neutral equivalent pointed to an isomeric dicarboxylic acid as the impurity. α,α'-Dimethylsuccinic acid was suspected, and the purification was continued on this basis. A 0.69-g. portion of the acid was placed in an inclined large test-tube and fractionally sublimed at 160° at 17 mm. In the early stages of heating, during which the material melted, there was considerable sublimation into the upper portions of the test-tube. Following this, the molten acid remained quiescent and no further sublimation was observed, although a temperature of 165° was maintained. Two fractions of sublimed acid were obtained: A, a solid, crystallizing near the heated melt, and B, a liquid, condensing in the cooled portion of the tube and which later crystallized. These two fractions were removed separately. Fraction A (21 mg.) melted at 120–135° and was probably crude *dl*-α,α'-dimethylsuccinic acid (m.p. 129°). Fraction B (9 mg.) melted at 34–37° and is believed to be the anhydride of *meso*-α,α'-dimethylsuccinic acid (m.p. 38°). Recrystallization from water yielded the acid, m.p. 194–195° (*meso*-α,α'-dimethylsuccinic acid melts at 192–194°). The solidified melt remaining in the bottom of the tube was recrystallized from water. Adipic acid, m.p. 149–151°, was obtained. This confirmed the indications that the crystalline product was adipic acid contaminated with *ca.* 5% dimethylsuccinic acid.

Isobutyric Acid.—The product obtained from the coupling of isobutyric acid (300 ml. or 3.2 moles) in 200 ml. of water by reaction with 30% hydrogen peroxide (1.2 moles) and ferrous sulfate (1.2 moles) in 1200 ml. of 1 *M* sulfuric acid was distilled at 100–200° (1 mm.). The distillate consisted of 28 g. of a mixture of white crystals and a viscous, pale-yellow liquid. A portion of this distillate was spread on a porous plate and washed with ether whereupon a crystalline product was obtained. Calcd. for dimethyladipic acid: neut. equiv., 87. Found: neut. equiv., 88. The solution obtained from determination of the neutral equivalent was washed with ether and concentrated to a small volume. Upon addition of concd. hydrochloric acid, the organic acid crystallized. This acid, after three recrystallizations from water, melted at 125–133°. After 6 more recrystallizations, the melting point was 143–144°. A sample of authentic *meso*-α,α'-dimethyladipic acid melted at 142–143°, and the mixture melting point was not depressed. The many recrystallizations presumably were necessary to free the *meso*-acid from the diastereoisomeric *dl*-acid (m.p. 75°). An unsuccessful search was made for tetramethylsuccinic acid (m.p. 200°).

***n*-Butyric Acid.**—The coupling of *n*-butyric acid was examined in order to gain information about the relative ease of attack at the α-, β- and γ-positions. The coupling was conducted as described under "Propionitrile," and the product was isolated by ether extraction. The crude product was esterified by heating with excess ethyl alcohol and a trace of sulfuric acid catalyst. Benzene was added, and the mixture was partially distilled to remove water formed in the esterification. More alcohol and benzene were added, and the distillation was continued. After the alcohol and benzene had been removed, potassium acetate was added to neutralize the acid catalyst, and the esters were distilled. The distillate (155 g.) was fractionated through a 25-mm. Podbielniak column. The variations in boiling point and refractive index during distillation indicated the presence of at least 6 components (Fig. 4). Saponification numbers determined on fractions 8, 11 and 19 corresponded to those for the diethyl esters of C_8-dibasic acids. Hydrolysis of the esters gave dibasic acids melting in the approximate ranges of the methyl-substituted adipic and pimelic acids listed in Table V.

TABLE V

C_8-Dibasic acid esters		Dibasic acids		
Fraction	Sapn. equiv.	Obsd. m.p., °C.	M.p., °C.	Reported for
8	116.2, 116.5	128	133	β,β'-Dimethyladipic acid[26] (high-melting isomer)
11	114.7, 114.0	104	104–105	β,β'-Dimethyladipic acid[26] (low-melting isomer)
19	115.1, 116.2	39	48–50	β-Methylpimelic acid[27]

---

(26) F. Faltis and H. Wagner, *Ann.*, **433**, 110 (1923).

(27) A. Einhorn, *ibid.*, **295**, 180 (1897).

