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Syntheses by Free-radical Reactions. IV. Additive Dimerizations of Butadiene with Radicals from Acyclic Ketone Peroxides

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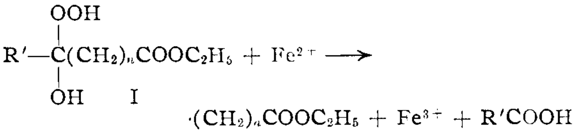
Long-chain, unsaturated dicarboxylic acid esters have been prepared by reductive cleavage of keto ester peroxides in the presence of butadiene. The synthesis is brought about by the additive dimerization of butadiene with the carbethoxy and the carbethoxyalkyl radicals generated from the ketone peroxides. Diketones were obtained similarly from acetonylacetone peroxide and the diene.

The principles of additive dimerization have been demonstrated in the synthesis of dicarboxylic acids,[1,2] nitriles,[2] glycols[2] and diketones.[2,3] In an extension of these principles, carbethoxy and carbethoxyalkyl radicals have been used for the first time in the preparation of long-chain, unsaturated dicarboxylic acid esters by reductive cleavage of acyclic keto ester peroxides in the presence of butadiene.

The sequence of reactions in the synthesis can be viewed as generation of a radical R· which combines with butadiene to form the resonance-stabilized allylic radical $RCH_2CH{=}CHCH_2\cdot$ that dimerizes. The radicals R· were generated *in situ* by ferrous sulfate reduction of the ketone peroxides obtained by reaction of an ethereal solution of hydrogen peroxide with the keto ester.[4] Although several types of peroxides may form in the reaction of ketones with hydrogen peroxide,[5] the ketone peroxides have been found to undergo reductive cleavage analogous to that of cyclohexanone peroxide[6] and cyclopentanone peroxide.[1] Thus, the ketone peroxides I represented as hydroxy hydroperoxides of ethyl oxomalonate ($n = 0$), ethyl acetoacetate ($n = 1$) and ethyl levulinate ($n = 2$) gave rise to the carbethoxy, carbethoxymethyl and carbethoxyethyl radicals, respectively.



$$R'-\underset{\text{OH}}{\overset{\text{OOH}}{\underset{|}{\overset{|}{C}}}}(CH_2)_nCOOC_2H_5 + Fe^{2+} \longrightarrow \cdot(CH_2)_nCOOC_2H_5 + Fe^{3+} + R'COOH$$

I

In reactions with butadiene, these radicals formed the esters EtOOC(CH$_2$)*n*-M-M-(CH$_2$)*n*COOEt (II), in which *n* equals 0, 1 or 2, and M is a butenylene group. Formation of the straight-chain dicarboxylic acid esters II[7] was demonstrated by hydrogenation of the esters and hydrolysis of saturated products to obtain sebacic acid, dodecanedioic acid and tetradecanedioic acid, respectively. The yields of crude esters ranged from about 50 to 70%; the yields of straight-chain esters separated by small-scale fractional distillation were much lower, *e.g.*, 20% or less. Products formed along with the straight-chain dimers were not investigated. They are presumed to have been, in part, the isomeric branched-chain dimers, since such products have been formed in analogous syntheses.[1,2]

Although the ketone peroxides were usually prepared in ethereal solution, aqueous 30% hydrogen peroxide and acetoacetic ester formed a peroxide that underwent reductive cleavage to the carbethoxymethyl radical which participated normally in additive dimerization. The types of radicals obtainable from peroxides of 2-substituted acetoacetic esters were not investigated. However, the 4-substituted ethyl trifluoroacetoacetate formed a peroxide that did not cleave to a trifluoromethyl radical but produced the carbethoxymethyl radical which was also obtained from ethyl acetoacetate. Thus, generation of the radical R′ by reductive cleavage of the ketone peroxide I has not been observed, although possibilities for that type of cleavage are formally presented, and such cleavage may have been an undetected competitive reaction.

The reductive cleavage of an aqueous mixture of acetonylacetone and hydrogen peroxide with ferrous sulfate gave 2-acetylethyl radicals that reacted with 1,3-butadiene to yield isomeric C_{16}-diketones. Hydrogenation of the isomeric ketones gave 2,15-hexadecanedione as one of the products.

