Synthesis of Aliphatic Acids with Terminal Substituents by a Free Radical Reaction[1]

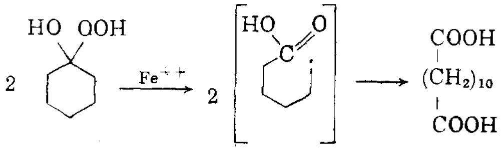
JOHN B. BRAUNWARTH AND GIFFORD W. CROSBY

The Pure Oil Co., Research Center, Crystal Lake, Ill.

Received July 31, 1961

Terminally substituted aliphatic acids and esters were prepared by the ferrous salt decomposition of 1-hydroxycycloalkyl hydroperoxides in the presence of certain halogen compounds and mercaptans. These liquid phase reactions are believed to be of a nonchain free radical type in which both transfer and radical combination take place.

The action of a ferrous salt solution on tertiary cycloalkyl hydroperoxides results in a ring cleavage and dimerization to form straight chain difunctional compounds.[2] Cooper and Davidson[3] found, for example, that the reductive cleavage of the peroxide formed from cyclohexanone and hydrogen peroxide (cyclohexanone peroxide) gave dodecanedioic acid. This reaction has been formulated as the reduction of a hydroperoxide to an open chain alkyl radical which undergoes dimerization.



The actual structure of cyclohexanone peroxide has been studied in some detail.[4-6] Although an equilibrium mixture of several peroxides has been shown to exist, the major constituents of the mixture were believed to form 1-hydroxycyclohexyl hydroperoxide as an intermediate in the reductive cleavage reactions as shown above. The same interpretation has been adopted in the present work because it is consistent with the reaction products obtained.

By conducting the ferrous salt decompositions of tertiary cycloalkyl hydroperoxides in the presence of 1,3-dienes, an additive dimerization occurred giving an unsaturated dibasic acid at the expense of cleaved radical dimer.[6,7] For example, when cyclohexanone peroxide was reduced with ferrous salt in the presence of butadiene, 8,12-eicosadiene-1,20-dioic acid, and two isomers were formed. Coffman and co-workers[8] have shown that the radical obtained by the reduction of 1-hydroxycyclohexyl hydroperoxide reacts with carbon monoxide giving an acyl radical which is converted to a carboxyl group. In this case pimelic acid was produced at the expense of dodecanedioic acid.

In the studies here reported, several other types of compounds were found to react with the reduced hydroperoxide and to decrease substantially the amount of its dimerization. The new additive products were open chain compounds derived from only one alicyclic molecule.

ω-Halogenated caproic acids were prepared from cyclohexanone peroxide, ferrous sulfate, and halogen compounds such as carbon tetrachloride, bromotrichloromethane, trichloromethanesulfenyl chloride, chlorine, and bromine. Polyhalogenated by-products were also formed when polyhalogen reactants were used. ω-Halogenated valeric acids were obtained by using cyclopentanone peroxide, but yields were somewhat lower. Table I shows the reaction products and yields.

Mercaptans were found to undergo reaction with the cleaved radical also. Caproic acid and ω-methylmercaptocaproic acid were isolated from the reaction of cyclohexanone peroxide, ferrous sulfate solution, and methyl mercaptan. Dimethyl disulfide was not isolated but may have been present. Reaction with benzenethiol gave caproic acid, phenylmercaptocaproic acid, and phenyl disulfide.

The formation of dodecanedioic acid from cyclohexanone peroxide in liquid phase has been explained as a radical dimerization. The rate of formation of the radical intermediate is governed by the rate of addition of ferrous salt solution. The identity of the principal product makes it clear that radical transfer reactions and disproportionation do not compete favorably with dimerization. However, when active halogen compounds are present, it is here proposed that the alkyl radical abstracts a halogen atom to form a molecule of halo acid, transferring the radical activity to the halogenation reagent. This new radical can be converted to a stable compound by combining with one of the alkyl radicals or by dimerizing.

The above sequence of peroxide reduction, radi-

---

[1] Presented at the 139th American Chemical Society Meeting at St. Louis, Mo., on March 27, 1961.

[2] E. G. E. Hawkins and D. P. Young, *J. Chem. Soc.*, 2804 (1950).