Table VI

Coupling of Pivalic Acid[a]: Effect of pH

pH[b] Init.	Final	Yield, %	Water used, ml. In initial charge	Water used, ml. Added during reacn.	Reagents for pH control Initial charge	Reagents for pH control Added during reaction
0.8	0.5	27	1200	750	10 ml. H_2SO_4	55 ml. H_2SO_4
1.7	1.4	15	1200	780	2 ml. H_2SO_4	11 ml. H_2SO_4
4.6	4.5	10	800	950	13.8 g. $NaH_2PO_4 \cdot H_2O$ 45.5 g. $Na_2HPO_4 \cdot 7H_2O$	190 g. $Na_3PO_4 \cdot 12H_2O$ 88.5 g. $Na_2HPO_4 \cdot 7H_2O$
6.8	5.5	7	800	970	38 g. $Na_3PO_4 \cdot 12H_2O$ 161 g. $Na_2HPO_4 \cdot 7H_2O$	304 g. $Na_3PO_4 \cdot 12H_2O$

[a] One mole each of hydrogen peroxide, ferrous sulfate and pivalic acid were employed in each of the experiments. At the beginning, 35% of the pivalic acid was charged into the reaction vessel with the reagents for pH control and the quantity of water indicated. The remainder of the pivalic acid was added along with the hydrogen peroxide and ferrous sulfate. When concentrated sulfuric acid was added during the experiment, it was in solution with the ferrous sulfate. The phosphates added were in solution with the pivalic acid. (The experiments using phosphate had copious beige precipitates throughout the reaction period.) Reaction temperatures of 25° and addition times of 15 min. were employed. At the end of the reaction, sulfuric acid was added, and pivalic acid was removed by steam distillation. The tetramethyladipic acid was isolated by filtration. [b] Determined with a glass electrode.

Pivalic Acid.—The reaction vessel was charged with 1200 ml. of water, 15 ml. of sulfuric acid and 102 g. (1 mole) of pivalic acid. While the mixture was vigorously agitated, 150 ml. of 6.67 *M* hydrogen peroxide and 750 ml. of 1.33 *M* ferrous sulfate solution (prepared from 278 g. of ferrous sulfate heptahydrate, 55 ml. sulfuric acid and 575 ml. water) were added simultaneously and equivalently from suitably calibrated burets. The temperature was held at 35° by means of an ice-bath during the 15 minutes required for addition. At the end of the addition, a heater and a condenser were attached to the flask, and about 500 ml. of a mixture comprising water and pivalic acid was distilled. Stirring was continued during the distillation and subsequent cooling. $\alpha,\alpha,\alpha',\alpha'$-Tetramethyladipic acid was isolated by filtration, washed with water and dried; weight, 37.5 g. (37%).

The crude acid was purified by solution in 100 ml. of concd. aqueous ammonia and filtration to remove iron compounds. Excess ammonia was boiled off, water was added to the resulting concentrated solution and 50 ml. of concd. hydrochloric acid was added to precipitate the acid; 30.6 g., m.p. 179–181°. Recrystallization using either glacial acetic acid (1 ml./g.), ethyl alcohol (2–3 ml./g.) or methyl ethyl ketone (*ca.* 5 ml./g.) gave $\alpha,\alpha,\alpha',\alpha'$-tetramethyladipic acid, m.p. 188–190°.

Variables in the Coupling of Pivalic Acid.—In the coupling of pivalic acid, the highest yield of tetramethyladipic acid was obtained at the lowest pH (Table VI, Fig. 5) and at highest concentration of pivalic acid (Table VII).

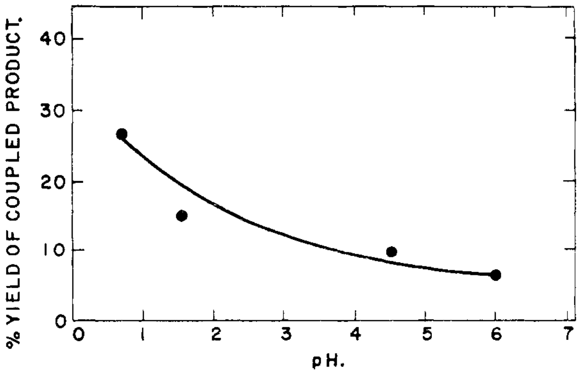


Fig. 5.—Yield *vs.* pH in the hydroxyl radical coupling of pivalic acid.