Experimental

All melting points were taken on a hot block and are uncorrected. The yields were calculated by assuming that the ketone peroxides were simple 1:1 ketone–hydrogen peroxide adducts and hence would yield one radical on reductive cleavage.

CAUTION.—Reactions of 90% hydrogen peroxide should be carried out in preliminary trials on a small scale, and all experiments should be performed behind a heavy barricade. Extreme precautions should be taken in the isolation and handling of ketone peroxides.

I. Generation and Reaction of Carbethoxy Radicals ($\cdot\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OC}_2\text{H}_5$).

A. Preparation of Ketone Peroxide from Ethyl Oxomalonate.—The ketone peroxide of ethyl oxomalonate was obtained by a variation of the procedure described by Milas and Panagiotakos.[8] An anhydrous ethereal solution of hydrogen peroxide was prepared by adding 20 g. of 90% hydrogen peroxide[9] to 300 ml. of commercial anhydrous ether and drying with 12 g. of anhydrous magnesium sulfate. This solution, when diluted to 500 ml. with anhydrous ether, was about 1.1 *M* as indicated by iodometric titration. A mixture of 28.3 g. (0.16 mole) of ethyl oxomalonate[10] and 145 ml. of 1.1 *M* ethereal hydrogen peroxide was stirred until the yellow color was discharged

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[1] M. S. Kharasch and W. Nudenberg, *J. Org. Chem.*, **19**, 1921 (1954).

[2] D. D. Coffman and E. L. Jenner, This Journal, **80**, 2872 (1958).

[3] D. D. Coffman and H. N. Cripps, *ibid.*, **80**, 2877 (1958).

[4] N. A. Milas and P. C. Panagiotakos, *ibid.*, **68**, 533 (1946).

[5] N. A. Milas, S. A. Harris and P. C. Panagiotakos, *ibid.*, **61**, 2430 (1939); R. Criegee, W. Schorrenberg and J. Becke, *Ann.*, **565**, 7 (1949).

[6] W. Cooper and W. H. T. Davidson, *J. Chem. Soc.*, 1180 (1952).

[7] D. D. Coffman and H. N. Cripps, U. S. Patent 2,811,551, Oct. 29, 1957.

[8] N. A. Milas and P. C. Panagiotakos, This Journal, **68**, 533 (1946).

[9] Buffalo Electrochemical Co.

[10] Cohelfred Chemical Laboratories.

(about 3 hours). The ether was removed under reduced pressure, leaving the colorless residue (26.5 g., 80%) of ketone peroxide.

Anal. Calcd. for $C_7H_{12}O_7$: active oxygen, 7.70. Found: active oxygen, 7.47.

B. **Reaction with 1,3-Butadiene.**—A mixture of 31 g. of 1,3-butadiene and 100 ml. of nitrogen-saturated methanol was placed in a creased flask equipped with a paddle-type stirrer, solid carbon dioxide-cooled condenser, nitrogen inlet, thermometer and two calibrated addition funnels. The reaction temperature was maintained at $-15 \pm 5°$. The addition funnels were charged with an aqueous ferrous sulfate solution (112 ml. of 0.12 *M* solution) and 38.6 g. (0.18 mole) of the peroxide from ethyl oxomalonate. The two oxidation–reduction components were added at equivalent rates to the vigorously stirred solution during 3 minutes. After the addition was complete, the reaction mixture was stirred for 10 minutes, and 100 ml. of distilled water was added. The excess butadiene was allowed to boil off at room temperature, and the mixture was extracted with ether (one 100-ml. and one 50-ml. portion). The ether extracts were washed with 50 ml. of 10% aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate (5 g.). Removal of the ether by distillation left a pale yellow oil (17.5 g., 77.5%) that was distilled through a one-foot column packed with platinum gauze.

Fraction	B.p. °C.	Mm.	Weight, g.	$n^{25}D$
1	85–150	11	1.4	1.4238
2	160–169	11	4.3	1.4541
3	170–179	11	4.4	1.4549
4	175–180	11	2.1	1.4401

Anal. Calcd. for $C_{14}H_{22}O_4$: sapn. equiv., 127. Found: sapn. equiv., fraction 2, 120.9, fraction 3, 114.4.