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

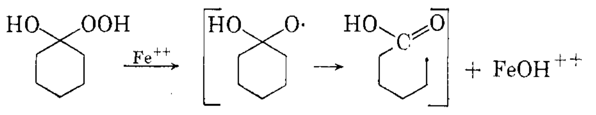
[4] N. Brown, M. J. Hartig, M. J. Roedel, A. W. Anderson, and C. E. Schweitzer, *J. Am. Chem. Soc.*, **77**, 1756 (1955).

[5] M. S. Kharasch and G. Sosnovsky, *J. Org. Chem.*, **23**, 1322 (1958).

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

[7] D. D. Coffman and H. N. Cripps, *J. Am. Chem. Soc.*, **80**, 2877 (1958).

[8] D. D. Coffman, R. Cramer, and W. E. Mochel, *J. Am. Chem. Soc.*, **80**, 2882 (1958).



$$\cdot(CH_2)_5\text{—}COOH + CCl_4 \longrightarrow Cl\text{—}(CH_2)_5\text{—}COOH + \cdot CCl_3$$

$$\cdot CCl_3 + \cdot(CH_2)_5\text{—}COOH \longrightarrow Cl_3C\text{—}(CH_2)_5\text{—}COOH$$

$$2\cdot(CH_2)_5\text{—}COOH \longrightarrow HOOC\text{—}(CH_2)_{10}\text{—}COOH$$

$$2\cdot CCl_3 \longrightarrow Cl_3CCCl_3$$

cal transfer, and radical combination reactions shows the way in which the products isolated from the carbon tetrachloride reaction may have been formed. In this case carbon tetrachloride decreased but did not completely inhibit the dimerization to dodecanedioic acid. When a reactant containing a weaker halogen-carbon bond was used, namely bromotrichloromethane the yield of ω-halocaproic acid was increased and the yield of dodecanedioic acid was further decreased. This is interpreted to mean that the carboxyalkyl radicals react promptly with the bromotrichloromethane and do not get a chance to build up to a concentration where extensive dimerization can occur. This is also consistent with the absence of trichloroheptanoic acid and the high yield of hexachloroethane from trichloromethyl radical dimerization. This type of reaction appears to be different from the terminating step in radical copolymerizations where the quantity of cross product is equal to or greater than the geometric mean of the quantities of the dimers.[9]

Still greater reduction of dodecanedioic acid yield occurred when chlorine or bromine was included in the reaction mixture of cyclohexanone peroxide and ferrous sulfate. At 0°, the halogenation was again directed to the omega position in the molecule, indicating that the usual chain reaction observed in liquid phase halogenation of alkanes was not occurring, even with excess halogen present.

Trichloromethanesulfenyl chloride was also found to produce ω-chlorocaproic acid from cyclohexanone peroxide and ferrous sulfate. In this case, the chlorine attached to sulfur reacted readily with the $\cdot(CH_2)_5COOH$ radical, since trichloromethyl disulfide was isolated in a substantial amount.

The unexpectedly high yields of some of the dimeric products derived from the halogenated and mercapto reactants suggest that these products may be formed in part by direct oxidation without the participation of the cycloalkyl hydroperoxide. Several possibilities exist. Fenton's solution, the ferrous salt reduction product of hydrogen peroxide, is an active oxidizing agent which may be present in the reaction mixture. It is known to oxidize bromotrichloromethane to hexachloroethane.[10] Ferric sulfate, a by-product of the primary reaction, is strong enough as an oxidizing agent to convert mercaptans to disulfides.[10] It will not, however, oxidize bromotrichloromethane. Sulfenyl chlorides can react with alcohols to give disulfides.[11]

In the formation of dodecanedioic acid from cyclohexanone peroxide, small amounts of caproic acid by-product have been reported.[3] When methyl mercaptan was included in the reaction mixture, caproic acid and ω-methylmercaptocaproic acid were obtained. This suggests that the $\cdot(CH_2)_5COOH$ radical may abstract the mercapto hydrogen atom and also combine with the $CH_3S\cdot$ radical. The moderate yield of dodecanedioic acid is interpreted as evidence for an intermediate concentration of $\cdot(CH_2)_5COOH$ radicals resulting from the intermediate reactivity of methyl mercaptan compared to other reactants studied.