Relative Susceptibilities of Carbon–Hydrogen Bonds to Hydroxyl Radical Attack.—In order to gain information on the deactivating effect of the carboxyl group, hydroxyl radicals were generated in a solution containing acetic and pivalic acids in 10:1 mole ratio. Pivalic acid was found to be 9 times as reactive as acetic acid on a molar basis or approximately 3 times as reactive as acetic acid per methyl group or per hydrogen.

Solutions containing 0.05 mole each of hydrogen peroxide and ferrous sulfate were added simultaneously to a solution containing 1 mole of acetic acid and 0.1 mole of pivalic acid in aqueous sulfuric acid. The reaction mixture (blanketed with nitrogen) was held at 30° during the 14 minutes required for the addition. The organic products were isolated by exhaustive batch extractions (12) first with ether and then with methyl ethyl ketone. After the organic extracts had been concentrated, the acids were taken up in aqueous alkali, and the resulting solution was washed with ether and acidified with phosphoric acid. The organic acids were again isolated by extraction. A portion of the mixed acids obtained after removal of the solvent was subjected to partition chromatography. (We are indebted to Dr. C. S. Cleaver for this separation.) The chromatogram of the mixture showed about equal quantities of $\alpha,\alpha,\alpha',\alpha'$-tetramethyladipic acid and of succinic acid. A large intermediate fraction was obtained which is presumably the cross-coupled product, α,α-dimethylglutaric acid.

Coupling of Propionamide.—Solutions of hydrogen peroxide and ferrous sulfate were added to an aqueous solution of propionamide at 75°. The reaction mixture was extracted 7 times with methyl ethyl ketone whereupon a low conversion (3%) to a black solid (m.p. 220–260°) was obtained. A portion of this solid was extracted with acetone in a Soxhlet extractor. The crystalline solid which precipitated from acetone appeared to be crude adipamide (m.p. 220–225°). This material was recrystallized from water to obtain a mixture, the melting point of which was between that of adipamide and that of the dimethylsuccinamides. A portion of the crude product was hydrolyzed in hot hydrochloric acid to obtain crude adipic acid, m.p. 133–138°. This material, after one recrystallization from water, melted at 143–146° both alone and when mixed with crude adipic acid (m.p. 143–145°), obtained by coupling propionic acid.

Coupling of *t*-Butyl Alcohol.—Solutions of hydrogen peroxide (1.05 moles) and ferrous sulfate (1 mole plus 1 mole of sulfuric acid) were added simultaneously and equivalently to an aqueous solution of *t*-butyl alcohol (285 ml. or 3 moles in 800 ml. of water containing 23 ml. of sulfuric acid) at 30°. A 36% yield of semi-solid product possessing a camphor-like odor was isolated. The product was purified by drying on a porous plate, whereupon a white crystalline material was obtained. After recrystallization from ethyl acetate, it melted at 85–87°. A melting point of 91° is reported[28] for $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylene glycol.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41; mol. wt., 146. Found: C, 65.65; H, 12.34; mol. wt., 153.

Coupling of Amines. *t*-Butylamine.—Solutions of hydrogen peroxide (1 mole) and ferrous sulfate (1 mole) containing sulfuric acid (1 mole) were added simultaneously and equivalently with vigorous stirring to a solution of amine salt prepared from *t*-butylamine (209 ml. or 2 moles) by solution in 1 l. of water containing 111 ml. (2 moles) of sulfuric acid. The reaction temperature was 30°, and the addition time was 10 minutes. The product was isolated

---

[28] W. Krestinski and N. Perssianzewa, *Ber.*, **63**, 182 (1930).

by passing the reaction mixture through an ion-exchange column (Nalcite HCR). In eluting the column with aqueous acid, the iron was removed first and the organic amines later. This technique was not entirely satisfactory because excessively large volumes of acid were required to remove the amine.