A 1.08-g. sample of fraction 3 was heated at reflux for 4 hours with 25 ml. of 10% aqueous sodium hydroxide. After cooling, acidification with 38% hydrochloric acid gave 0.35 g. of a carboxylic acid. Recrystallization of 0.12 g. of the acid from 10 ml. of distilled water yielded 0.06 g. of white isomeric acids, m.p. 118–165°.

Anal. Calcd. for $C_{10}H_{14}O_4$: neut. equiv., 97.1. Found: neut. equiv., 99.8.

A 2.5-g. sample of the crude unsaturated esters, 35 ml. of absolute ethyl alcohol and 0.1 g. of platinum oxide were placed in a Parr hydrogenation apparatus and hydrogenated at 38 lb./sq. in. The hydrogenation mixture was filtered and saponified with a solution of 3.0 g. of sodium hydroxide in 50 ml. of distilled water (reflux time, 8 hours). Acidification yielded 1.76 g. of crude sebacic acid. Recrystallization from water gave 0.67 g. of sebacic acid, m.p. 130.5–132°. A mixed melting point with an authentic sample was not depressed.

Anal. Calcd. for $C_{10}H_{18}O_4$: neut. equiv., 101.1. Found: neut. equiv., 102.8.

II. **Generation and Reaction of Carbethoxymethyl Radicals ($\cdot CH_2CO_2C_2H_5$). A. Preparation of Ketone Peroxide from Ethyl Acetoacetate.**—Using the procedure described in I, the reaction of 13.0 g. (0.1 mole) of ethyl acetoacetate and 84 ml. of a 1.19 *M* ethereal hydrogen peroxide solution gave 15.5 g. (95%) of colorless ketone peroxide that appeared to be relatively stable toward shock and grinding.

Anal. Calcd. for $C_6H_{12}O_5$: active oxygen, 9.75. Found: active oxygen, 9.54.

B. **Reaction with 1,3-Butadiene.**—By means of the procedure and apparatus described in I, 30.8 g. (0.19 mole) of the ketone peroxide from ethyl acetoacetate and a solution of 53.0 g. (0.19 mole) of ferrous sulfate heptahydrate in 110 ml. of nitrogen-saturated distilled water were added to a mixture of 38 g. of 1,3-butadiene in 100 ml. of nitrogen-saturated methanol during 5 minutes. Isolation of the products afforded 4.11 g. of ethyl acetoacetate along with two higher boiling fractions: fraction 1, b.p. 75–131° (0.7 mm.), 4.4 g. (13.1%); fraction 2, b.p. 131–135° (0.7 mm.), 5.2 g. (15.2%), $n^{25}D$ 1.4560.

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.30; sapn. equiv., 141; quant. hydrog., 0.0142 g. H_2/g. Found for fraction 2: C, 68.16; H, 9.28; sapn. equiv., 143; quant. hydrog., 0.0174 g. H_2/g.

In a precision fractionation of 36.6 g. of the crude unsaturated esters, approximately 80% boiled at 131–148° (2.0 mm.), $n^{25}D$ 1.4563–1.4569.

A 4.03-g. (0.014 mole) sample of the C_{16}-unsaturated ester was hydrogenated in ethyl alcohol using a platinum oxide catalyst. Saponification of the saturated ester followed by acidification yielded 2.90 g. (90%) of light tan powder. Recrystallization of the crude isomeric acids from one liter of water gave 1.6 g. (49.6%) of dodecanedioic acid, m.p. 127.5–128.5°. A mixed melting point with an authentic sample showed no depression.

Anal. Calcd. for $C_{12}H_{22}O_4$: neut. equiv., 115.1. Found: neut. equiv., 113.8.

Saponification of a 3.8-g. (0.0134 mole) sample of the unsaturated ester followed by acidification yielded 2.5 g. (83%) of crude unsaturated acids. Recrystallization of 2.0 g. of the crude acids from a mixture of 75 ml. of water and 15 ml. of dioxane gave 1.5 g. (49.6%) of unsaturated acid in the form of white needles, m.p. 159.5–160.5°.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.03; neut. equiv., 113.1. Found: C, 63.92; H, 8.00; neut. equiv., 110.2.