Experimental[12]

Cyclohexanone Peroxide.[6]—To a stirred mixture of cyclohexanone (1 mole) and methanol (750 ml.) was added 30% hydrogen peroxide (0.49 mole) followed by the dropwise addition of concd. sulfuric acid (25 ml.). Temperature was kept below 20° by external cooling. After the acid addition was completed the hydroperoxide solution was ready for use.

Cyclohexanone Peroxide and Carbon Tetrachloride Reaction.—Carbon tetrachloride (0.5 mole) was added to the above prepared hydroperoxide solution and then a ferrous salt solution was added dropwise over a 2-hr. period while the mixture was rapidly stirred at 0°. The ferrous salt solution was prepared immediately before using by dissolving 147 g. (0.53 mole) of ferrous sulfate heptahydrate and 25 ml. of sulfuric acid in 300 ml. of water. The reaction mixture was diluted with 2 l. of water and the organic phase collected by extraction with benzene. The benzene solution was washed with water, dried over anhydrous calcium sulfate, filtered, and distilled to remove benzene and unchanged cyclohexanone. The residue was refluxed overnight with 200 ml. of methanol and 1 g. of *p*-toluenesulfonic acid catalyst. The methanol–ester mixture was diluted with water and extracted with benzene, and the benzene layer water washed and dried over calcium sulfate. The solution was filtered and fractionally distilled through a 12-in. Vigreux column, whereupon methyl ω-chlorocaproate, 13.8 g., (17% yield based on peroxide) was collected at 103°/12 mm.

Anal. Calcd. for $C_7H_{13}ClO_2$: C, 51.2; H, 7.9; Cl, 21.5; mol. wt., 165. Found: C, 51.5; H, 8.2; Cl, 22.2; mol. wt., 163.

To verify the location of the chlorine atom, the above ester (7.0 g.) was diluted with 25 ml. of methanol and refluxed with 3.5 g. of potassium cyanide for 1.5 hr. after which another addition of 3.5 g. of potassium cyanide was made and refluxing continued for 17 hr. The nitrile product was hydrolyzed by refluxing it with 14 g. of potassium hydroxide in 30 ml. of water until the evolution of ammonia ceased. Methanol was removed by distillation. The residue was acidified with dilute hydrochloric acid and extracted with ether. After evaporation of the ether, the product was recrystallized from hot water, m.p. 103°. This material did not depress the melting point of an authentic sample of pimelic acid.

---

(9) C. Walling, "Free Radicals in Solution," John Wiley and Sons, New York, 1957, pp. 145–147.

(10) Unpublished work.

(11) H. Gilman, "Organic Chemistry," Vol. I, 2nd ed., John Wiley and Sons, New York, 1943, p. 922.

(12) Elemental analyses were performed by the Analytical Research and Service Division of The Pure Oil Research Center. All boiling points and melting points are uncorrected. Molecular weights were determined cryoscopically in benzene.