TABLE VII

COUPLING OF PIVALIC ACID,[a] EFFECT OF PIVALIC ACID CONCENTRATION

Mean[b] concn. of pivalic acid, moles/l.	Yield of tetramethyladipic acid %	Pivalic acid		H_2SO_4 (concd.) ml.		Water, ml.	
		Total used, moles	% total charged initially	Initial charge	Added with $FeSO_4$	Initial charge	Added with reagents
0.51	37	1	100	15	55	1200	750
.51	32[c,d]	1	100	0	55	1200	750
.51	31[c,d]	1	100	0	55	1200	750
.42	33	1.25	37	5	55	1200	750
.31	28	1	36	5	55	1200	750
.31	27	1	35	10	55	1200	750
.28	23	0.75	44	20	40	1000	450
.28	19[d]	0.75	44	5	15	1000	450
.18	19	1	56	75	55	3000	450

[a] In each experiment, one mole of hydrogen peroxide and of ferrous sulfate were employed. These reagents were added simultaneously and equivalently (along with the indicated proportion of the pivalic acid) to a vigorously stirred mixture at 35–40°. The addition required 15 min. The sulfuric acid added was in the solution containing the ferrous sulfate. The unreacted pivalic acid was removed by steam distillation, and the tetramethyladipic acid was isolated by filtration. [b] This parameter is an arbitrarily chosen index to give a basis of comparison between experiments using different quantities of pivalic acid and of water and also different modes of addition of the pivalic acid. It is based on the amounts of pivalic acid and of water added half way through the reaction. It is assumed that 40% of the hydroxyl radicals formed (or of the H_2O_2 charged) react with pivalic acid. This is the order of magnitude of the yields observed. Accordingly, at the half-way point, 0.2 mole of pivalic acid (40% of 0.5 mole) had been consumed. The mean concentration was calculated as follows: P_i = moles pivalic acid charged initially; P_a = moles pivalic acid added during expt.; V_i = liters of water in initial charge; V_a = liters of water added during expt.; mean concentration = $(P_i + 0.5P_a - 0.2)/(V_i + 0.5V_a)$. [c] These runs are duplicates. [d] These runs gave yields somewhat lower than those of companion experiments, probably because of the use of less sulfuric acid.

The acidic fractions of eluate were made alkaline by the addition of 20 *M* sodium hydroxide solution, and the diamine was extracted with chloroform. The chloroform extracts were combined and distilled to obtain 7.0 g. (10%) of $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylenediamine, b.p. 78–79° (13 mm.), reported[29] b.p. 186° (753 mm.).

Anal. Calcd. for $C_8H_{20}N_2$: C, 66.60; H, 13.97; N, 19.42; neut. equiv., 72.13. Found: C, 67.18; H, 13.86; N, 17.22; neut. equiv., 74.4.

_n_-Propylamine.—The reaction of *n*-propylamine salt with the hydroxyl free radical was carried out at 25° employing an aqueous solution prepared from the amine (3.35 moles) and an equimolar quantity of sulfuric acid. At the end of the reaction period 225 ml. of 20 *M* sodium hydroxide was added. This brought the *p*H to 1.5, but did not precipitate any iron. Urea (60 g. or 1 mole) was added, and the mixture was heated under reflux with stirring for 48 hours. An additional 48 g. (0.8 mole) of urea was added, and heating was continued for 24 hours. This raised the *p*H to 6.5 and precipitated the iron in a dense form which was easily filtered. To the filtrate was added 350 ml. of 20 *M* sodium hydroxide. Water and ammonia were then distilled. Methanol was added to facilitate removal of the ammonia. During the concentration, a quantity of solid precipitated, and an organic phase lighter than the aqueous phase separated. The organic phase (57 g.) was distilled under reduced pressure to obtain the fractions listed in Table VIII. There was considerable decomposition in the distillation flask during distillation.

TABLE VIII

DISTILLATION OF COUPLED PRODUCTS FROM *n*-PROPYLAMINE

Fraction	Weight, g.	B.p. °C.	Mm.
Cold trap	22.0	...	..
1	8.0	31–42	20
2	7.0	74	5
3	1.5	76	5
Residue	12.0		

A 1-ml. portion of fraction 2 was treated with 2.4 ml. of benzoyl chloride and 5 ml. of 20 *M* sodium hydroxide in 15 ml. of water. The derivative separated as an oil. The aqueous layer was decanted, and alcohol was added to induce crystallization. The crude derivative (m.p. 155–157°) was twice recrystallized from ethyl alcohol, m.p. 159–160°. An authentic sample of the dibenzoyl derivative was similarly prepared from hexamethylenediamine. After recrystallization from alcohol, it melted at 160–161°. The mixture m.p. was 160–161°. This identified hexamethylenediamine as a major constituent of the reaction product.