The infrared spectrum of this acid indicated the presence of internal double bonds chiefly in the *trans* configuration. Although the acid was not investigated further, it was almost certainly 4,8-dodecadienedioic acid.

C. **Generation of Carbethoxymethyl Radicals from Aqueous Ethyl Acetoacetate and Hydrogen Peroxide.**—A homogeneous mixture of 26.0 g. (0.2 mole) of ethyl acetoacetate with 25.2 g. (0.2 mole) of 27% aqueous hydrogen peroxide and an aqueous solution (100 ml.) of 57.0 g. (0.205 mole) of ferrous sulfate heptahydrate were added at equivalent rates to a stirred mixture of 38 g. (0.7 mole) of 1,3-butadiene and 100 ml. of nitrogen-saturated methanol at about $-15°$. Isolation of the product in the usual fashion yielded 19.4 g. (68%) of crude unsaturated esters. Hydrogenation and hydrolysis gave 6.5 g. (28.2%) of dodecanedioic acid, identified by melting point (127.5–128.5°) and by a mixed melting point with an authentic specimen.

D. **Carbethoxymethyl Radicals from Ethyl 4,4,4-Trifluoroacetoacetate.**—The ketone peroxide was prepared in the usual fashion from 40.0 g. (0.22 mole) of ethyl 4,4,4-trifluoroacetoacetate and 195 ml. of a 1.12 *M* ethereal hydrogen peroxide solution. The yield was 47.8 g. (100%).

Anal. Calcd. for $C_6H_9F_3O_5$: active oxygen, 7.35. Found: active oxygen, 7.17.

Reductive cleavage of 47.0 g. (0.22 mole) of the ketone peroxide with aqueous ferrous sulfate heptahydrate (61 g. or 0.22 mole in 100 ml. of nitrogen-saturated distilled water) in the presence of 1,3-butadiene (60 ml. or *ca.* 0.8 mole) gave 16.0 g. (52%) of C_{16}-unsaturated esters, b.p. 145–152° (1.5–1.7 mm.). Hydrogenation and saponification of 6.66 g. (0.023 mole) of the esters yielded 2.5 g. (45.5%) of isomeric acids, m.p. 104–119°. The acids yielded dodecanedioic acid, m.p. 128.5–130°, by recrystallization from water. A mixed melting point with authentic dodecanedioic acid was not depressed.

III. **Generation of 2-Carbethoxyethyl Radicals ($\cdot CH_2CH_2CO_2C_2H_5$). A. Preparation of Ketone Peroxide of Ethyl Levulinate.**—Reaction of 14.42 g. (0.1 mole) of ethyl levulinate with an equivalent quantity of ethereal hydrogen peroxide (88 ml. of a 1.16 molar solution) gave 17.0 g. (96%) of ketone peroxide.

Anal. Calcd. for $C_7H_{14}O_5$: active oxygen, 8.99. Found: active oxygen, 9.05.

B. **Reaction with 1,3-Butadiene.**—The reactor was charged with 200 ml. of aqueous methanol (1:1 by vol.) cooled to $-30°$, and 50 ml. (*ca.* 0.6 mole) of liquefied 1,3-butadiene was added in an atmosphere of nitrogen. Then 34 g. (0.19 mole) of the ketone peroxide and a solution of 55 g. (0.197 mole) of ferrous sulfate heptahydrate in 100 ml. of nitrogen-saturated distilled water were added at equal rates during a four-minute period. After one-half of the oxidation–reduction components had been added, a further 25 ml. of liquefied butadiene was put in. Work-up of the reaction mixture gave 3.4 g. (11.2%) of C_{18}-unsaturated ester, b.p. 127–162° (0.9–1.0 mm.), $n^{25}D \sim 1.4579$.

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74; sapn. equiv., 155.2; quant. hydrog., 0.0129 g. H_2/g. Found: C, 68.66; H, 9.88; sapn. equiv., 144.8–164.5; quant. hydrog., 0.0137 g. H_2/g.

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.	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.

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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.

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

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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.

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

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

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

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

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).