TABLE I

REACTIONS OF CARBOXYALKYL RADICAL

Carboxylalkyl Radical	Reactant	Radical Transfer Products[a]	Yields,[b] Mole %	Radical Combination Products[a]	Yields,[b] Mole %
$(CH_2)_5COOH$	CCl_4	$Cl(CH_2)_5COOH$	17	$HOOC(CH_2)_{10}COOH$	30
				C_2Cl_6	Trace
				$Cl_3C(CH_2)_5COOH$	6
$(CH_2)_5COOH$	$CHCl_3$[c]	$Cl(CH_2)_5COOH$	9	$HOOC(CH_2)_{10}COOH$	19
				$Cl_3C(CH_2)_5COOH$	6
$(CH_2)_5COOH$	$BrCCl_3$	$Br(CH_2)_5COOH$	50	$HOOC(CH_2)_{10}COOH$	13
				C_2Cl_6	77
$(CH_2)_4COOH$	$BrCCl_8$	$Br(CH_2)_4COOH$	17	$HOOC(CH_2)_8COOH$	6
				C_2Cl_8	54
$(CH_2)_5COOH$	Br_2	$Br(CH_2)_5COOH$	54	$HOOC(CH_2)_{10}COOH$	7
$(CH_2)_4COOH$	Br_2	$Br(CH_2)_4COOH$	20	$HOOC(CH_2)_8COOH$	5
$(CH_2)_5COOH$	Cl_2	$Cl(CH_2)_5COOH$	55	$HOOC(CH_2)_{10}COOH$	3
$(CH_2)_5COOH$	$ClSCCl_3$	$Cl(CH_2)_5COOH$	40	$HOOC(CH_2)_{10}COOH$	20
				$Cl_3CSSCCl_3$	70
$(CH_2)_5COOH$	o-$NO_2C_6H_4SCl$	$Cl(CH_2)_5COOH$	20	$HOOC(CH_2)_{10}COOH$	10
				$NO_2C_6H_4SSC_6H_4NO_2$	25
$(CH_2)_5COOH$	CH_3SH	$CH_3(CH_2)_4COOH$	26	$HOOC(CH_2)_{10}COOH$	21
				$CH_3S(CH_2)_5COOH$	12
$(CH_2)_5COOH$	C_6H_5SH	$CH_3(CH_2)_4COOH$	10	$HOOC(CH_2)_{10}COOH$	34
				$C_6H_5SSC_6H_5$	47
				$C_6H_5S(CH_2)_5COOH$	3

[a] Acid products were isolated as methyl esters. [b] Basis, hydrogen peroxide. [c] Isolation of both chloro and trichloro acids suggests that a complex reaction took place and that additional products may be present in this reaction mixture.

A white crystalline material was noted on the walls of the distillation column and was characterized as hexachloroethane by melting point and mixed melting point.

Methyl 7,7,7-trichloroheptanoate (5.7% based on peroxide) was collected at 85–90°/1.4 mm.

Anal. Calcd. for $C_8H_{13}Cl_3O_2$: C, 38.8; H, 5.3; Cl, 43.0; mol. wt., 247. Found: C, 42.6; H, 5.8; Cl, 38.8; mol. wt. 230.

The structure of the trichloro ester was confirmed by hydrolyzing it in the presence of sulfuric acid to give pimelic acid.

Methyl dodecanedioate, 19 g. (30%), was collected at 122°/0.1 mm. The ester was hydrolyzed and the resulting dodecanedioic acid was identified by melting point and mixed melting point.

The above procedure was used for the reduction of the hydroperoxide in the presence of chloroform. Yields are shown in Table I.

Cyclohexanone Peroxide Cleavage in the Presence of Bromotrichloromethane.—The experimental procedure was similar to that of the hydroperoxide decomposition in the presence of carbon tetrachloride. Bromotrichloromethane (0.50 mole) was added to the hydroperoxide solution (0.49 mole). At the completion of the ferrous salt addition the reaction mixture was filtered to collect 44.7 g. (76.9%) of hexachloroethane.

Methyl ω-bromocaproate was collected at 95–100°/4.5 mm. The yield was 51.5 g., (50.2% based on peroxide).

Anal. Calcd. for $C_7H_{13}BrO_2$: C, 40.2; H, 6.2; Br, 38.3; mol. wt. 209. Found: C, 40.5; H, 6.2; Br, 37.8; mol. wt. 200.

The ω-halo ester was characterized as described above by conversion to the cyano ester and hydrolysis of the latter to pimelic acid.

The distillation residue was methyl dodecanedioate, 8.2 g. (13%).

Cyclopentanone Peroxide Cleavage in the Presence of Bromotrichloromethane.—Preparation of the cyclopentanone peroxide was similar to that of cyclohexanone peroxide. To the hydroperoxide made from hydrogen peroxide (0.49 mole) and cyclopentanone (1 mole) was added 99.2 g. (0.5 mole) of bromotrichloromethane followed by the ferrous salt solution. The following products were obtained: hexachloroethane, 31.2 g. (53.7% based on peroxide). Methyl ω-bromovalerate, 92–96°/12 mm., 16.0 g. (16.8% based on peroxide).

Anal. Calcd. for $C_6H_{11}BrO_2$: C, 36.9; H, 5.7; Br, 41.0; mol. wt., 195. Found: C, 36.5; H, 5.5; Br, 42.7; mol. wt., 186.