Action of Hydroxyl Radicals on Ketones. Acetone.—The reaction of acetone with hydroxyl radicals has been found to yield acetic acid and acetonylacetone as the principal products.

A solution of 300 ml. of water and 440 ml. of acetone was treated with solutions containing one mole each of hydrogen peroxide and of ferrous sulfate. The reaction mixture was kept at 25° throughout a 30-minute addition period. The mixture was extracted with ether, the extract was dried, and the ether was distilled. Distillation of the residue under reduced pressure gave three fractions.

TABLE IX

PRODUCT FROM ACETONE AND HYDROXYL RADICALS

Fraction	Weight, g.	B.p. °C.	Mm.	$n^{25}D$
1	2.5	32	45	1.3740
2	6.1	37–50	45	1.3749
3	2.6	62	7	1.4190
Residue	2.4	...	..	....

The sharp odor, together with the boiling points and refractive indices, indicated that fractions 1 and 2 were acetic acid (14% yield). Calcd. for acetic acid: neut. equiv., 60. Found: neut. equiv., 64.

Fraction 3, a light-brown liquid with a mild pleasant odor, was identified as acetonylacetone (4% yield). The bisphenylhydrazone and corresponding pyrrole were prepared as derivatives. A 0.5-ml. sample of fraction 3 was dissolved in 2.5 ml. of ethanol and 2.5 ml. of water. Phenylhydrazine (1 ml.) and 0.5 ml. of acetic acid were added, and the mixture was boiled 6 minutes. The resulting bisphenylhydrazone was recrystallized twice from ethyl alcohol, m.p. 115–118°. The bisphenylhydrazone prepared from an authentic sample of acetonylacetone melted at 117–119°; the melting point of the mixture was 115–118°. When the quantity of the acetic acid used in the preparation of the hydrazone was tripled, the derivative obtained melted at 92–93° after two recrystallizations from alcohol. This derivative is 2,5-dimethyl-1-anilinopyrrole. An authentic specimen melted at 93–94°, and the mixture m.p. was 92–93°.

Cyclopentanone.—Solutions containing equimolar quantities of hydrogen peroxide and of ferrous sulfate were added simultaneously to an aqueous solution of cyclopentanone at 15°. Nitrogen was swept through the flask prior to and throughout the addition. After completion of the addition, the reaction mixture was extracted 4 times with methyl ethyl ketone, and the latter was distilled from the extract. The cyclopentanone was then distilled at moderately reduced pressure. Further distillation *in vacuo* yielded three fractions. One of these is believed, from its boiling point (36–41° (1 mm.)) and odor, to be valeric acid.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.80; H, 9.87; neut. equiv., 102.1. Found: C, 59.23; H, 9.98; neut. equiv., 106.9.

---

(29) M. Konowalow, *Chem. Zentr.*, **77**, II, 306 (1906).

A higher boiling fraction (b.p. 90–130° (0.3 mm.)) appears to be cyclopentanonylcyclopentanone.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49; carbonyl, 83.1. Found: C, 72.79; H, 8.69; carbonyl, 89.0.

An unidentified intermediate fraction (b.p. 69–90° (0.5 mm.)) was obtained as a crystalline solid. The total yield of acid and diketone was 36%.

WILMINGTON, DELAWARE

[CONTRIBUTION NO. 430 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Syntheses by Free-radical Reactions. II. Additive Dimerizations Effected by Hydroxyl Radicals

BY D. D. COFFMAN AND E. L. JENNER

RECEIVED NOVEMBER 25, 1957

A new one-step synthesis that yields long-chain, unsaturated dicarboxylic acids, diketones, glycols and other difunctional compounds has been found in the reaction of a 1,3-diene, a monofunctional compound, and hydroxyl radicals generated from hydrogen peroxide with ferrous sulfate. The products have the structure R–M–M–R in which R is a radical generated from the monofunctional compound by hydrogen abstraction and M is an unsaturated unit of composition corresponding to the 1,3-diene.

The action of hydroxyl radicals on saturated aliphatic compounds has been shown to bring about oxidative coupling.[1] This synthesis requires the removal of a hydrogen atom to form a carbon radical that dimerizes. The hydroxyl radicals were generated by reaction of ferrous sulfate with hydrogen peroxide.

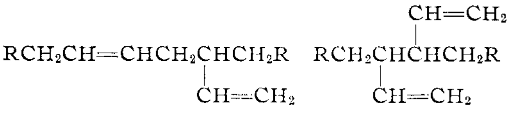
$$H_2O_2 + Fe^{2+} \longrightarrow \cdot OH + OH^- + Fe^{3+}$$
$$RH + \cdot OH \longrightarrow R\cdot + H_2O$$
$$2R\cdot \longrightarrow R\text{–}R$$

Additive Dimerization.—It has now been found that the action of similarly generated hydroxyl radicals on saturated aliphatic compounds in the presence of a 1,3-diene yields novel long-chain products incorporating both components. In this new synthesis, the aliphatic free radical adds to the diene to produce a new free radical which dimerizes. The series of reactions may be represented as

$$\cdot R + M \longrightarrow R\text{–}M\cdot$$
$$2R\text{–}M\cdot \longrightarrow R\text{–}M\text{–}M\text{–}R$$

This sequence, in which the unsaturated compound (M) is converted to a dimer containing residues (R) of the saturated compound as terminating groups, is called *additive dimerization*. The products of this reaction sequence, *i.e.*, the additive dimers, comprise straight-chain (A) and branched-chain (B) compounds formed by 1,4- and 1,2-incorporation of the diene.

$$R(CH_2CH{=}CHCH_2)_2R \qquad (A)$$



$$RCH_2CH{=}CHCH_2\underset{CH{=}CH_2}{CH}CH_2R \qquad RCH_2\underset{CH{=}CH_2}{CH}\overset{CH{=}CH_2}{CH}CH_2R \qquad (B)$$

It is likely that the preferential formation of dimers comes about through a gradation of radical reactivities. The hydroxyl radical is extremely reactive and relatively non-selective. It extracts a hydrogen atom from the saturated organic reactant which, except for water, is the most abundant species (1–10 *M*) in the system. The aliphatic radical so obtained adds rapidly to the diene (present at concentrations of 0.01–0.1 *M*) to form a resonance-stabilized radical of greatly reduced reactivity. The new radical does not abstract a hydrogen atom and adds another butadiene molecule only reluctantly. The very high rate of radical generation employed (on the order of 2 moles of radicals per liter per hour) leads to a high concentration of substituted butenyl radicals. As a result, dimerization becomes almost the exclusive reaction of these radicals. The reaction system differs from polymerization systems in that here the steady state concentration of radicals is very much higher.

Related syntheses have been described by Kharasch[2] who utilized radicals generated from organic peroxides. Thus, the reductive cleavage of *t*-hydroperoxides in the presence of butadiene gave unsaturated diethers,[2] and reaction of cyclohexanone peroxide with ferrous sulfate in the presence of butadiene gave long-chain, unsaturated α,ω-dicarboxylic acids.[3] Similarly, the reduction in the presence of 1,3-dienes of cyclic *t*-hydroperoxides and of peroxides derived from keto acids has given long-chain diketones and dicarboxylic acids.[4]

The use of radicals generated by the action of hydroxyl radicals on saturated organic compounds affords a convenient route to additive dimers with a wide selection of terminal functionalities derived from commonly available organic compounds. The preparation of an organic hydroperoxide is not required. The additive dimerization is brought about safely and rapidly by simply adding equimolar quantities of hydrogen peroxide and ferrous sulfate to an aqueous system containing the aliphatic reactant and the 1,3-diene.

Butadiene has been used chiefly as the unsaturated component, but chloroprene, isoprene and cyclopentadiene react similarly, and even acrylonitrile and maleic acid will function as the unsaturated component. Saturated aliphatic reactants have included ketones, acids, alcohols, esters, acetaldehyde, propionitrile and cyclohexylamine. The scope of this synthesis with respect to the

---

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

(2) M. S. Kharasch, F. S. Arimoto and W. Nudenberg, *J. Org. Chem.*, **16**, 1556 (1951).

(3) M. S. Kharasch and W. Nudenberg, *ibid.*, **19**, 1921 (1954).

(4) D. D. Coffman and H. N. Cripps, THIS JOURNAL, **80**, 2877, 2880 (1958).