The dibasic acid derivative was prepared as described previously. M.p. 149°; mixed m.p. with adipic acid, 150°.

The distillation residue was characterized as methyl sebacate (6%, based on peroxide) by hydrolysis to the free acid.

Cyclohexanone Peroxide Reduction in the Presence of Bromine.—To the hydroperoxide solution (0.49 mole) as described previously was added 47.7 g. (0.3 mole) of bromine followed by the dropwise addition of ferrous sulfate solution at 0°. Products were isolated as before. Methyl ω-bromocaproate, 52.6 g. (54% yield based on peroxide) was collected at 120–123°/13 mm.

Anal. Calcd. for $C_7H_{13}BrO_2$: C, 40.2; H, 6.2; Br, 38.3; mol. wt., 209. Found: C, 40.7; H, 6.3; Br, 37.2; mol. wt., 198.

The ω-halo ester was characterized as described above by conversion to the cyano ester and hydrolysis of the latter to pimelic acid.

The distillation residue contained methyl dodecanedioate, 4.4 g. (7 mole % based on peroxide).

A similar reaction was carried out substituting chlorine for bromine. Temperature during the ferrous salt addition was maintained at −40°. Yields are given in Table I as well as yields for the reaction of bromine and cyclopentanone peroxide.

Cyclohexanone Peroxide Reduction in the Presence of Trichloromethanesulfenyl Chloride.—The procedure was similar to those previously described. To the peroxide solution (0.49 mole) was added trichloromethanesulfenyl chloride (0.51 mole) followed by the dropwise addition of the ferrous salt solution at 0°. Products were worked up as before. Using an 18-in. Fenske column, 31.7 g. (39.5 %) of methyl ω-chlorocaproate distilled at 56°/0.6 mm. The structure was confirmed by conversion of this product to pimelic acid.

Using a 6-in. Vigreux column, 50.8 g. of perchlorodimethyl disulfide was collected at 58 to 60°/0.08 mm. The yield based on peroxide was 69.8%.

Anal. Calcd. for $C_2Cl_6S_2$: S, 21.2; mol. wt., 301. Found: S, 20.6; mol. wt., 290.

The distillation residue contained methyl dodecanedioate, 12.3 g. (19.5%).

Reaction of Cyclohexanone Peroxide with *o*-Nitrobenzenesulfenyl Chloride.—To a 500-ml. reaction flask was charged 50 g. (0.18 mole) of powdered ferrous sulfate, 75 ml. of methanol, and 7 ml. of concd. sulfuric acid. At −20° a solution containing 200 ml. of ether, 37 g. (0.19 mole) of *o*-nitrobenzenesulfenyl chloride, and 22.8 g. (0.17 mole) of commercial cyclohexanone peroxide was added to the ferrous sulfate mixture with stirring. After stirring the reaction product an additional 15 min., 100 ml. of water was added.

Crystalline *o*-nitrophenyl disulfide 6.7 g. (25%) was separated by filtration. The melting point and mixed melting point showed the material to be *o*-nitrophenyl disulfide.

The ether phase was evaporated and the residue esterified with methanol and distilled: methyl ω-chlorocaproate, 5.5 g. (20%); methyl dodecanedioate, 1.9 g. (10%).

Preparation of Methyl Methylmercaptocaproate.—The procedure was similar to that used for the reaction of carbon tetrachloride and cyclohexanone peroxide. To the peroxide solution (0.49 mole) was added 25.7 g. (0.535 mole) of methyl mercaptan followed by the dropwise addition of ferrous salt solution. Following the esterification procedure, the reaction product was distilled through a 12-in. Vigreux column. No attempt was made to isolate the methyl disulfide which may have been present. Crude methyl caproate 16.6 g. (26.1%) was collected at 145–149°. At 117 to 129°/15 mm., 9.1 g. (11.5%) of methyl methylmercaptocaproate was collected.

Anal. Calcd. for $C_8H_{16}O_2S$: S, 18.1; mol. wt., 176; sapon. equiv., 176. Found: S, 18.6; mol. wt., 172; sapon. equiv., 185.

To confirm the location of the methylmercapto group in the terminal position, the methyl methylmercaptocaproate was hydrolyzed and the free acid converted to the phenylhydrazide derivative,[13] m.p. 78°. A mixed melting point with the phenylhydrazide prepared from the reaction product of sodium methyl mercaptide and ω-chlorocaproic acid was not depressed.

Methyl dodecanedioate was isolated in 21% yield.

Reduction of Cyclohexanone Peroxide in the Presence of Benzenethiol.—Ferrous salt reduction of 0.49 mole of cyclohexanone peroxide in the presence of benzenethiol (0.53 mole) was carried out. Filtration of the reaction mixture gave 25.4 g. (46.6%) of phenyl disulfide. After recrystallization from ethanol this material did not depress the melting point of a known sample of phenyl disulfide.

Isolation of the other reaction products was carried out by esterification and distillation: methyl caproate, 6.3 g. (9.7 %); methyl phenylmercaptocaproate, (3.2%) collected at 98–102° at 0.01 mm. Hydrolysis of this ester gave phenylmercaptocaproic acid.

Anal. Calcd. for $C_{12}H_{16}O_2S$: S, 14.3; neut. equiv., 224. Found: S, 12.7; neut. equiv., 216.

Methyl dodecanedioate, 22.0 g. (34.1%).

---

[13] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, New York, 1950, p. 158.

Extent of Formaldehyde Reaction with Selected Amides[1]

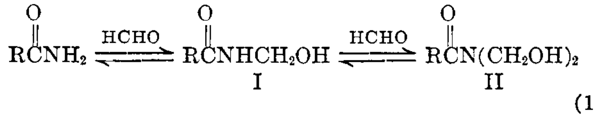
SIDNEY L. VAIL, CLIFFORD M. MORAN, AND HARRY B. MOORE

Southern Regional Research Laboratory, New Orleans, La.[2]

Received January 18, 1962

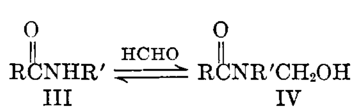
Various formamides and acetamides of the general structures $RCONH_2$, $RCONHR'$, and RCONH-X-NHCOR, where X = alkylene or substituted alkylene, were treated with an excess of formaldehyde to produce the *N*-methylol derivatives. The extent of the reaction was determined by titration of the unchanged formaldehyde. Contrary to previous reports, methylolation of *N*-substituted amides goes to 50–100% of completion in many of the cases studied. Methylolation is more nearly complete with the bisformamides than with the bisacetamides. Five new bisamides were synthesized by the reaction of diamines with esters.

The industrial uses of amide-formaldehyde reaction products in textile treating, resin manufacturing, etc., are widespread. Methylolation (or hydroxymethylation) of an unsubstituted amide can theoretically proceed through the following steps:



$$R\overset{\overset{O}{\|}}{C}NH_2 \xrightleftharpoons{\text{HCHO}} \underset{\text{I}}{R\overset{\overset{O}{\|}}{C}NHCH_2OH} \xrightleftharpoons{\text{HCHO}} \underset{\text{II}}{R\overset{\overset{O}{\|}}{C}N(CH_2OH)_2} \qquad (1)$$

or in case of substituted amide:



$$\underset{\text{III}}{R\overset{\overset{O}{\|}}{C}NHR'} \xrightleftharpoons{\text{HCHO}} \underset{\text{IV}}{R\overset{\overset{O}{\|}}{C}NR'CH_2OH} \qquad (2)$$

Extensive work by Einhorn and co-workers[3a,b] in the early 1900's indicated that reaction 1 generally proceeds only to the mono derivative and reaction 2, where R′ = alkyl, generally fails to occur. A later review by Walker[4] presented substantiation of this earlier work, but melamine and some cyclic ureas were shown to be exceptions and could be fully methylolated. Textile finishing in the wash-wear field would scarcely have pro-

---

[1] Presented at the 1961 combined Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., December 7-9, 1961.

[2] One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

Mention of trade names and firms does not imply their endorsement by the Department of Agriculture over similar products or firms not mentioned.

(3) (a) A. Einhorn *et al.*, *Ann.*, **343**, 207 (1905); (3) (b) *ibid.*, **361**, 113 (1908).

[4] J. F. Walker, "Formaldehyde," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1953, p. 290.